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Vision in a Phase 3 Trial of Natalizumab for Multiple Sclerosis: Relation to Disability and Quality of Life

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Background: Low-contrast visual acuity (LCVA), a sensitive measure of visual function in multiple sclerosis (MS), demonstrated treatment effects as a secondary outcome measure in the Phase 3 trial of natalizumab, AFFIRM. In these posttrial analyses, we studied the relation of visual function to quality of life (QOL), magnetic resonance imaging (MRI) measures, and Expanded Disability Status Scale (EDSS) scores.

Methods: At baseline and at 52 and 104 weeks in AFFIRM, patients underwent binocular testing of LCVA (1.25% and 2.5% contrast) and high-contrast visual acuity (HCVA). Vision-specific QOL was assessed by the Impact of Visual Impairment Scale (IVIS), whereas the SF-36 Health Survey and Visual Analog Scale were administered as generic QOL measures and the EDSS as a measure of neurologic impairment.

Results: Among QOL measures, IVIS scores showed the most significant correlations with visual dysfunction at all time points in the trial (r= −0.25 to −0.45, $P < 0.0001$ for LCVA and HCVA). Higher MRI T1- and T2-lesion volumes were also associated with worse vision scores at all time points ($P < 0.0001$). Clinically meaningful worsening (progression) of LCVA was noted in substantial proportions of patients in AFFIRM and was prevalent even among those without EDSS progression over 2 years (21.9% with LCVA progression at 2.5% contrast; 26.2% at 1.25% contrast). HCVA worsened in only 3.7% of patients without EDSS progression.

Conclusions: Loss of visual function, particularly as measured by LCVA, was common in AFFIRM, occurring in >20% of patients. Both LCVA and HCVA scores reflect vision-specific aspects of QOL, but LCVA provides information about disability progression not entirely captured by the EDSS. Vision represents a key dimension of outcome assessment for MS and adds valuable information on disability and QOL that can be useful to clinicians.

Journal of Neuro-Ophthalmology 2015;35:6–11
doi: 10.1097/WNO.0000000000000173

Patients with multiple sclerosis (MS) experience a variety of symptoms that can affect quality of life (QOL) and contribute to disability (1,2). Visual impairment is a common symptom in MS with up to 50% of patients developing optic neuritis and up to 77% of patients manifesting subclinical changes in visual function (3–7). To that extent, visual function, specifically low-contrast visual acuity (LCVA), has emerged as an important candidate in MS that captures aspects of the disease not routinely quantified by disability or QOL measures (3,8,9).

The Expanded Disability Status Scale (EDSS) is the leading disability measure in MS (10,11). The EDSS includes high-contrast visual acuity (HCVA) but does not capture all aspects of visual dysfunction and, at higher disability levels, is geared more towards physical dysfunction (10,11). Similarly, generic QOL measures, such as Short Form-36 (SF-36) capture overall but not vision-specific, decline in QOL (1,2). Furthermore, the influence of visual dysfunction on these QOL measures is not well studied (1,2).

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Supported by Biogen Idec, Inc.

L. J. Balcer has received consulting honoraria from Biogen Idec and Vaccinex and is a member of a clinical trial advisory board for Biogen Idec. D. M. Miller has received consulting fees from Biogen Idec and research support from Teva Neuroscience. A. Zhang is an employee of Biogen Idec. S. L. Galetta has received speaking and consulting honoraria from Biogen Idec and Vaccinex.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the full text and PDF versions of this article on the journal's Web site (www.jneuro-ophthalmology.com).

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Despite the prevalent use of visual function testing (VFT), EDSS and QOL metrics, neurologists, and neuro-ophthalmologists continue to face the challenge of incorporating these outcome measures when evaluating for disease progression (4,5,12). Exploring associations between LCVA, disability, QOL, and magnetic resonance imaging (MRI) can help bridge this gap in our knowledge and provides further support for a multidimensional approach to MS symptoms. In the Phase III, placebo-controlled AFFIRM trial of natalizumab (Biogen Idec Inc, Weston, MA) (13), LCVA detected treatment effects on sustained visual loss and visual improvement in patients with MS (12,14). Treatment with natalizumab also was associated with improved QOL (1,13), MRI outcomes (13,15–17) and disability (18).

In these post-hoc analyses of AFFIRM data, we provide a novel approach to evaluating LCVA and its association to global disease metrics, including QOL, disability, and MRI outcomes in a large standardized clinical trial setting.

METHODS

We evaluated the association of high and low-contrast vision to the following: 1—Overall QOL, 2—Vision-specific QOL, 3—MRI metrics, and 4—Neurologic impairment.

Patients

The AFFIRM trial included 627 patients randomized to natalizumab and 315 patients randomized to placebo. Key inclusion criteria were male and female patients between 18 and 50 years of age, diagnosis of relapsing–remitting multiple sclerosis (RRMS), and baseline EDSS score of 0.0–5.0. Participants also had to have brain MRI lesions consistent with MS and at least 1 medically documented relapse within 12 months before study start date (13). Exclusion criteria included treatment with cyclophosphamide or mitoxantrone within the previous year or treatment with interferon beta, glatiramer acetate, cyclosporine, azathioprine, methotrexate, or intravenous immune globulin within the previous 6 months. Patients who had received treatment with interferon beta, glatiramer acetate, or both for more than 6 months were also excluded (13). The study protocols were approved by central and local institutional review boards (13).

Visual Function Testing

Binocular LCVA and HCVA were measured using Sloan letter charts at 1.25%, 2.5% (low), and approximately 100% (high) contrast levels (Precision Vision, La Salle, IL). Binocular vision testing scores best reflect daily activities and can be subject to summation or inhibition providing more useful associations with QOL and MRI outcomes that monocular vision (3,9,19). Patients were asked to read each of 3 charts at 2 m using standardized protocols (13,14), and the number of letters identified correctly (maximum of 60 per chart) was recorded (14). Clinically meaningful changes in visual function were defined as a ≥7-letter reduction in score (1,8,12,14). Although both 1.25% and 2.5% low-contrast visual acuity scores were analyzed, 1.25% low-contrast scores are discussed only in cases where results differed between the 2 contrast levels.

Overall and Vision-specific QOL Measures

The following QOL instruments were completed at baseline and at weeks 24, 52, and 104.

SF-36 Health Survey

The SF-36 measures the patient's general health status from his/her perspective (1,20). It is composed of 8 multiitem scales with scores ranging from 0 to 100. Higher scores indicate better QOL. Resulting data can be used to calculate 2 summary scores: the Physical Component Summary (PCS), consisting of physical functioning, physical role, bodily pain, and general health elements and the Mental Component Summary (MCS), consisting of vitality, social functioning, emotional role, and mental health elements. The PCS and MCS summary scores, used in this analysis, were computed as standardized scores with a mean score of 50 (and SD of 10) corresponding to the US general population.

Visual Analog Scale

The visual analog scale (VAS) measures overall well-being as reported by the patient. To complete the VAS, patients were asked to draw a vertical line on a scale representing "poor" to "excellent" to show "how you feel now." Responses were converted to a scale of 0–100. Higher scores indicate better self-report QOL ratings (1).

Impact of Visual Impairment Scale

The Impact of Visual Impairment Scale (IVIS), a subscale of the MS Quality of Life Inventory, measures vision-specific QOL. It is a 5-item scale that captures noncognitively based difficulties with visual recognition that cannot be corrected with visual aids. Scores range from 0 to 15, with higher scores representing worse QOL (21) (See **Supplemental Digital Content**, Table E1, http://links.lww.com/WNO/A111). In AFFIRM, the IVIS was administered to a subset of English-speaking patients only.

MRI Measures

MRI parameters included T1-hypointense, T2-, and gadolinium-enhancing (Gd+) lesion volume; the number of Gd+, new T1, and new T2 lesions; and brain parenchymal fraction (BPF, a measure of brain atrophy).

Neurologic Disability

Neurologic disability was evaluated using the EDSS, an ordered scale that ranges from 0.0 to 10.0 in 0.5-point increments, with higher scores indicating more severe neurologic impairment (10,13). EDSS was scored every 12 weeks during the study period. The EDSS incorporates

HCVA, relies on the neurologic examination in the early stages of disability and on gait dysfunction in later stages of disability. Untreated patients with MS will progress by 1.0–2.0 points on this scale over 5 years (10,11).

Statistical Analyses

In this post-hoc study, unless otherwise noted, the following cross-sectional analyses were performed at baseline and at 52 and 104 weeks for the entire patient cohort, regardless of treatment group.

VFT and QOL

Correlations between VFT scores and QOL measures were evaluated using the Pearson correlation coefficient. Linear regression models were used to examine the relation between VFT scores and QOL scores adjusting for baseline age.

VFT and MRI

Correlations between VFT score and MRI parameters were evaluated using the Pearson correlation coefficient.

VFT and Neurologic Disability

Sustained progression (worsening) was defined as either a $\geq$1.0-point increase (for patients with baseline scores $\geq$1.0) or a $\geq$1.5-point sustained increase (for patients with baseline scores of 0.0) maintained over 12 weeks. Patients with nonsustained changes or changes that did not meet these criteria were categorized as having stable disability.

Agreement between patient groups that had clinically meaningful VFT worsening ($\geq$7 letters per chart) and EDSS progression was examined using McNemar's test. Time to 12-week sustained 7-letter visual worsening in VFT scores from baseline among patients with stable EDSS over 2 years was assessed using the Kaplan–Meier method and the Cox proportional hazards model, adjusted for baseline VFT, EDSS, and age.

A composite measure of disease progression that included both EDSS and 7-letter visual progression was analyzed in a Cox proportional hazard model to determine its sensitivity to treatment effect.

RESULTS

A total of 942 patients (627 in the natalizumab group and 315 in the placebo group) were enrolled in the AFFIRM trial. Table E2 (see **Supplemental Digital Content**, http://links.lww.com/WNO/A112) summarizes baseline age, VFT scores, QOL, MRI measures, and disability scores.

Association Between VFT Scores and QOL

Cross-sectional correlation analyses at baseline, 52 weeks, and 104 weeks showed a consistent pattern of correlations between reduced visual function and worse QOL scores (See **Supplemental Digital Content**, Table E3, http://links.lww.com/WNO/A113). Worse PCS and IVIS scores were modestly but consistently associated with lower VFT scores at all time points, with linear correlations ranging from 0.08 to 0.14 for the PCS ($P < 0.05$) and -0.25 to -0.45 for the IVIS ($P < 0.0001$). In fact, among all QOL measures, IVIS showed the strongest and the most significant correlations with vision, with worse IVIS scores occurring in patients with worse visual function.

At each time point, SF-36 MCS and VAS scores were reduced among patients with worse scores for LCVA but not for HCVA (correlations: 0.08–0.09 for PCS, $P < 0.05$; 0.09–0.13 for VAS, $P < 0.01$) except for the 104-week time point, where VAS scores were significantly correlated with HCVA (r = 0.08; $P < 0.01$).

At baseline, linear regression analyses showed that 7-letter reductions in 2.5% LCVA and HCVA scores were associated with a 0.5-point and 1.3-point worsening of vision-specific QOL by the IVIS, respectively ($P < 0.001$).

Association Between VFT Scores and MRI Measures

At baseline and at 52 and 104 weeks, there were modest and significant correlations between worse VFT scores and higher T1- and T2-lesion volumes ($P < 0.0001$) (See **Supplemental Digital Content**, Table E4, http://links.lww.com/WNO/A114). Better LCVA scores were correlated with lower Gd+ lesion volume and number at baseline but this was not observed for HCVA. In addition, better LCVA scores were associated with a lower number of new T1 and T2 lesions at 1 year ($P < 0.01$) and higher BPF.

Association Between VFT Scores and Disability

At 2 years, the proportions of patients with visual worsening as measured by HCVA were significantly different between patients with and without EDSS progression (Fig. 1). The proportions of patients with visual progression as measured by LCVA (2.5% and 1.25%) were not significantly different between patients with and without EDSS progression. Notably, substantial proportions of patients without EDSS progression still had visual progression at 2.5% and 1.25% contrast on LCVA (21.9% and 26.2%, respectively). A composite measure of disease progression including both VFT and EDSS scores showed sensitivity to natalizumab treatment effects. Specifically, 34% relative reduction was seen in cumulative probability of either EDSS or HCVA progression in patients treated with natalizumab relative to placebo (hazard ratio [HR], 0.66; 95% confidence interval [CI], 0.50–0.86; P = 0.002) (See **Supplemental Digital Content**, Table E5, http://links.lww.com/WNO/A115). A 32% relative reduction was seen in the cumulative probability of either EDSS or LCVA (2.5%) progression (HR, 0.68; 95% CI, 0.55–0.84; P = 0.0003) in patients treated with natalizumab.

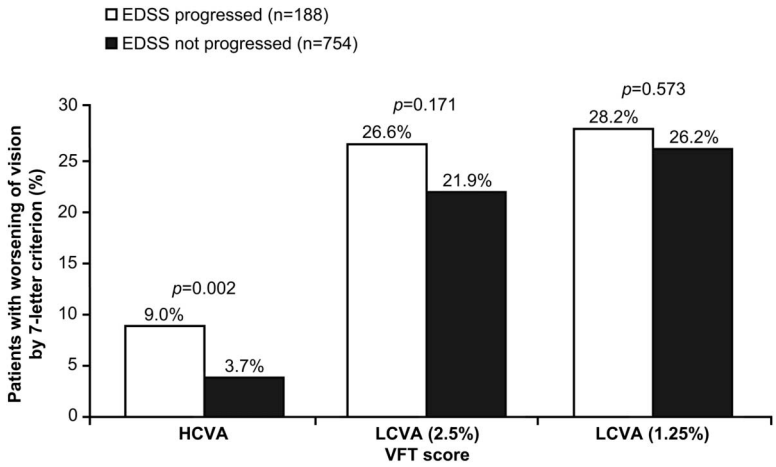

FIG. 1. Proportions of patients with worsening vision by EDSS progression status over 2 years. Using 7-letter criterion for clinically meaningful visual change, a significantly greater number of patients with EDSS progression had worsening in HCVA compared with those with no EDSS progression. Notably, there were no significant differences in LCVA worsening between patients with and without EDSS progression. *P* values are from McNemar's test. EDSS, Expanded Disability Status Scale; HCVA, high-contrast visual acuity; LCVA, low-contrast visual acuity; VFT, visual function testing.

DISCUSSION

These results from the Phase 3 trial of natalizumab (AFFIRM) show that even among this group of patients with relatively early RRMS, visual dysfunction is associated with reductions in QOL. Important measures of overall disease activity, including MRI lesion burden, are higher in those with reduced vision. Neurologic disability, however, as measured by EDSS progression did not seem to capture all patients with clinically meaningful visual loss. This disconnect between EDSS and visual progression occurred only for LCVA, providing evidence that this visual measure captures aspects of neurologic impairment not entirely captured by the EDSS.

A greater understanding of the relation between vision, neurologic disability, and QOL, as illustrated in this study, adds to the body of evidence on LCVA as a measure of visual dysfunction that is associated with QOL (22), MRI (23,24), and retinal neuronal and axonal thinning (25–27) and will help clinicians to incorporate LCVA as a measure of impairment in clinical practice (1,3,5).

QOL measures are objective outcomes that may be influenced by several factors (1,2). Our study further validates the use of these measures in the context of visual impairment and explores the complex relationship between high- and low-contrast vision and the different measures of QOL. Modest associations were observed over time between reduced VFT and QOL measures. Although reductions in LCVA scores were significantly associated with worse scores for all QOL measures at all time points in the AFFIRM trial, HCVA scores were associated with only PCS and IVIS at all time points and with VAS only at 2 years.

Seven-letter changes in LCVA and HCVA scores were associated with substantial changes in IVIS scores, indicating a strong association with this vision-specific QOL parameter. HCVA had stronger correlations with IVIS. Our findings confirm the associations seen by Mowry et al (22) with the advantage of standardized testing in a clinical trial setting and reflect the fact that HCVA deficits are more noticeable to patients and thus greatly affect vision-specific QOL, whereas LCVA changes are more subtle but yet may impact many aspects of patients' lives. Interestingly, both the IVIS used in the study and the NEI-FVQ-25 used by Mowry et al (22) showed significant associations with visual function. The NEI-VFQ-25 is more commonly used (22,28). However, both scales are well validated and can be used to capture vision-specific QOL.

Although the correlations between LCVA and MRI metrics were the modest, they tended to persist over the course of the trial. Wu et al (24) demonstrated correlations between LCVA and MRI T2-lesion burden and between HCVA and BPF. Reduced LCVA has also established associations with neuronal and axonal loss captured by OCT (25–27). Our findings provide further evidence that visual dysfunction reflects MRI lesion burden and brain atrophy (23,24) and can be used to reflect disease activity.

Of interest, LCVA but not HCVA detected visual loss even in patients without EDSS progression. HCVA may not detect visual loss in patients without EDSS progression because HCVA changes may influence the total disability score, especially at lower EDSS scores (10,11). LCVA, however, is not measured by the functional systems that make up the EDSS and provides information about visual function not captured by the EDSS (23). Furthermore, the EDSS may not be sensitive to subtle changes in certain disease aspects especially in patients with more physical disability of gait impairment (10,11). Thus, LCVA could

be capturing other aspects of disease activity that are not well measured by the EDSS.

Our results add vision-specific data to recent analyses on disability data from the AFFIRM trial that showed that sustained improvements in EDSS scores were associated with improvements in patient-reported QOL measures for both the PCS and MCS (18) and expand our knowledge on how vision, specifically LCVA, along with vision-specific QOL measures, provide added value to our understanding of QOL and disability.

The AFFIRM trial did not capture other comorbid ocular conditions; however, in this relatively young patient population, conditions that affect LCVA are uncommon and unlikely to affect our results (3,8). The trial did not capture history of acute ON before or during the study period. To be eligible, patients were required to be relapse-free within 50 days of the first dose and to have a stable EDSS score. Capturing acute events of ON will be important for interpreting mechanisms for visual loss and improvement in ongoing and future trials, which now routinely include structural and functional measures of vision.

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