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Evolution of Visual Outcomes in Clinical Trials for Multiple Sclerosis Disease-Modifying Therapies

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Abstract

Background—The visual pathways are increasingly recognized as an ideal model to study neurodegeneration in multiple sclerosis (MS). Low-contrast letter acuity (LCLA) and optical coherence tomography (OCT) are validated measures of function and structure in MS. In fact, LCLA was the topic of a recent review by the Multiple Sclerosis Outcome Assessments Consortium (MSOAC) to qualify this visual measure as a primary or secondary clinical trial endpoint with the Food and Drug Administration (FDA) and other regulatory agencies. This review focuses on the use of LCLA and OCT measures as outcomes in clinical trials to date of MS disease-modifying therapies.

Methods—A Pubmed search using the specific key words “optical coherence tomography,” “low-contrast letter acuity,” “multiple sclerosis,” and “clinical trials” was performed. An additional search on the clinicaltrials.gov website with the same key words was used to find registered clinical trials of MS therapies that included these visual outcome measures.

Results—As demonstrated by multiple clinical trials, LCLA and OCT measures are sensitive to treatment effects in MS. LCLA has been used in many clinical trials to date, and findings suggest that 7 letters of LCLA at the 2.5% contrast level are meaningful change. Few clinical trials using the benefits of OCT have been performed, although results of observational studies have solidified the ability of OCT to assess change in retinal structure. Continued accrual of clinical trial and observational data is needed to validate the use of OCT in clinical trials, but preliminary work suggests that an intereye difference in retinal nerve fiber layer thickness of 5–6 μm is a clinically meaningful threshold that identifies an optic nerve lesion in MS.

Conclusions—Visual impairment represents a significant component of overall disability in MS. LCLA and OCT enhance the detection of visual pathway injury and can be used as measures of axonal and neuronal integrity. Continued investigation is ongoing to further incorporate these vision-based assessments into clinical trials of MS therapies.

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LOW-CONTRAST LETTER ACUITY AS AN OUTCOME MEASURE IN CLINICAL TRIALS

The afferent visual system has been established as an ideal model to study pathogenesis of multiple sclerosis (MS) and to evaluate neuroprotection and other aspects of novel therapeutic agents. Optic nerve disease is nearly ubiquitous in MS (1,2). Before the use of low-contrast letter acuity (LCLA) as an outcome measure for research and clinical trials in MS, an informative measure of visual dysfunction in patients with MS was lacking. In the 1990s, the National MS Society Clinical Outcomes Assessment Task Force searched for a sensitive visual outcome measure that could be added to the multiple sclerosis functional composite (MSFC). The MSFC was developed and included a timed 25-foot walk (ambulation), 9-hole peg test (arm function), and Paced Auditory Serial Addition Task (PASAT, cognition). Visual outcomes were not initially included because high-contrast visual acuity (HCVA), particularly as included in the Expanded Disability Status Scale (EDSS) score, did not show adequate sensitivity to change over time or demonstrate treatment effects in data sets used to develop the MSFC (3,4).

While the Pelli-Robson contrast sensitivity charts used in the Optic Neuritis Treatment Trial (ONTT) were temporarily out of print at the time of consideration of visual outcome measures for the MSFC, the ONTT had established the groundwork for use of low-contrast visual measures in MS clinical trials. The results of ONTT suggested that contrast sensitivity could capture sustained visual dysfunction, or lack of complete recovery, after acute optic neuritis to a degree that was not possible for HCVA. For consideration of inclusion in the MSFC for MS clinical trials, a low-contrast (gray letters on white background) version of the Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity charts (standard HCVA charts used in ophthalmology clinical trials) was identified that incorporated Sloan letters. As such, the charts were scored letter-by-letter (number of letters identified correctly). These LCLA charts enabled the measurement of acuity at various contrast levels, thus potentially capturing loss of contrast vision at smaller letter size characteristic of neurological disease (“notch” loss of contrast) (4,5). Such was not the case for Pelli-Robson contrast sensitivity charts, which used a single large letter size (20/680 Snellen equivalent at 1 m) at varying contrast levels.

The Sloan LCLA charts were first used as an exploratory outcome measure in the International MS Progressive Avonex Clinical Trial (IMPACT) study, a randomized clinical trial of interferon beta-1a vs placebo in patients with secondary progressive MS (SPMS). In parallel, an observational study (forerunner of the MS Collaborative Vision Study) demonstrated that, although both LCLA and Pelli-Robson contrast sensitivity outperformed HCVA in terms of distinguishing patients with MS from disease-free controls, LCLA was better than Pelli-Robson at identifying MS-related visual dysfunction (3,6,7). Patients with MS were found to have significantly lower LCLA scores compared with disease-free controls, especially at the lowest contrast levels (2.5% and 1.25%). Meanwhile, the IMPACT trial vision substudy showed the decline in LCLA scores from baseline measurements during the first year; this decline in visual function was predictive of reductions in EDSS scores for neurologic impairment during year 2 of the IMPACT trial. This finding was robust even

when accounting for baseline MSFC composite scores (8). Collectively, the results of IMPACT and observational studies of visual outcomes not only introduced and popularized measures of low-contrast vision in MS research and clinical trials but also established the Sloan LCLA as a now standard method for capturing visual impairment.

The performance of LCLA in MS clinical trials was further evaluated in AFFIRM, a Phase 3 randomized trial of natalizumab vs placebo in relapsing–remitting multiple sclerosis (RRMS). Before the design of AFFIRM, 10-letter (2-line) change in score was considered clinically meaningful for HCVA testing based on data regarding test–retest reliability (6). The AFFIRM trial analyses (9–11), a sustained decrease in LCLA defined as 10-letter decrement for 12 weeks was reduced in the natalizumab group by 47% in comparison with placebo at the 2.5% contrast level and by 35% at the 1.25% contrast level (proportions of 10% vs 18% with sustained visual loss) (9,10). Similarly, in the SENTINEL trial, an active-arm comparison with interferon beta-1a as an add-on, the cumulative proportions of patients with similarly defined sustained visual loss for the natalizumab + interferon beta-1a group were 10% vs 12% for the placebo + interferon beta-1a group (11).

Observational studies performed in parallel with AFFIRM and SENTINEL showed that a 7-letter reduction in LCLA was associated with clinically meaningful worsening of vision-specific quality of life (4 points or greater on the 25-item National Eye Institute Visual Functioning Questionnaire [NEI-VFQ-25]). Thinning of the retinal nerve fiber layer (RNFL) by OCT was also greatest among patients who had 7-letter reductions in LCLA (7,12). Thus, although a 10-letter reduction in LCLA score was initially used in AFFIRM for analyses of sustained visual loss (11), a 7-letter threshold was later determined to be optimal and used for analyses of visual improvement in AFFIRM (9). It was at this point that MS clinical trials and research studies using LCLA as an endpoint incorporated the 7-letter cutoff as a threshold for clinically meaningful change.

The Phase 3 CARE-MS trial of alemtuzumab vs interferon beta-1a in RRMS further reinforced the use of LCLA as a measure monitoring treatment effects on vision. The number of patients demonstrating improvement in LCLA at the 12-month follow-up was significantly increased in the alemtuzumab group; this group also showed significant improvement in LCLA scores between the 12- and 18-month follow-up points (13).

In a pooled analysis of the OPERA I and II trials, 45% of patients had visual system involvement at baseline (determined by presence of optic atrophy on the EDSS). Ocrelizumab-treated patients had greater improvements in LCLA scores at 2.5% contrast from baseline to week 96 (31.7%) compared with interferon beta-1a–treated subjects (26.6%). This was particularly true among those with visual involvement at baseline (36.6% vs 25.5%). These results suggest a potential benefit of ocrelizumab on visual outcomes when compared with interferon beta-1a, and, importantly, further confirm the capacity of LCLA scores to demonstrate treatment effects in MS clinical trials (14).

A trial of 4-aminopyridine (4-AP) vs placebo demonstrated significantly higher rates of responders in the active treatment group when applying the 7-letter threshold for LCLA at 2.5% contrast (15). Improvement of at least 7 letters in LCLA was seen in 7 of 28 eyes for

patients receiving 4-AP, compared with clinically significant improvement in 1 of 28 eyes in the placebo group (15).

OPTICAL COHERENCE TOMOGRAPHY AS AN OUTCOME MEASURE IN CLINICAL TRIALS

MRI estimates of MS demyelinating lesion burden and brain atrophy are commonly used in clinical trials. Current disease-modifying therapies reduce the risk of inflammation and neurodegeneration by modulating or suppressing the immune system. Although MRI remains the standard for measuring structure of central nervous system components in MS, both logistical aspects (time and expense) and physiologic factors (age, hydration status, and disease-modifying therapy) have the need to find additional, non-MRI techniques to assess neurodegeneration in MS in vivo. An article comparing outcomes from the RIVITaLISe and IPPoMS trials in progressive MS found MRI to have poor signal to noise ratios, with limited correlation with clinical measures (16).

OCT is a noninvasive and reliable technique that uses near-infrared light in a manner similar to ultrasound to image and to measure thickness for retinal tissues (17). Spectral domain OCT (SD-OCT) has improved on the initial time domain OCT during the last decade, allowing 2–3 μm of resolution for thickness measurement. With the advent of SD-OCT, the RNFL containing unmyelinated axons can be measured along with the layer containing retinal ganglion cell neurons (usually combined with the ganglion cell-inner plexiform layer [GCIPL]). RNFL and GCIPL thinning occur after acute optic neuritis and also throughout the course of MS even in the absence of acute optic neuritis episodes (18). Observational studies and clinical trials in MS have shown reduced RNFL and GCIPL thickness to be associated with MS both in cross-sectional and longitudinal studies and across all MS subtypes (18–25). Patients with “benign” MS and clinically isolated syndromes (first demyelinating events) are similarly affected by RNFL and GCIPL thinning by OCT, suggesting a ubiquity and previous underestimation of visual pathway involvement. Losses of RNFL and GCIPL thickness are associated with reduced scores for LCLA, vision-specific quality of life (NEI-VFQ-25 and 10-item Neuro-Ophthalmic Supplement to the NEI-VFQ-25), global MS disability (EDSS), cognitive function, brain atrophy, and radiological disease activity by MRI (7,8,18,26–40). Longitudinal OCT studies have shown higher rates of RNFL and GCIPL thinning in patients with MS compared with healthy controls; thinner RNFL and GCIPL measures were predictive of worse disability over time in these studies (18,32). OCT has higher resolution and may be a more sensitive measure of neurodegeneration than MRI volumetric measures, requiring smaller sample sizes to detect significant differences.

Clinical Trials Using Optical Coherence Tomography in Multiple Sclerosis

SD-OCT measures are sensitive to treatment effects. A recent retrospective analysis of the effect of glatiramer acetate (GA, n = 48), natalizumab (n = 46), and interferon beta-1a administered subcutaneously (IFNsc, n = 35) and intramuscularly (IFN_{IM}, n = 28) on SD-OCT measures showed that both the IFNsc and GA groups had faster rates of GCIPL thinning compared with natalizumab (IFNsc 0.37 μm/yr faster, $P < 0.001$; GA 0.14 μm/yr

faster, $P = 0.035$) (41). These findings suggest that immunomodulatory therapies such as natalizumab may have a greater effect on preserving retinal thickness; these results also mirror the comparative effects of this group of therapies on brain atrophy in large-scale studies.

A prospective open-label study of alemtuzumab showed a 1.5-μm (95% CI 0.2–2.9; $P = 0.032$) increase in RNFL thickness from baseline to the 2-year follow-up in 26 patients with RRMS. RNFL thinning was also associated with increases (worsening) in the EDSS score ($r = −0.42$, $P = 0.047$) and was also reported (42). Further evaluation of the mechanisms underlying the effects of therapies on RNFL and GCIPL thickness in MS is needed, with continued comparison with MRI measures of global structure, quality of life, and visual function.

Fingolimod therapy has been associated with macular edema. As such OCT has been used to evaluate the effect of fingolimod on the macula in the TRANSFORMS and FREEDOMS II treatment trials (efficacy of fingolimod in patients with highly active RRMS, and ophthalmic evaluations in clinical studies of fingolimod (FTY720) in multiple sclerosis). OCT scanning is now recommended as a safety measure for baseline evaluation and at 3 months after treatment initiation for patients on fingolimod therapy.

The Mesenchymal Stem Cells in Multiple Sclerosis (MSCiMS) trial tested the safety and feasibility of treatment with a candidate cell-based therapy in 10 patients with SPMS involving the visual pathways. The trial used OCT and LCLA measures as secondary outcomes. Baseline OCT measurements confirmed that eyes with a previous history of optic neuritis or symptoms of Uhthoff's phenomenon had reduced RNFL thickness by 15.3% compared with unaffected MS eyes ($P = 0.0399$). There was also a 28.7% reduction in RNFL thickness among MS eyes compared with healthy control eyes ($P = 0.0093$) at baseline (43). After mesenchymal stem cells were administered in 10 patients, no significant effects on RNFL or macular volumes were identified, although an improvement in LCLA was found ($P = 0.011$). The authors of the study suggest that the lack of change in OCT measures supports the idea that structural change for unmyelinated axons, as are contained within the RNFL, was not a significant effect of this treatment (44). Another study of mesenchymal stem cells in MS was conducted using OCT as a secondary outcome measure. This randomized, double-blind, crossover placebo-controlled trial of 9 patients also did not show differences in OCT measurements between treatment groups over the 12-month follow-up period (45). Further clinical testing is needed to assess the role of mesenchymal stem cells for treatment in MS.

In a prospective, single-site, 2-year, Phase II, double-blind, randomized, placebo-controlled trial of lipoic acid in MS (n = 51), OCT was performed at baseline and at Months 12 and 24. No significant differences in annualized rates of change between the placebo and the treatment group were found (RNFL thinning 0.279 vs 0.286 μm, $P = 0.99$). A post hoc analysis of 47 participants showed annualized thinning rates of 0.31 μm/yr for RNFL and 0.29 μm/yr for GCIPL; these rates did not differ between eyes with a history of optic neuritis vs. those without an optic neuritis history. Eyes with baseline RNFL thickness greater than 75 μm had more annualized RNFL thinning (0.85 μm/yr). Although rates of RNFL and

GCIPL thinning were comparable with those found in other longitudinal studies in progressive MS (46,47), rates of decline in RNFL and GCIPL did not mirror MRI measures of brain atrophy in this cohort (48). This could be evidence of a plateau or a floor effect of retinal atrophy in patients with progressive MS or could point to a differential effect of lipoic acid in the brain compared with the retina.

Forty-one patients with baseline and 24-month follow-up OCT and LCLA measures were analyzed as a subset in the STRIVE study, a Phase 4, multicenter, observational, open-label study of natalizumab in anti-JC virus antibody-negative early patients with RRMS. Natalizumab treatment was associated with only mild loss of LCLA (sustained visual loss in 12% of subjects at 2.5% contrast level and 22% of subjects at 1.25% contrast level) and with relative preservation RNFL thickness (thinning by 1.365 μm, 95% CI 0.404–2.326). In a convenience sample of healthy non-MS subjects for comparison (n = 35), the magnitude of RNFL thinning was 0.2 μm during the same period (49).

The first randomized, placebo-controlled trial of non-myeloablative autologous bone marrow–derived stem cell therapy in MS (ACTiMuS) is being conducted to assess the possibility of neurorepair in progressive patients with MS. This study will use OCT as a secondary outcome, measuring RNFL and macular volume to assess for improvement in the visual pathway (50).

Another ongoing trial, a randomized, placebo-controlled, Phase II trial of ibudilast in progressive patients with MS (SPRINT-MS), is using OCT analysis of RNFL, GCIPL, and macular volume thickness as secondary outcome measures. OCT images from eligible subjects (n = 331 enrolled) will be performed every 24 weeks over a 100-week trial period to assess the capacity of ibudilast to act as a neuroprotective agent and to evaluate the utility of OCT as an imaging marker in patients with progressive MS (51).

In an ongoing study to better understand the mechanisms of action of alemtuzumab in MS (ALAIN01), OCT measures are being used as secondary outcomes. This single-center, single-arm, explorative Phase 4 study of 15 patients with RRMS over 3 years will collect various immunological assays to evaluate the potential neuroprotective properties of alemtuzumab, including those pertaining to the retina (52).

LOGISTICS AND LIMITATIONS

Table 1 lists clinical trials for MS that have used LCLA and OCT as outcomes. Several additional completed and ongoing studies targeting acute optic neuritis before MS diagnosis using LCLA and OCT include those for clemastine, phenytoin, and Lingo-1 (RENEW) (53–55). Unfamiliarity of OCT to many neurologists has limited its utility in MS clinical trials and clinical use. Proper training in scanning techniques and quality control measures for evaluating the scans are essential for use of OCT in MS both clinically and in research studies (56,57). Operator and reader interpretation variability can affect the results of a study. Studies of interrater reliability using semiautomatic retinal layer segmentation have shown good agreement between raters in the inner retinal layers, including RNFL and GCIPL (58,59).

Multiple technologies for OCT exist, including the initial time domain and the current spectral domain platforms, which can lead to difficulty interpreting results across various OCT spectrums. Within SD-OCT, various platforms exist; most commonly Spectralis or Cirrus OCT are used. A recent study comparing time domain Stratus OCT with spectral domain Spectralis and Cirrus OCT showed that while on an individual level, the devices demonstrate differences in measurements, relatively small disparities in mean RNFL and GCIPL thickness between Cirrus and Spectralis indicate that data from these devices could be pooled together in clinical trials, as long as participants are scanned on the same machine consistently during the trial (60).

CONCLUSIONS

Visual impairment represents a significant component of overall disability in MS. Such visual loss was not captured by neurologic disability scales or composite performance measures such as the MSFC before the introduction of LCLA. LCLA is a standardized test of low-contrast acuity that captures visual dysfunction not previously captured by HCVA. LCLA decrements among patients with MS are most appreciable at the 1.25% and 2.5% contrast levels, and 7-letter reductions in scores have been shown to be clinically meaningful. Importantly, LCLA scores have the capacity to identify both sustained worsening and improvement of visual function, and capture treatment effects of therapy.

Treatment response markers improving patient selection and therapy guidance remain an unmet need for health care providers. There have been ample findings in support of the utility of OCT measures in assessing neurodegeneration and neuroprotection, including recent meta-analyses (61). The use of OCT in MS clinical trials is increasing. Several studies of both relapsing and progressive MS that use OCT are active and are recruiting patients (listed on www.clinicaltrials.gov). OCT reading centers in these studies help standardize the evaluation of scan quality, grading, and data management. Importantly, ongoing international collaborative studies of OCT measures will soon establish OCT-based criteria for identifying both occult and clinically evident optic nerve lesions based on intereye differences in RNFL and GCIPL thickness (62,63). Preliminary studies suggest that 5–6 μm of intereye RNFL difference and 3–4 μm of intereye GCIPL differenceis a meaningful change (62,63). Such studies will be critical for establishing the optic nerve as a lesion site for an additional imaging-based MS diagnostic criterion (64).

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TABLE 1

MS clinical trials and their inclusion of LCLA and OCT measures

NCT Number	Name of Trial	Agent	N	MS Subtype	LCLA	OCT
NCT00027300	AFFIRM	Natalizumab	939	RRMS	X	
NCT00030966	SENTINEL	Natalizumab + interferon beta-1a	1,196	RRMS	X	
NCT00211887	COMBIRX	Interferon and glatiramer acetate	1,008	RRMS	X	
NCT00340834	TRANSFORMS	Fingolimod	92	RRMS	X	X
NCT00355134	FREEDOMS II	Fingolimod	1,083	RRMS	X	X
NCT00395200	MSCiMS	Mesenchymal stem cells	10	SPMS	X	X
NCT01228266	CMM-EM	Mesenchymal stem cells	9	RRMS		X
NCT00530348	CARE-MS 1	Alemtuzumab	563	RRMS	X	
NCT00548405	CARE-MS2	Alemtuzumab	798	RRMS	X	
NCT01188811	Lipoic acid for secondary progressive multiple sclerosis	Lipoic acid	54	SPMS		X
NCT01247324	OPERA I	Ocrelizumab	821	RRMS	X	X
NCT01412333	OPERA II	Ocrelizumab	821	RRMS	X	X
NCT01485003	STRIVE	Natalizumab	41	RRMS	X	X
NCT01815632	ACTiMuS	Bone marrow–derived cellular therapy	80	Progressive		X
NCT01982942	SPRINT-MS	Ibudilast	331	Progressive		X
NCT02419378	ALAIN01	Alemtuzumab	15	RRMS		X
N/A *	IMPACT	Interferon beta-1a	434	SPMS	X	
N/A *	4-AP	4-aminopyridine	22	RRMS/progressive	X	X

NCT number is the clinicaltrials.gov identifier.

* Study does not have a clinicaltrials.gov number identified in publications.

LCLA, low-contrast letter acuity; MS, multiple sclerosis; N/A, not applicable; OCT, optical coherence tomography; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis.