Seeing the Finish Line: Can Baseline OCT Values Predict Long-Term Disability and Therapeutic Management in Multiple Sclerosis?

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Multiple Sclerosis (MS) exhibits heterogeneity in its clinical course, making it difficult for patients and their physicians to forecast the disease course and to make personal and therapeutic decisions. Validating biomarkers to aid disease prognosis would further help personalize MS care. Yet, only a few biomarkers have been validated, such as brain and spinal cord MRI or oligoclonal bands[1, 2]. Considering that the retina is part of the grey matter of the central nervous system and is accessible to laser technologies such as optical coherence tomography (OCT), the studies of how MS damages the retina have provided significant insights about the disease course. Thus, retina-based biomarkers are being actively pursued to develop personalized medicine for people with MS (e.g., through the IMSVISUAL consortium collaboration[3]).

In this issue of *Neurology*, Lambe and colleagues, from John Hopkins University, report the diagnostic ability of retinal atrophy measured by OCT to predict disability worsening ten years later[4]. They prospectively studied a cohort of 132 people with MS. They used a stringent definition of disability worsening, namely an increase of 2 points on the Expanded Disability Status Scale (EDSS) for subjects with EDSS <6.0 and 1 point for cases with EDSS >6.0. They found that an average baseline thickness of the ganglion cell plus inner plexiform layer (GCIPL) below 70 μm confers four times greater odds of increasing disability a decade later (class I evidence). Specifically, 14 out of 45 patients (31%) with baseline GCIPL thickness <70μm experienced EDSS worsening throughout follow-up (as compared to 7 of 72 patients (10%) patients with GCIPL thickness >70μm). Indeed, the risk of EDSS worsening in cases with GCIPL thickness <70μm was even higher for specific subgroups, up to 6 times increased odds for RRMS patients, up to 14

times increased odds for patients with disease duration shorter than nine years, and up to 8 times for patients with baseline EDSS <2.0.

This risk analysis was conducted by averaging both eyes' GCIPL thickness (excluding eyes with previous optic neuritis). Besides, they analyzed the contribution of each eye with GCIPL thickness <70µm, finding a dose-effect. Having both eyes below <70µm creates a five-fold increased odds of disability progression, whereas having only one eye <70µm provides a 1.5 odds ratio of EDSS worsening ten years later. In parallel fashion, baseline GCIPL values <70µm also predicted a three-fold increased odds of worsening low contrast letter visual acuity. It is essential to mention that such GCIPL cut-off applies only to eyes without previous optic neuritis since such OCT values likely represent more disseminated injury to the brain's pathways and not the focal injury associated with optic neuritis.

These results are of enormous importance because they provide strong evidence for the use of a test easily done in the outpatient clinic or in collaboration with the ophthalmology department that will support clinical decisions (**Figure 1**). The GCIPL thickness biomarker is of clinical relevance because MS progresses slowly, and the uncertainty in the course of MS provokes anxiety in patients. Patients showing this GCIPL biomarker at early stages of MS have four times higher odds of progression to the next level of disability (e.g., from 2.0 to 4.0 or from 4.0 to 6.0), with substantial consequences on quality of life. Accordingly, such information will be critical for therapeutic decisions, supporting the adoption of more highly effective therapeutics in patients with low baseline GCIPL values.

These results are supported by previous medium-term studies using either previous generation OCT devices[5], other retina metrics, such as the thickness of the retinal nerve fiber

layer[6], or shorter follow-up[7], that demonstrated 2-4 times higher risk of EDSS worsening for patients with more retina atrophy. Here, the authors take advantage of the improved accuracy of new OCT devices and the realization of GCIPL thickness as a more sensitive metric of retinal damage. A limitation acknowledged by authors is that follow-up was done at a fixed visit, and not every six months, as usually performed in clinical trials. For this reason, they used a more stringent definition of EDSS worsening compared to clinical trials. Moreover, they did not adjust for the use of disease-modifying therapies, which have been shown to modify the long-term course of the disease, as confirmed recently by the MSBase meta-anlysis[8]. Multicenter studies involving thousands of patients with enough follow-up (at least ten years) will help to refine and personalize this biomarker and integrate it into the clinical workflow of people with MS

GCIPL thickness, similarly to brain volume, is significantly damaged at the earliest stages of MS, particularly in the first five years[9]. Indeed, immunotherapies have been shown to delay disability accumulation[8], and new neuroprotective or neurorepair therapies are under development[10]. For this reason, it is of the utmost importance to have access to informative biomarkers at early stages of the disease to help inform the best therapeutic strategy. Risk assessment should be a conversation between the patient and their neurologist, based on patients' preferences and supported by the evidence provided by the current knowledge and diagnostic tests.

References

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Figure 1. GCIPL thickness biomarker in the clinical care of people with MS. People with MS at the clinical visit are tested for GCIPL thickness by OCT. If the GCIPL thickness is below <70 μm in both eyes (eyes without previous optic neuritis), the absolute risk that ten years later they suffer disability progression (2 points in the EDSS) is 30%, compared with 10% for the ones above this cut-off. Baseline clinical, MRI and OCT data may be used in future to inform individual MS therapeutic decision making.