

# Evaluating loss of visual function in multiple sclerosis as measured by low-contrast letter acuity

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## ABSTRACT

**Background:** Disturbances in visual function are common in patients with multiple sclerosis (MS) and are often accompanied by substantial impairments in daily functioning and quality of life. Lesions associated with these impairments frequently involve the afferent visual pathway.

**Expert Clinical Opinion:** Because these impairments are often not readily apparent on commonly used high-contrast acuity tests, low-contrast charts (e.g., low-contrast Sloan letter charts) have gained validity in the assessment of visual dysfunction in patients with MS. Decrements in low-contrast letter acuity are associated with MS and correlate with increasing disability, MRI abnormalities, and reduced retinal nerve fiber layer (RNFL) thickness as measured by optical coherence tomography (OCT). These findings suggest that low-contrast letter acuity testing is a potentially useful addition to disability scales such as the Multiple Sclerosis Functional Composite, serving as another surrogate marker for MS disability. Assessment of RNFL thickness by OCT, which is also associated with visual impairment, also may be considered for inclusion in clinical trials evaluating treatments for MS.

**Future Directions:** The effects of disease-modifying therapies on visual dysfunction in patients with MS have been evaluated only recently. Two phase 3 studies of natalizumab showed that low-contrast letter acuity testing, included as an exploratory outcome, demonstrated treatment effects. Other ongoing studies have incorporated low-contrast acuity and OCT measures of RNFL thickness. The availability and wider use of low-contrast letter acuity tests, in combination with ocular imaging techniques, may improve assessment of treatment efficacy in patients with MS.

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## GLOSSARY

**DMT** = disease-modifying therapy; **EDSS** = Expanded Disability Status Scale; **IFN** = interferon; **IMPACT** = International Multiple Sclerosis Secondary Progressive Avonex Controlled Trial; **MS** = multiple sclerosis; **MSFC** = Multiple Sclerosis Functional Composite; **MVP** = Multiple Sclerosis Vision Prospective; **NEI-VFQ** = National Eye Institute Visual Function Questionnaire; **OCT** = optical coherence tomography; **ON** = optic neuritis; **QoL** = quality of life; **RNFL** = retinal nerve fiber layer; **RRMS** = relapsing-remitting MS; **VFQ** = Visual Function Questionnaire.

**INTRODUCTION** Disturbances of visual function are a common manifestation of multiple sclerosis (MS).<sup>1-3</sup> In particular, acute demyelinating optic neuritis (ON) is a presenting symptom in approximately 15%–20% of patients with MS,<sup>2,4-6</sup> and it may develop in up to 50% of patients during the course of the disease.<sup>6,7</sup> In addition, up to 77% of patients with MS with no apparent visual symptoms or history of ON manifest subclinical changes in visual function, and these changes may involve the optic nerves or chiasm, or postchiasm regions of the

optic tract.<sup>8-10</sup> A number of anatomic and functional assessments may be used to detect ophthalmic abnormalities in patients with MS, but the estimated prevalence of subclinical optic involvement among patients with MS may be lower than the true prevalence given that no single test can identify all lesions.<sup>8</sup> For example, a small study of visually asymptomatic patients with relapsing-remitting MS (RRMS) reported that decrements in the estimated percentage of working neural channels across the visual field (measured by high-pass resolution perimetry) were

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universal, even in patients with no history of overt ON.<sup>9</sup> This decrement remained after 5.5–10 years of follow-up, even though patients remained asymptomatic when evaluated by minimum angle of resolution, a conventional test of visual acuity based on the finely graduated letter chart.<sup>9</sup> These findings suggest that visual impairments may remain undetected for long periods, depending on the sensitivity of the visual function test.

Visual acuity deficits reduce quality of life (QoL) in patients with MS.<sup>11–15</sup> Compared with a published reference group of individuals without ocular disease, patients with MS (with or without a history of ON) demonstrated impairments in vision-specific health-related QoL assessed by the 25-item National Eye Institute Visual Function Questionnaire (VFQ-25).<sup>14</sup> The effect on the VFQ-25 was similar to that caused by glaucoma or cataracts.<sup>14</sup> Similarly, Ma et al.<sup>11</sup> reported that patients with MS scored worse on 10 of the 12 VFQ-25 subscales compared with a control group. Vision-specific decreases in health-related QoL have also been observed using the 51-item National Eye Institute Visual Function Questionnaire (NEI-VFQ).<sup>12</sup> In patients (45% with clinically definite MS) who had been treated for an acute episode of ON 5–8 years earlier, NEI-VFQ scores were lower on most subscales compared with a disease-free reference group.<sup>12</sup> The majority of NEI-VFQ subscales showed greater dysfunction with increased neurologic disability.<sup>12</sup> In a study evaluating QoL in patients with MS, Rudick et al.<sup>13</sup> reported that the visual Functional System Score was the only Kurtzke Functional System Scale that significantly correlated with the total QoL score and all 4 QoL subscales of a 41-question modified version of the Farmer QoL Index.

Traditional tests of visual acuity (i.e., Snellen finely graduated letter chart) assess high-contrast visual acuity and may not identify all patients with MS with visual disturbances. In patients with MS with apparently normal high-contrast visual acuity, measurement of low-contrast letter acuity and visual evoked potentials may uncover previously undetected visual deficits.<sup>16–21</sup> Low-contrast testing identifies the minimum size at which letters of a particular contrast level (i.e., shade of gray on white background) can be perceived.<sup>22</sup> Low-contrast letter acuity has been found to be an informative measure of visual dysfunction in clinical trials of treatments for MS.<sup>17,23–25</sup> This article reviews the types of visual dysfunction that occur in patients with MS, the importance and value of assessing low-contrast letter acuity, and the potential for low-contrast acuity to demonstrate treatment effects in MS clinical trials.

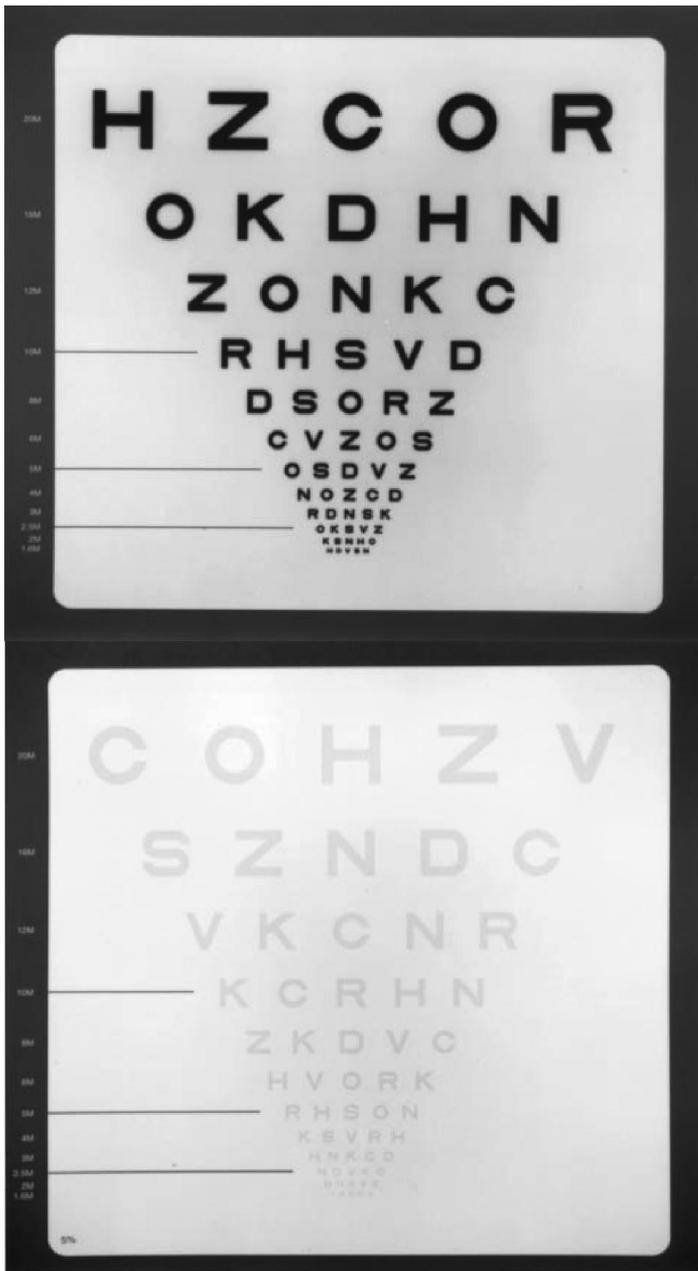
**VISUAL DEFICITS IN MS** Acute demyelinating ON is characterized by a rapid decline in visual acuity, pain with eye movement, visual field defects, afferent pupillary defects, color vision impairment, delayed visual evoked potential, and optic nerve enhancement on orbital MRI.<sup>1,3</sup> MRI studies have demonstrated that demyelinating lesions at any point along the afferent optic pathway may cause visual deficits. This includes defects in the chiasm, tracts, radiations, and striate cortex.<sup>3,26–29</sup> The specific defects observed can vary widely depending on the stage at which the patient is examined, but the classic field loss is a central scotoma.<sup>1</sup> The decline in visual acuity typically occurs over a 7–10-day period, and some recovery can be expected within 30 days of onset.<sup>3</sup> Most patients (85%–90%) experience recovery of acuity over 1–3 months<sup>1</sup>; however, some visual deficits may persist.<sup>1,3</sup> Chronic ON may also occur and is characterized by a gradual decline in vision accompanied by visual field loss, afferent pupillary abnormalities, and optic disc pallor.<sup>3</sup> ON typically develops in 1 eye; however, subacute visual deficits may also be present in the other eye. The pattern of visual field defects in the other eye is variable, although diffuse loss and peripheral rim defects were the most common forms. Visual defects in the other eye are more likely in patients with a markedly depressed visual acuity in the affected eye.<sup>30</sup>

Optical coherence tomography (OCT) is capable of imaging the histologically identifiable layers of the retina in real time with high resolution, accuracy, and reproducibility. The technique allows the direct visualization and measurement of retinal nerve fiber layer (RNFL) thickness and macular volume.<sup>31,32</sup> The RNFL is a structure that consists of isolated axons and some glia; therefore, measurement of its thickness reflects the burden of axons without the potential structural effects of myelin degeneration.<sup>33</sup> The use of OCT in patients with MS and ON has demonstrated decreases in RNFL thickness and optic nerve thickness, indicating axonal loss in the anterior portion of the optic pathway of both affected and apparently unaffected eyes.<sup>24,31,34–39</sup> Reductions in RNFL thickness were associated with optic nerve atrophy and impairments in visual acuity, visual field, and color vision.<sup>24,34,37</sup> In patients who had experienced a single ON event, those whose RNFL thickness was less than 75  $\mu\text{m}$  at time points 3 or more months after the acute ON event had less complete visual field recovery than those whose RNFL thickness was greater than 75  $\mu\text{m}$ .<sup>34</sup> These data suggest that decrements in RNFL thickness may predict persistent visual dysfunction after ON.<sup>34</sup> The use of OCT in MS clinical trials may provide a meaningful outcome for assessing therapies.<sup>31</sup>

**MEASUREMENT OF LOW-CONTRAST LETTER ACUITY DEFICITS IN MS** Low-contrast letter charts. Low-contrast Sloan letter charts are readily available and provide a practical, quantitative, and standardized assessment of visual function (figure 1).<sup>17</sup> Each chart consists of rows of gray letters (decreasing in size from top to bottom) on a white background. A set consists of 7 charts, each with a different level of contrast ranging from 100% to 0.6% (e.g., Precision Vision, LaSalle, IL).<sup>17</sup> Letter scores indicate the number of letters identified correctly, and each chart is scored separately.

Snellen visual acuity equivalent (e.g., 20/20) is also assessed in some cases and is based on the lowest line of the 100% contrast chart for which the patient is able to identify 3 of the 5 letters.<sup>17</sup> Other types of low-contrast letter charts have been developed (e.g., low-contrast Snellen; Pelli-Robson; Smith-Kettlewell Institute Low Luminance; and Early Treatment Diabetic Retinopathy Study charts),<sup>40-43</sup> but most studies of low-contrast letter acuity in patients with MS have used low-contrast Sloan letter charts (hereafter referred to as Sloan charts). Low-contrast letter acuity testing with Sloan charts is easy to administer and has been shown to have high interrater reliability in patients with MS and in healthy volunteers.<sup>17</sup>

**Figure 1** Sloan letter charts<sup>17</sup>



For example, the 100% and 5% contrast charts are shown. Balcer LJ, Baier ML, Pelak VS, et al. *Mult Scler.* 2000;6:163-171, copyright © 2000 by Sage Publications. Reprinted by permission of SAGE.

**Construct and predictive validity.** Several lines of evidence support the construct validity of Sloan charts for assessing visual acuity in patients with MS. Compared with healthy volunteers, patients with MS have worse low-contrast letter acuity scores, especially at lower contrast levels.<sup>17,23,24</sup> In a substudy of the International Multiple Sclerosis Secondary Progressive Avonex Controlled Trial (IMPACT), mean letter scores were generally lower for patients with MS compared with healthy volunteers at all 4 of the contrast levels studied, with the greatest difference at the lowest contrast level (0.6%).<sup>17</sup> This was despite similar median visual acuities based on the Snellen visual acuity equivalent (100% contrast level). Similar results were observed in patients from the Multiple Sclerosis Vision Prospective (MVP) cohort study.<sup>23</sup> Although patients with MS and healthy volunteers had similar letter scores at 100% contrast, patients with MS had lower letter acuity scores for Sloan charts with contrast levels of 5%, 2.5%, and 1.25%.<sup>23</sup>

Studies in patients with MS also demonstrated correlations between low-contrast letter acuity and measures of disability such as the Expanded Disability Status Scale (EDSS) and the Multiple Sclerosis Functional Composite (MSFC). The EDSS assesses pyramidal, cerebellar, brain stem, bowel/bladder, sensory, and cerebral functions; scores increase with increasing disability.<sup>44</sup> The MSFC is a composite of 3 quantitative tests of neurologic function (arm, leg, and cognitive); scores decrease with increasing disability.<sup>45</sup> These disability scales are useful for assessing longitudinal changes in patients with MS. In patients with RRMS or secondary progressive MS participating in studies of IM interferon-beta-1a (IFN $\beta$ -1a), low-contrast letter acuity scores were significantly correlated with MSFC (positive correlation) and EDSS scores (negative correlation), with the correlation tending to be strongest with MSFC scores.<sup>25</sup>

The relationship between low-contrast letter acuity scores and brain MRI abnormalities in MS has also been demonstrated.<sup>25,29</sup> In 1 study, patients with MS who had lower (worse) scores for low-contrast letter acuity had greater T2 lesion volumes on brain MRI scans and greater lesion volumes in visual pathway regions of the brain after adjusting for age and disease duration.<sup>29</sup> On average, there was a 3-mm<sup>3</sup> increase in T2 lesion volume within the whole brain for each 1-line (5-letter) worsening of low-contrast letter acuity score. A 1-line worsening in high-contrast acuity corresponded to a 5.5-mm<sup>3</sup> increase in T2 lesion volume, suggesting greater sensitivity of low-contrast testing.<sup>29</sup> Another study demonstrated stronger correlations between brain parenchymal fraction and low-contrast (i.e., 1.25% and 2.5%) visual acuity than for high-contrast acuity.<sup>25</sup>

Evidence from patients with MS suggests that lower (worse) scores for low-contrast letter acuity scores are associated with reduced RNFL thickness measured by OCT (table 1).<sup>24</sup> A study compared 90 patients with MS with 36 disease-free controls, all with Snellen acuity equivalents of 20/20 or better.<sup>24</sup> After adjusting for age, there was a 3- to 4- $\mu$ m decrease in RNFL thickness for each 1-line reduction in low-contrast letter acuity score (table 1). There was a modest but highly significant correlation between mean RNFL thickness and visual function scores ( $p < 0.0001$ ).<sup>24</sup>

Baier et al.<sup>25</sup> reported that low-contrast letter acuity scores were predictive for changes in MS disability and functionality. In this substudy of the IMPACT trial, 65 patients underwent low-contrast letter acuity testing. Change in low-contrast letter acuity scores from baseline to 1 year significantly predicted change in EDSS scores from year 1 to 2, after controlling for change in MSFC scores from baseline to 1 year (table 2).<sup>25</sup> Thus, use of low-contrast letter acuity testing imparted additional value to the

**Table 1** Association of worsening in visual function score and reduction in RNFL thickness in patients with MS (n = 180)<sup>24</sup>

Low-contrast Sloan letter chart (contrast level) (%)	Reduction in mean RNFL thickness ( $\mu$ m [95% CI]) <sup>a</sup>
1.25	3.8 (2.7-4.9)
2.5	3.1 (2.0-4.2)

Abbreviations: CI = confidence interval; MS = multiple sclerosis; RNFL = retinal nerve fiber layer.

<sup>a</sup>Change associated with a 1-line (5-letter) decrease in visual function score.

Adapted with permission from Fisher et al. Relation of visual function to retinal nerve fiber layer thickness in multiple sclerosis. *Ophthalmology*; 113:324-332, Copyright Elsevier (2006).

**Table 2** Predictive value of change in low-contrast letter acuity and MSFC score from baseline to year 1 for change in EDSS from year 1 to 2 in an IMPACT substudy<sup>25</sup>

Predictor variables	Coefficient (SE) <sup>a</sup>	p
Change in MSFC score	-2.06 (2.32)	0.38
Change in 5% contrast chart <sup>b</sup>	1.0 (0.39)	0.01
Change in MSFC score	-1.72 (2.28)	0.45
Change in 1.25% contrast chart <sup>b</sup>	0.93 (0.31)	0.004

Abbreviations: EDSS = Expanded Disability Status Scale; IMPACT = International Multiple Sclerosis Secondary Progressive Avonex Controlled Trial; MSFC = Multiple Sclerosis Functional Composite; SE = standard error.

<sup>a</sup>Using rank scores.

<sup>b</sup>After adjusting for change in MSFC from baseline to year 1. Adapted with permission from Baier ML et al. Low-contrast letter acuity testing captures visual dysfunction in patients with multiple sclerosis. *Neurology* 2005;64(6):992-995.

MSFC with respect to prediction of subsequent changes in the EDSS.<sup>25</sup>

An analysis of data from an IMPACT substudy and patients enrolled in the observational MVP cohort study evaluated the inclusion of low-contrast letter acuity testing as a potential fourth component of the MSFC.<sup>23</sup> In the MVP cohort study, low-contrast letter acuity at the 1.25% level was better in distinguishing between patients with MS and healthy controls than high-contrast (Snellen) acuity ( $p < 0.0001$ ).<sup>23</sup> In patients with MS in the MVP cohort and the IMPACT substudy, low-contrast letter acuity scores significantly correlated with MSFC and EDSS scores in patients with MS (table 3).<sup>23</sup> Nevertheless, these correlations were moderate because low-contrast letter acuity measured aspects of neurologic disability were not captured by the MSFC or EDSS.<sup>23</sup> When visual function as measured by low-contrast letter acuity was added to other components of the MSFC to compute a 4-component MSFC Z-score, each component, including low-contrast letter acuity, had similar correlations with composite scores, demonstrating that each component contributed similarly to the overall score.<sup>23</sup>

## VISUAL ACUITY TESTING IN CLINICAL TRIALS OF DISEASE-MODIFYING THERAPIES

With the exception of natalizumab, data relevant to the effects of disease modifying therapies (DMTs) on low-contrast letter acuity in patients with MS with or without ON are scarce. To our knowledge, no study to date has evaluated the effects of glatiramer acetate or IFN $\beta$ -1b on visual function in patients with MS. Low-contrast letter acuity was assessed in subsets of patients from a phase 3 study of IM IFN $\beta$ -1a in

**Table 3** Rank correlations of low-contrast Sloan letter scores (1.25% contrast level) and MSFC component scores with MSFC-3, MSFC-4, and EDSS scores in patients with MS from the MVP cohort and IMPACT substudy<sup>23</sup>

	T25FW	9HPT	PASAT3	MSFC-3	MSFC-4	EDSS
<b>MVP cohort<sup>a</sup></b> (n = 130)						
Sloan charts	0.51	0.54	0.38	0.56	0.77	-0.45
T25FW		0.67	0.42	0.79	0.79	-0.80
9HPT			0.41	0.85	0.84	-0.66
PASAT3				0.73	0.67	-0.26 <sup>b</sup>
MSFC-3					0.94	-0.69
MSFC-4						-0.69
<b>IMPACT substudy<sup>c</sup></b> (n = 56)						
Sloan charts				0.57	0.85	-0.43 <sup>b</sup>
MSFC-3					0.88	-0.54
MSFC-4						-0.56

Abbreviations: 9HPT = 9-Hole Peg Test; EDSS = Expanded Disability Status Scale; IMPACT = International Multiple Sclerosis Secondary Progressive Avonex Controlled Trial; MSFC-3 = Multiple Sclerosis Functional Composite (3 components); MSFC-4 = MSFC-3 + Sloan charts; MVP = Multiple Sclerosis Vision Prospective; PASAT3 = Paced Auditory Serial Addition Test (3-sec interval); T25FW = Timed 25-Foot Walk.

$p < 0.0001$  for all correlations except those indicated by <sup>b</sup>.

<sup>a</sup>Z scores for Sloan charts, MSFC-3, and MSFC-4 calculated using group means and standard deviations from single visit (baseline) as reference.

<sup>b</sup> $p = 0.001$ .

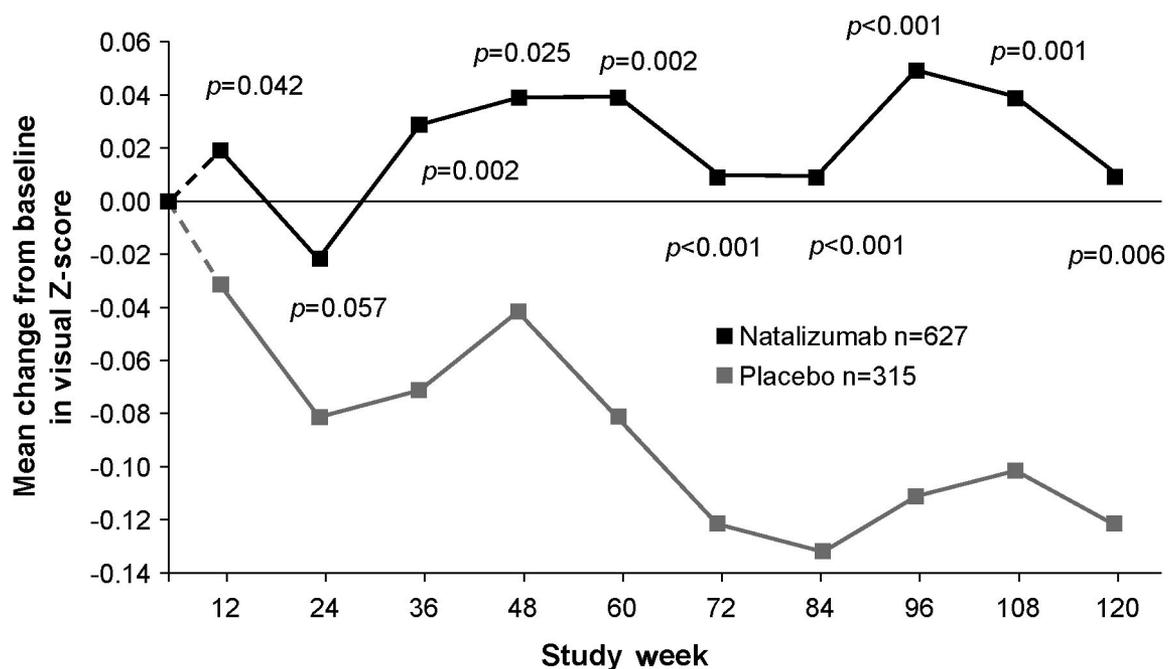
<sup>c</sup>Z scores calculated using group means and standard deviations from baseline visit as reference.

Adapted with permission from Balcer LJ, et al. Contrast letter acuity as a visual component for the multiple sclerosis functional composite. *Neurology* 2003;61:1367-1373.

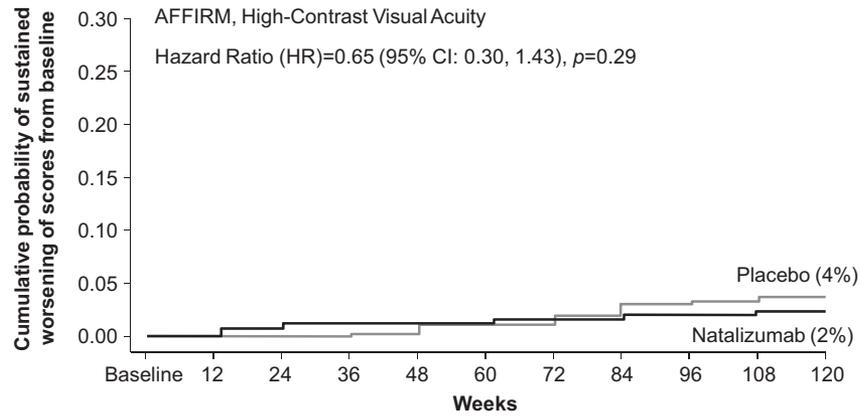
patients with RRMS and a study of IM IFN $\beta$ -1a in patients with secondary progressive MS; however, treatment effects on visual function were not reported.<sup>23,25</sup> In a small (N = 27), noncontrolled study, patients with ON as the initial symptom of RRMS were treated with IV methylprednisolone followed by subcutaneous IFN $\beta$ -1a.<sup>31</sup> An interim analysis conducted after  $\leq 16$  months of follow-up found that RNFL thickness in the ON-affected eye was less than that in the unaffected eye. However, these differences did not reach statistical significance.<sup>31</sup> Furthermore, because the study had no controls, no conclusions can be drawn about the effects of subcutaneous IFN $\beta$ -1a on visual function.

The ability of low-contrast letter acuity testing to capture treatment effects was demonstrated for the first time in the phase 3 studies of natalizumab as monotherapy (AFFIRM study) and in combination with IM IFN $\beta$ -1a (SENTINEL study) in patients with RRMS.<sup>22</sup> Changes in visual acuity were measured using low-contrast letter acuity charts at high contrast (black on white) and 2.5% and 1.25% low-contrast levels.<sup>22</sup> Figure 2 shows mean change from baseline in low-contrast (2.5%) letter acuity scores over time in the AFFIRM study.<sup>22</sup> Patients in the placebo group showed a significant worsening of low-contrast letter acuity compared with patients in the natalizumab group as early as 12 weeks.<sup>22</sup> There was no significant difference between treatment groups for visual acuity measured at the high-contrast (100%) level.<sup>22</sup>

**Figure 2** Mean changes from baseline in low-contrast letter acuity scores (2.5% contrast level) in patients who received natalizumab vs placebo in the AFFIRM study<sup>22</sup>

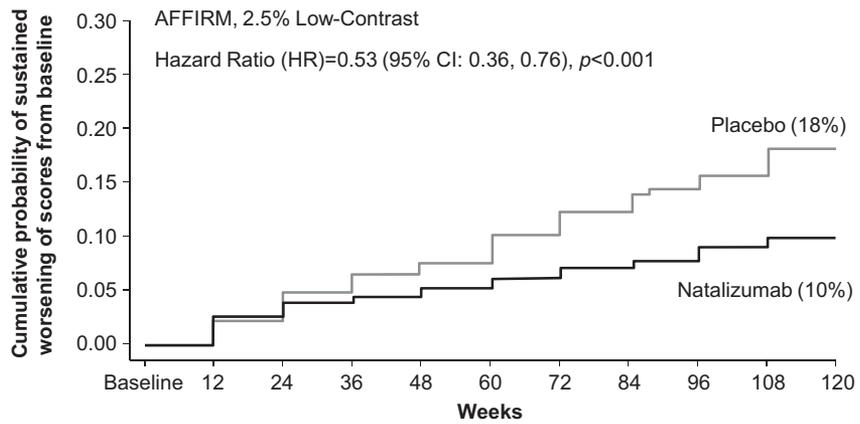


**Figure 3** Kaplan-Meier plots of time to sustained worsening of visual acuity scores among patients receiving natalizumab compared with placebo in the AFFIRM study<sup>22</sup>



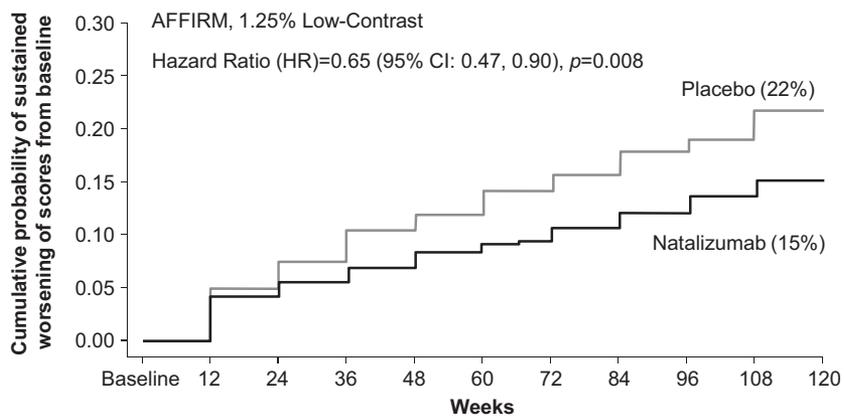
No. at Risk

Placebo	307	305	301	296	292	291	284	278	276	272
Natalizumab	619	616	605	602	597	589	586	580	571	563



No. at Risk

Placebo	307	301	287	278	272	266	255	247	242	233
Natalizumab	619	609	590	582	573	561	553	546	531	519



No. at Risk

Placebo	307	296	278	267	261	254	245	235	232	222
Natalizumab	619	598	580	569	556	544	534	520	504	491

The cumulative probability of a sustained decrease in low-contrast letter acuity (defined as  $\geq 2$ -line [10-letter] reductions in letter scores sustained over 12 weeks) was also reduced in the nataliz-

umab group compared with placebo (figure 3). In the AFFIRM study, the risk of sustained worsening with natalizumab (vs placebo) was reduced by 47% at the 2.5% contrast level ( $p < 0.001$ ) and by 35% at the

1.25% contrast level ( $p = 0.008$ ).<sup>22</sup> There was no significant difference between groups in sustained visual acuity worsening measured at the 100% contrast level.<sup>22</sup> Differences were less pronounced in the SENTINEL study, in which placebo plus IFN $\beta$ -1a was compared with a natalizumab plus IFN $\beta$ -1a combination.<sup>22</sup> The difference between treatment groups was most robust at the 1.25% contrast level at the end of the 2-year study. The cumulative probability of sustained low-contrast (1.25%) visual acuity loss was 28% lower in the natalizumab plus IM IFN $\beta$ -1a group compared with the placebo plus IM IFN $\beta$ -1a group ( $p = 0.038$ ). The risk reduction at the 2.5% contrast level was not statistically significant.<sup>22</sup> Overall, these data suggest that low-contrast letter acuity is a sensitive indicator of treatment effects in patients taking DMTs for MS.<sup>22</sup>

**CONCLUSION** Visual dysfunction is a unique aspect of neurologic status in patients with MS. Although acute ON is the most well-recognized ophthalmological manifestation of MS, patients may experience declining visual function in the absence of ON. Deficits in visual acuity have a marked effect on QoL in patients with MS. Measures of low-contrast letter acuity have a greater sensitivity to changes in visual function in patients with MS compared with assessments of high-contrast visual acuity. Low-contrast letter acuity is predictive for the presence of MS and is significantly correlated with other disease markers (e.g., disability scores, MRI findings, and RNFL thickness). Furthermore, low-contrast letter acuity scores are predictive for changes in MS disability and functionality. It has been suggested that low-contrast letter acuity testing may have utility as a fourth component of the MSFC. Despite the impact of visual abnormalities on daily functioning and QoL in patients with MS, the effects of DMTs on low-contrast letter acuity are not well studied. However, 2 phase 3 studies of natalizumab showed that low-contrast letter acuity testing, included as an exploratory outcome, can demonstrate treatment effects, and other trials have subsequently incorporated low-contrast acuity and OCT measures of RNFL thickness.

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#### DISCLOSURE

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