Is OCT a Viable Tool to Monitor Disease-Modifying Treatments in RRMS Yet?

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Optical coherence tomography (OCT) is considered a key research tool to monitor neurodegenerative processes in central nervous systems (CNS) disorders. This is particularly applicable to multiple sclerosis (MS), in which retinal changes (peripapillary retinal nerve fibre layer [pRNFL] and ganglion cell-inner plexiform layer [GCIPL] thicknesses) tend to reflect MRI markers of CNS damage and atrophy especially in eyes not affected by previous optic neuritis.[1]

Its application to individual clinical monitoring in MS, although still debatable, is nevertheless gaining credence as a viable tool. Retinal thinning rates are greater in early disease,[2] when inflammatory activity is prominent, compared with longer duration disease, which tends to be dominated by progression.[3] Disease-modifying therapies (DMTs), by reducing inflammatory activity, can also reduce the rate of CNS neuroaxonal loss and consequent conversion to secondary progression,[4,5] which is quantifiable by volumetric MRI and, more conveniently, OCT. Therefore, the efficacy of DMTs at ameliorating CNS degeneration could be theoretically quantified with OCT.

A few studies have demonstrated that OCT retinal thinning rates vary between low and high efficacy DMTs in MS. High efficacy DMTs such as alemtuzumab[6] and natalizumab[7] have lower retinal thinning rates, that are close to healthy control levels, compared with lower efficacy injectables (interferon-beta and glatiramer acetate [GA]) in people with MS, albeit in studies with small treatment arms.

In this issue of *Neurology*, Lambe and colleagues from John Hopkins MS Center, make an important contribution to this knowledge base by determining the retinal atrophy rates for rituximab, an anti-CD20 B cell depleting monoclonal antibody, in patients with relapsing-remitting MS (RRMS), compared with age and sex matched natalizumab and GA treated patients in a real world observational study.[8] This is particularly pertinent because of the increasing popularity of ocrelizumab, another anti-CD20 monoclonal antibody, for the treatment of MS around the world since its approval several years ago. This observational study recruited RRMS patients prospectively for rituximab treatment per standard of care (n=35) and retrospectively for GA (n=49) and natalizumab (n=88) treatments between 2008-2018. Patients were followed up with serial OCTs for a median of 2.8 years (rituximab 1.9 years, natalizumab 3.0 years, GA 2.7 years, healthy controls 3.1 years). The gap time between DMT initiation and first monitoring OCT also varied between groups (median 0.3 years for rituximab, 0.9 years for natalizumab, 2.2 years for GA).

The study provides the following key findings. First, rituximab has a treatment lag effect by about 12 months on the GCIPL retinal atrophy rate, similar to natalizumab. The GCIPL atrophy rates were faster during the first 12 months of rituximab treatment compared with the rates after 12 months (p=0.02, -0.69 μm/yr pre-12 months vs -0.14 μm/yr post-12 months). For natalizumab the corresponding rates were -0.45 μm/yr pre-12 months vs -0.13 μm/yr post-12 months (p=0.04) and for GA, -0.39 μm/yr vs −0.30 μm/yr (p=0.78). The authors performed sensitivity analyses that included only OCT assessments performed at approximately yearly intervals, as the original data had varying intervals of OCT scans and gap times. The rituximab findings statistically survived this analysis, showing faster GCIPL atrophy rates in the first 12 months compared with afterwards (p=0.02, difference in GCIPL rates 0.91 μm/yr) but the natalizumab results did not achieve statistical significance (-0.18 μm/yr pre-12 months vs -0.17 μm/yr post-12 months).

Second, after 12 months of treatment the GCIPL atrophy rates for rituximab and natalizumab were similar (-0.14 μm/yr vs -0.13 μm/yr respectively, p=0.94) and comparable with healthy controls (-0.15 μm/yr).

The authors acknowledge several limitations associated with a single-center observational study. Two treatment groups (natalizumab and GA) were recruited retrospectively and a lower proportion within these groups had OCT assessments starting within 12 months (i.e. had a longer gap time). Furthermore, the OCT assessments were conducted at variable intervals. In addition, relatively few rituximab patients had serial OCT assessments beyond 12 months which may have influenced the comparison with GA treatment post-12 months. Some of the challenges relating to imbalances, missing data, and confounding variables were

addressed by the employment of adjusted linear-mixed effects regression models with a priori defined research hypotheses. Also, this study did not include the assessment of MRI scans to understand the influence of optic radiation lesion load on GCIPL thinning. Finally, as with other retrospective studies, this study may have had potentially biased estimates of GCIPL atrophy rates and lack of power to detect the differences among the groups.

Overall, the study provides class IV evidence for the effects of rituximab on GCIPL atrophy in RRMS and suggests a delay in the response of this neuroprotective effect after 12 months of treatment. The findings of this study do provide additional evidence for beneficial effects of high efficacy DMTs in slowing neurodegeneration in RRMS. At the same time it reinforces the need for larger sample-sized, prospective, multi-center studies to provide sufficient statistical power in order to evaluate the modulatory effects of DMTs on retinal atrophy. This is crucial, with the increasing armamentarium of the DMT landscape in MS. Eventually, the hope is that this could pave the way to utilizing OCT either by itself or with other paraclinical tools to guide personalized treatments for people with MS.

Bibliography

1. Saidha S, Al-Louzi O, Ratchford JN, et al. Optical coherence tomography reflects brain atrophy in multiple sclerosis: A four-year study. Ann Neurol. 2015 Nov;78(5):801–813.

2. Pulido-Valdeolivas I, Andorrà M, Gómez-Andrés D, et al. Retinal and brain damage during multiple sclerosis course: inflammatory activity is a key factor in the first 5 years. Sci Rep. 2020 Aug 7;10(1):13333.

3. Balk LJ, Cruz-Herranz A, Albrecht P, et al. Timing of retinal neuronal and axonal loss in MS: a longitudinal OCT study. J Neurol. 2016 Jul;263(7):1323–1331.

4. Brown JWL, Coles A, Horakova D, et al. Association of Initial Disease-Modifying Therapy With Later Conversion to Secondary Progressive Multiple Sclerosis. JAMA. 2019 Jan 15;321(2):175–187.

5. Kalincik T, Diouf I, Sharmin S, et al. Effect of Disease-Modifying Therapy on Disability in Relapsing-Remitting Multiple Sclerosis Over 15 Years. Neurology. 2021 Feb 2;96(5):e783–e797.

6. Chan JK, Hernandez Martínez de Lapiscina E, Taylor C, et al. Long-Term Stability of Neuroaxonal Structure in Alemtuzumab-Treated Relapsing-Remitting Multiple Sclerosis Patients. J Neuroophthalmol. 2020;40(1):37–43.

7. Button J, Al-Louzi O, Lang A, et al. Disease-modifying therapies modulate retinal atrophy in multiple sclerosis: A retrospective study. Neurology. 2017 Feb 7;88(6):525–532.

8. Lambe J, Risher H, Filippatou AG, et al. Modulation of retinal atrophy with ritixumab in multiple sclerosis. Neurology. 2021;XX:xx-xx.

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