

# Patient-centered outcomes

## Translating clinical efficacy into benefits on health-related quality of life

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### ABSTRACT

**Background:** Multiple sclerosis (MS) is a neurodegenerative disease associated with marked impairments in health-related quality of life (HRQoL). Although standard clinical end points such as the Expanded Disability Status Scale and annualized relapse rate remain useful in assessing MS activity and severity, these measures do not fully reflect the patient's experience of the disease. The impact of MS on employment status, social and family relationships, sexual satisfaction, pain, fatigue, enjoyment of life, vision, bladder/bowel control, cognition, and emotional well-being can be profound and may influence the patient's adherence to long-term treatment. Generic HRQoL instruments such as the Medical Outcome Survey Short Form-36 and the Functional Status Questionnaire initially were used in MS studies. However, MS-specific and hybrid instruments that possess greater sensitivity now have been developed.

**Expert Clinical Opinion:** The effects of interferon-beta on HRQoL have been evaluated in several studies, and improvements on some dimensions of HRQoL, particularly in patients with mild disability, have been reported. Two large pivotal studies of natalizumab prospectively included HRQoL assessments as tertiary efficacy end points. The impact of natalizumab on HRQoL outcomes in patients with relapsing-remitting MS was evident at 2 years regardless of sustained disease progression or relapse status.

**Future Directions:** Patient-centered outcomes are becoming increasingly important in evaluations of MS therapies. Therefore, inclusion of HRQoL assessments in pivotal clinical studies eventually should become standard practice. Increasing our understanding of minimally important clinical change in these measures will be an important step in helping researchers and clinicians interpret these results beyond statistical significance. **NEUROLOGY 2010;74(Suppl 3):S24-S35**

### GLOSSARY

**DMT** = disease-modifying therapy; **EDSS** = Expanded Disability Status Scale; **FAMS** = Functional Assessment of Multiple Sclerosis; **FSQ** = Functional Status Questionnaire; **GA** = glatiramer acetate; **HRQoL** = health-related quality of life; **IFN** = interferon; **IM** = intramuscular; **LMSQoL** = Leeds Multiple Sclerosis Quality of Life scale; **MCS** = Mental Component Summary; **MOS** = Medical Outcomes Study; **MS** = multiple sclerosis; **MSCRG** = Multiple Sclerosis Collaborative Research Group; **MSIS** = Multiple Sclerosis Impact Scale; **MSQLI** = Multiple Sclerosis Quality of Life Inventory; **MSQoL** = Multiple Sclerosis Quality of Life instrument; **PCS** = Physical Component Summary; **PES** = Pain Effects Scale; **RRMS** = relapsing-remitting MS; **SC** = subcutaneous; **SF-36** = Short Form-36; **SIP** = Sickness Impact Profile; **SPMS** = secondary progressive MS.

**INTRODUCTION** Multiple sclerosis (MS) is a progressive, degenerative neurologic disorder most frequently characterized by an initial relapsing-remitting course (RRMS), often followed by disability progression with or without relapses (secondary progressive MS [SPMS]). Symptoms associated with MS include fatigue, imbalance, loss of mobility, sensory changes, pain, loss of bladder and bowel control, spasticity, visual disturbances, cognitive deterioration,

depression, and sexual dysfunction.<sup>1</sup> The chronic, progressive nature of MS amplifies the effects of these symptoms, inevitably leading to impairments in activities of daily living and functional capacity.<sup>2</sup>

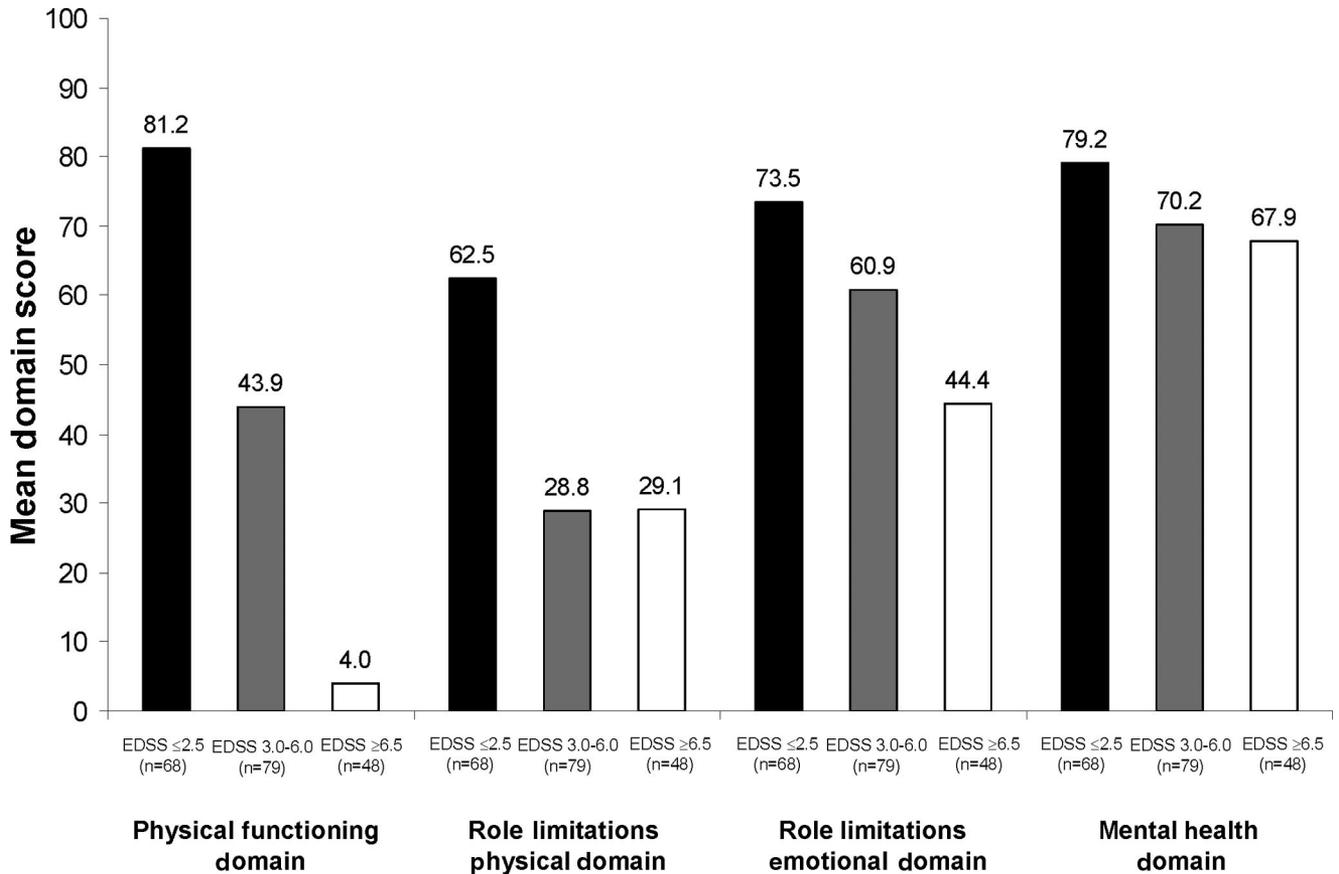
In clinical studies in patients with MS, therapeutic response usually is assessed by measuring a sustained change from baseline on the Expanded Disability Status Scale (EDSS), relapse rate, cognitive deterioration, and new or active brain lesions on

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**Figure 1** Mean scores in patients with multiple sclerosis (MS) for 4 Medical Outcomes Study Short Form-36 health dimensions in 3 Expanded Disability Status Scale (EDSS) severity groups<sup>9</sup>



MRI.<sup>1,3-6</sup> Objective outcome measures provide valuable information for disease management but only partially capture patients' overall experience of their disease. MS is associated with significantly impaired quality of life.<sup>2</sup> Instruments that measure changes in health-related quality of life (HRQoL) complement clinical data and increasingly are used to provide a broader and more comprehensive picture of patient-centered clinical outcomes.<sup>7</sup>

A robust body of literature documents the status of HRQoL in patients with MS, which is markedly worse than that of the general population.<sup>2,8-10</sup> For example, patients with MS in 1 cohort had significantly lower scores than with age- and gender-matched healthy controls across 8 subscales of a generic quality of life measure, the Medical Outcomes Study (MOS) Short Form-36 (SF-36).<sup>2</sup> Ratings for overall physical health, physical role limitations, and emotional role limitations particularly were impaired, ranging from 35% to 45% lower than control subjects. Employment status also was affected; 48% more healthy controls worked full or part-time compared with patients with MS.<sup>8</sup> When compared with patients with other chronic diseases, patients with mild MS describe quality of life limita-

tions that are roughly similar to age-matched controls with congestive heart failure or chronic obstructive pulmonary disease. Moreover, the degree of HRQoL impairment for patients with mild MS is greater than that in age-matched patients with type 2 diabetes mellitus or in persons who had an acute myocardial infarction in the past 12 months.<sup>2</sup>

Correlation between disability and HRQoL scores often is not linear, and there is evidence of a ceiling effect. The impact of mild MS on HRQoL measures, particularly role-physical and vitality scores, became apparent in 1 study well before the development of significant impairments in ambulation.<sup>2</sup> In another study, HRQoL scores declined dramatically as patients progressed from mild to moderate MS but to a much lesser degree as they progressed from moderate to severe disease; this was true particularly for female patients.<sup>8</sup> Other studies have shown a strong correlation between increasing EDSS scores and reduction in HRQoL scores for physical domains. However, the relationship between EDSS scores and psychological or mental HRQoL dimensions is less robust (figure 1).<sup>2,8-11</sup> This latter finding is expected, reflecting the divergent validity of the measures<sup>12</sup>; psychological

HRQoL dimensions would be expected to correlate significantly with measures such as the Beck Depression Inventory (convergent validity).

Herein, we compare and contrast generic and MS-specific HRQoL instruments and discuss the effects of disease-modifying therapies (DMTs) on HRQoL in patients with MS.

**HRQoL ASSESSMENT MEASURES** HRQoL assessment tools measure health status across a range of physical, mental, emotional, and social domains. A number of generic and disease-specific instruments have been used to measure HRQoL in patients with MS, as have hybrid instruments that combine a generic instrument with an MS-specific component.

**Generic instruments.** Generic HRQoL instruments commonly used in MS studies include the MOS SF-36,<sup>13</sup> the Functional Status Questionnaire (FSQ),<sup>14</sup> and the Sickness Impact Profile (SIP).<sup>15</sup> The MOS SF-36, which is widely used in clinical and epidemiologic research, consists of 8 multiitem scales that assess physical functioning, role limitations due to physical problems (role-physical), social functioning, bodily pain, general mental health, role limitations due to emotional problems (role-emotional), vitality, and general health perceptions.<sup>13</sup> Each scale is scored from 0 to 100, with higher scores indicating better HRQoL. Two composite scores—the Physical Component Summary (PCS) and the Mental Component Summary (MCS)—are derived from the SF-36. Mean PCS or MCS scores of 50 ( $\pm 10$  SD) are interpreted as representative of the general population. Clinically meaningful differences in HRQoL are suggested by a 5-point ( $\pm 0.5$  SD) change from baseline.<sup>16</sup>

The FSQ is a validated 34-item patient-completed questionnaire that provides a quick and comprehensive assessment of functional disability in primary care patients.<sup>14</sup> The FSQ covers physical function, psychological function, social/role function, and general well-being (i.e., employment status, number of days in bed, daily activities, sexual function, self-perceived health, and social relationships). This instrument was designed to be completed at home or the physician's office in ~15 minutes. Patient responses are summarized on a 1-page report that presents results on a visual analog scale ranging from 0 to 100, with a score of 100 representing maximum functional ability.

The 136-item SIP is a reliable and validated measure of self-perceived health-related behavioral changes for physical, psychosocial, and independent categories (i.e., sleep/rest, eating, work, home management, and recreation/pastimes).<sup>15</sup> Designed to be applicable to different disease states, levels of disease severity, demographic

populations, and cultures, the SIP measures changes over time and differences between groups. The SIP is completed by the patient or administered by healthcare personnel in about 30 minutes.

**MS-specific instruments.** The generic instruments described above are used widely in clinical and research settings across different disease states.<sup>7</sup> In addition, hybrid instruments (i.e., generic instruments with items added for MS) and MS-specific instruments for HRQoL assessment have been developed. Hybrid instruments contain generic measures that allow comparison both within the MS population and across different neurologic conditions and symptom-specific measures that are condition-dependent and sensitive to study interventions. Reliable and validated MS-specific HRQoL instruments include the Multiple Sclerosis Quality of Life Inventory (MSQLI),<sup>17</sup> the Multiple Sclerosis Quality of Life-54 scale (MSQoL-54),<sup>18</sup> the Functional Assessment of Multiple Sclerosis (FAMS),<sup>19</sup> the Multiple Sclerosis Impact Scale (MSIS-29),<sup>20</sup> and the Leeds Multiple Sclerosis Quality of Life scale (LMSQoL).<sup>21</sup>

**Multiple Sclerosis Quality of Life Inventory.** The MSQLI is a validated 138-item instrument that uses the SF-36 to obtain core HRQoL data (physical component and mental component), plus 9 MS-specific scales: fatigue, pain, sexual satisfaction, bladder function, bowel control, visual impairment, perceived cognitive deficits, mental health status, and social support. Administration of the MSQLI is time consuming, but the short form containing 81 items can be administered in under an hour.<sup>17</sup> Reliability and construct validity were evaluated in a field test of 300 patients with EDSS scores ranging from mild to severe. The 9 MS-specific scales exhibited test-retest reliability (Cronbach  $\alpha = 0.77$ – $0.97$ ).<sup>22</sup> Moderate to strong correlations between the MSQLI and other HRQoL measures of fatigue, perceived deficits, and mental health status were demonstrated (Pearson  $r > 0.45$ ).

**Multiple Sclerosis Quality of Life-54.** The MSQoL-54 also uses the SF-36 as a core measure in conjunction with 18 MS-specific items that address health distress, overall quality of life, satisfaction with sexual function, and cognitive function. The SF-36 component of the MSQoL-54 was expanded to include single items related to bladder or bowel function (in the social function scale), extent to which pain interferes with enjoyment of life (in the pain scale), and restlessness/fatigue (in the energy/fatigue scale).<sup>18</sup> Possible disadvantages of the MSQoL-54 include the absence of a scale measuring visual function and the limitation of bladder and bowel dysfunction measurements to single items.<sup>22</sup> The MSQoL-54 has been validated in a sample of 179 patients with MS. Internal consistency (Cronbach  $\alpha = 0.75$ – $0.96$ ) and test-retest

reliability (product-moment correlations = 0.67–0.96) were considered acceptable.<sup>18</sup> Construct validity was demonstrated by significant associations between MSQoL-54 scales and the degree of MS severity, ambulation status, days lost from work or school, hospitalizations, and symptoms of depression.

**Functional Assessment of Multiple Sclerosis.** The final version of the FAMS includes 59 items that cover mobility, physical symptoms, emotional well-being (depression), general contentment, fatigue, family/social well-being, and additional patient concerns.<sup>19</sup> High levels of internal consistency (Cronbach  $\alpha$  = 0.82–0.96) and test-retest reliability ( $r$  = 0.85–0.91) were demonstrated. When compared with the EDSS, only the mobility subscale of the FAMS showed a significant association, which suggests that the EDSS does not reflect other important dimensions of HRQoL.<sup>19</sup> The FAMS does not assess visual function or bowel function.<sup>22</sup>

**Multiple Sclerosis Impact Scale-29.** The MSIS-29 was the first MS-specific HRQoL instrument to be developed using psychometric methods.<sup>20</sup> It consists of 20 questions that address the physical (MSIS-29 Physical) aspects of MS and 9 questions that address the psychological (MSIS-29 Psychological) aspects.<sup>20</sup> The MSIS-29 has been validated in a number of MS populations, and short-term longitudinal stability and responsiveness have been demonstrated in a few studies.<sup>23,24</sup> The long-term performance of the MSIS-29 Physical has been assessed in 1 longitudinal study that demonstrated moderately strong correlations between score changes in the EDSS and the MSIS-29 Physical; effect sizes for MSIS-29 Physical change were moderate to large.<sup>25</sup> However, a response shift phenomenon was noted in more disabled patients who had stable disease over time in that these patients tended to report improved MSIS-29 Physical scores.

**Leeds Multiple Sclerosis Quality of Life scale.** The LMSQoL scale was developed from focus groups of patients with MS in the United Kingdom.<sup>20</sup> This 8-item instrument is completed by the patient and measures his or her perception of function across the dimensions of family/social (2 items), fatigue/energy (2 items), psychological status (3 items), and self-confidence/appearance (1 item). Adequate internal consistency (Cronbach  $\alpha$  = 0.79) and test-retest reliability ( $\rho$  = 0.85) was shown. Construct validity for the LMSQoL scale was demonstrated with better correlation to general well-being ( $r$  = 0.83) than physical function ( $r$  = 0.39).

**THE USE OF HRQoL END POINTS IN CLINICAL TRIALS** During the last 10 years, HRQoL measures have been included in phase 3 randomized, con-

trolled trials usually as secondary or tertiary outcome measures. For scientifically rigorous investigations, HRQoL measures must meet the same criteria of meaningfulness and dependability that are used to evaluate other outcome measures. These criteria are typically referred to as reliability and validity, and an important aspect of the latter is responsiveness to change.<sup>12,26</sup> In considering the HRQoL results reported in this article, phase 3 randomized, controlled trials are powered for the primary end point, usually disability progression, and recruit relatively large numbers of patients. Thus, because these studies were not powered for the HRQoL secondary end point, the strength of the intervention may have more of an impact on patients' HRQoL than the data suggest. In addition, numerous HRQoL measures have been used in the studies described in this article, making cross-study comparisons of HRQoL differences more difficult than cross-study comparisons of the primary end points, which often are assessed similarly across studies.

### EFFECTS OF IFN $\beta$ AND GLATIRAMER ACETATE ON HRQoL IN PATIENTS WITH MS

HRQoL outcomes were not included in the majority of pivotal studies of the immunomodulatory DMTs interferon-beta (IFN $\beta$ ) and glatiramer acetate (GA) in patients with RRMS,<sup>3-6</sup> although there has been a preliminary report on the effect of intramuscular (IM) IFN $\beta$ -1a on the SIP in the pivotal Multiple Sclerosis Collaborative Research Group (MSCRG) study.<sup>27</sup> Two randomized, placebo-controlled studies have evaluated the effects of IFN $\beta$  on HRQoL in patients with SPMS. The International Multiple Sclerosis Secondary Progressive Avonex<sup>®</sup> Controlled Trial of IM IFN $\beta$ -1a in patients with SPMS used the MSQLI,<sup>28</sup> and the European Study Group on IFN $\beta$ -1b in SPMS included the SIP as a tertiary outcome measure.<sup>29</sup> Most of the other studies that evaluated the effects of IFN $\beta$  on HRQoL measures were open labeled or observational in design. Although these latter studies contribute to our understanding of the effects of DMTs on HRQoL in patients with MS, marked differences in treatment duration, methods, patient population, and HRQoL instruments hinder comparisons between studies (table).<sup>10,27-36</sup>

Treatment with IM IFN $\beta$ -1a (Avonex) over 2 years improved scores on 8 of 11 MSQLI scales in patients with SPMS compared with baseline in the randomized, double-blinded International Multiple Sclerosis Secondary Progressive Avonex<sup>®</sup> Controlled Trial study. There were significantly greater improvements with IM IFN $\beta$ -1a vs placebo on the SF-36 MCS ( $p$  < 0.05), fatigue ( $p$  < 0.02), bowel control ( $p$  < 0.05), sexual satisfaction ( $p$  = 0.01), the Perceived Deficits Questionnaire ( $p$  < 0.04),

**Table** Effects of DMTs on HRQoL outcomes in patients with MS<sup>10,27-36</sup>

DMT	Study design/duration	Diagnosis (N) <sup>a</sup>	HRQoL instrument	Findings
<b>IM IFN<math>\beta</math>-1a (Avonex<sup>®</sup>)</b>				
IMPACT Study <sup>28</sup>	R, DB, PBO-controlled/2 y	SPMS (IFN $\beta$ -1a [156]; PBO [165])	MSQLI	Significant improvement vs PBO ( $p < 0.05$ ) on all measures except SF-36 physical component, bladder control, visual impairment  IFN $\beta$ -1a: improved on all domains except bladder control  PBO: improved only on fatigue impact
MSCRG Study <sup>27</sup>	R, DB, PBO-controlled/2 y	RRMS (IFN $\beta$ -1a [81]; PBO [77])	SIP	Preliminary report of a significant improvement in physical SIP scores with IFN $\beta$ -1a vs PBO over 2 y in patients with baseline overall SIP score $\geq 10$ ( $p = 0.045$ )
Vermersch et al. <sup>30</sup>	Prospective comparison with normal population/1 y	RRMS (106)	SF-36	Trend toward improvement on 5 of 8 scales  Deterioration in physical function ( $p = 0.03$ )  Improvement in health transition ( $p = 0.001$ )  No significant effect on PCS or MCS
Zivadinov et al. <sup>31</sup>	Open labeled/1 y	RRMS (24)	FAMS	No significant difference between baseline, 6-mo and 1-y scores for any of the 6 subscales
<b>SC IFN<math>\beta</math>-1b (Betaseron<sup>®</sup>)</b>				
Freeman et al. <sup>29</sup>	R, DB, PBO-controlled/up to 3 y	SPMS (IFN $\beta$ -1b [270]; PBO [261])	SIP	Slower rate of physical deterioration at 6 and 12 mo and last visit ( $p < 0.05$ ) vs PBO  Trend toward improvement through 36 mo for IFN $\beta$ -1b; significantly greater vs PBO at 18 mo ( $p < 0.05$ )
Parkin et al. <sup>32</sup>	Observational/6 mo	RRMS (remitted [62]; recently relapsed [40])	MSQoL-54	Remitted scored more favorably than relapsed ( $p \leq 0.05$ ): physical, role, and social function, pain, energy/vitality, sexual function, overall QoL, change in health, and PCS
Rice et al. <sup>33</sup>	Prospective comparison of treated patients vs historical controls/5.2 y (mean)	RRMS (treated patients [80]; controls [112])	SF-36	Higher QoL across all disability levels for physical function, role-physical, general health vs controls ( $p < 0.002$ )  EDSS score $< 3.0$ : higher physical function, role-physical general health, social function levels vs controls ( $p < 0.05$ )
<b>Various DMTs</b>				
Arnoldus et al. <sup>34</sup>	Open labeled/6 mo	RRMS (IM IFN $\beta$ -1a [15]; SC IFN $\beta$ -1b [36])	SF-36	Improved role-physical functioning ( $p = 0.032$ )  Transient increase in bodily pain at 1 mo ( $p < 0.001$ ) with improved scores through 6 mo
Simone et al. <sup>35</sup>	Open labeled/2 y	MS-unspecified (IM IFN $\beta$ -1a [14]; SC IFN $\beta$ -1a [16]; SC IFN $\beta$ -1b [11]; untreated controls [77])	MSQoL-54	MCS and emotional well-being scores deteriorated at 2 y ( $p = 0.014$ )  No significant between-group differences on all other MSQoL-54 scores

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Table		Continued		
DMT	Study design/duration	Diagnosis (N) <sup>a</sup>	HRQoL instrument	Findings
Lily et al. <sup>36</sup>	Open labeled/up to 3 y	RRMS or SPMS (IFN $\beta$ -1b [99], IFN $\beta$ -1a [68], glatiramer [8], other treatments [2])	LMSQoL	Improvements in LMSQoL scores not reflected by EDSS scores
				No significant differences between treatments at 1 or 2 y
<b>Natalizumab (Tysabri<sup>®</sup>)</b>				
Rudick et al. <sup>10</sup>	R, DB, PBO or IFN $\beta$ -1a-controlled/2 y	RRMS <sup>b</sup> (natalizumab [627]; PBO [315]; natalizumab + IFN $\beta$ -1a [589]; IFN $\beta$ -1a alone [582])	SF-36	AFFIRM: higher PCS scores from 24 wk through 2 y vs PBO ( $p \leq 0.03$ ); higher MCS scores at 2 y vs PBO ( $p = 0.011$ )
<b>AFFIRM: natalizumab monotherapy</b>				
<b>SENTINEL: combination therapy with IM IFN<math>\beta</math>-1a</b>				SENTINEL: higher PCS scores at 1 y and 2 y for combination vs IFN $\beta$ -1a monotherapy ( $p \leq 0.02$ ); no significant difference in MCS

Abbreviations: DB = double blind; DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale; FAMS = Functional Assessment of Multiple Sclerosis; HRQoL = health-related quality of life; IFN $\beta$  = interferon beta; IM = intramuscular; LMSQoL = Leeds Multiple Sclerosis Quality of Life scale; MCS = Mental Component Summary of SF-36; MS = multiple sclerosis; MSQoL-54 = Multiple Sclerosis Quality of Life-54 scale; PBO = placebo; PCS = Physical Component Summary of SF-36; QoL = quality of life; R = randomized; RRMS = relapsing-remitting multiple sclerosis; SC = subcutaneous; SF-36 = Short Form-36; SIP = Sickness Impact Profile; SPMS = secondary progressive multiple sclerosis.

<sup>a</sup>Patients completing evaluation period (observed case) unless otherwise noted.

<sup>b</sup>Intent-to-treat population.

the Mental Health Inventory ( $p < 0.05$ ), the MOS Pain Effects Scale ( $p < 0.05$ ), and the MOS Modified Social Support Survey ( $p < 0.02$ ). There were no differences between IFN $\beta$ -1a and placebo on changes in bladder control or visual impairment.<sup>28</sup>

In the pivotal randomized, placebo-controlled MSCRG study, there was a significant improvement in the physical SIP score with IFN $\beta$ -1a vs placebo over 2 years in patients with RRMS and a baseline overall SIP score  $\geq 10$  ( $p = 0.045$ ).<sup>27</sup> In contrast, no effects on HRQoL measures were observed in patients with RRMS receiving IM IFN $\beta$ -1a as assessed using the SF-36<sup>30</sup> or FAMS.<sup>31</sup> The lack of observed treatment effect in the latter 2 studies may have been attributable to less stringent study designs (case controlled and open labeled), smaller sample sizes, shorter duration of follow-up (1 vs 2 years), and the use of different HRQoL instruments (SF-36 or FAMS vs SIP) (table).

Studies also have examined the effect of subcutaneous (SC) IFN $\beta$ -1b (Betaseron<sup>®</sup>) on HRQoL outcomes (table).<sup>29,32,33</sup> In 1 randomized, double-blinded, placebo-controlled trial of 270 patients with SPMS, SC IFN $\beta$ -1b treatment for up to 3 years resulted in a trend for a slower rate of decline on measures of physical function vs placebo, as measured by the SIP and a study-specific scale.<sup>29</sup> In an observational study of 102 patients with RRMS, those in

remission ( $n = 62$ ) had more favorable scores on several dimensions of the MSQoL-54 compared with patients who had recent relapses ( $n = 40$ ). In addition, all patients, regardless of remission status, with EDSS scores of 3.0 or less had significantly better scores on the physical function, role-physical, health distress, social function, and sexual function scales compared with those with greater degrees of disability.<sup>32</sup> Long-term treatment with SC IFN $\beta$ -1b in 80 patients with RRMS resulted in significantly better HRQoL scores on the SF-36 for physical function, role-physical, and general health compared with untreated historical controls across all levels of disability. Moreover, patients with mild disability on the EDSS had higher HRQoL scores compared with untreated controls with the same level of disability.<sup>33</sup>

Three open-labeled studies, ranging in duration from 6 months to 3 years, evaluated various DMTs in patients with MS (table). These studies included heterogeneous patient populations (i.e., unspecified MS, RRMS, or SPMS), and different types of DMTs were administered. In 1 study of 51 patients with RRMS, treatment with IFN $\beta$  (IM IFN $\beta$ -1a or SC IFN $\beta$ -1b) significantly improved the mean role-physical functioning score of the SF-36 during the first 6 months of therapy; bodily pain increased during the first month but returned to baseline levels at months 3 and 6.<sup>34</sup> A 2-year course of treatment with IM or SC IFN $\beta$ -1a or SC IFN $\beta$ -1b in 41 patients

with MS (diagnoses not specified) resulted in a negative effect on mental health and emotional well-being composites of the MSQoL-54 compared with untreated patients. No significant differences in other HRQoL measures were noted between treated patients and untreated controls.<sup>35</sup> A third open-labeled study observed patients with RRMS (n = 182) or SPMS (n = 28) for up to 3 years during treatment with IFN $\beta$ -1a (n = 68), IFN $\beta$ -1b (n = 99), GA (n = 8), or other unspecified DMTs (n = 2).<sup>36</sup> Results demonstrated significant improvements on the LMSQoL throughout the 3-year follow-up that did not correspond with changes in EDSS scores; EDSS scores remained at baseline levels for 2 years, then increased (worsened). Regression analysis identified poor HRQoL at baseline as the only disease characteristic associated with the response to DMT. There were no significant differences between treatments at either the 1- or 2-year follow-up.

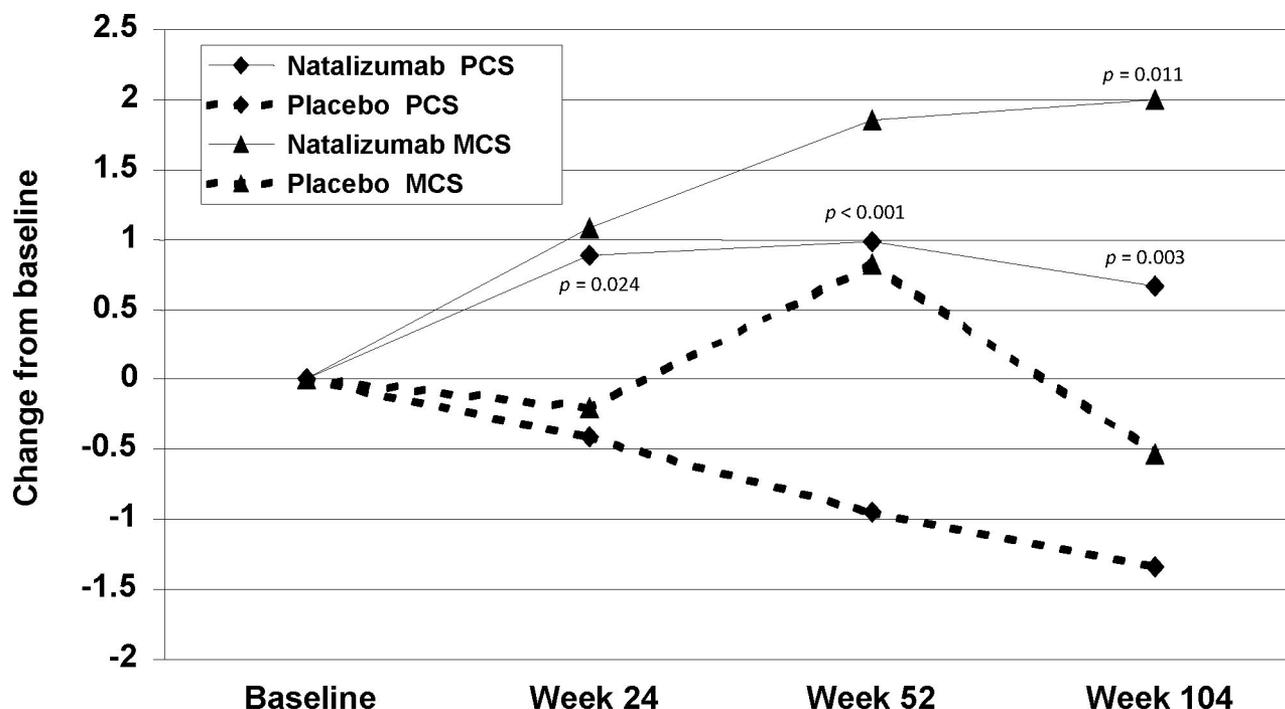
One study compared changes in neuropsychological status in patients with RRMS after treatment with GA or placebo and found no significant differences between treatment arms.<sup>37</sup>

**EFFECTS OF NATALIZUMAB ON HRQoL IN PATIENTS WITH MS** HRQoL was prospectively assessed in AFFIRM<sup>38</sup> and SENTINEL,<sup>39</sup> the pivotal phase 3 studies of natalizumab in the treatment of MS. Both studies used the MSQLI, which includes the SF-36.

In AFFIRM, natalizumab monotherapy improved both the PCS ( $p = 0.003$ ) and MCS ( $p = 0.011$ ) scores of the SF-36 compared with placebo at the 2-year end point. Between-group differences on the PCS achieved statistical significance at 6 months and were sustained throughout the study period. Scores on the MCS were numerically higher for natalizumab compared with placebo but did not achieve statistical significance until end point (figure 2).<sup>10</sup>

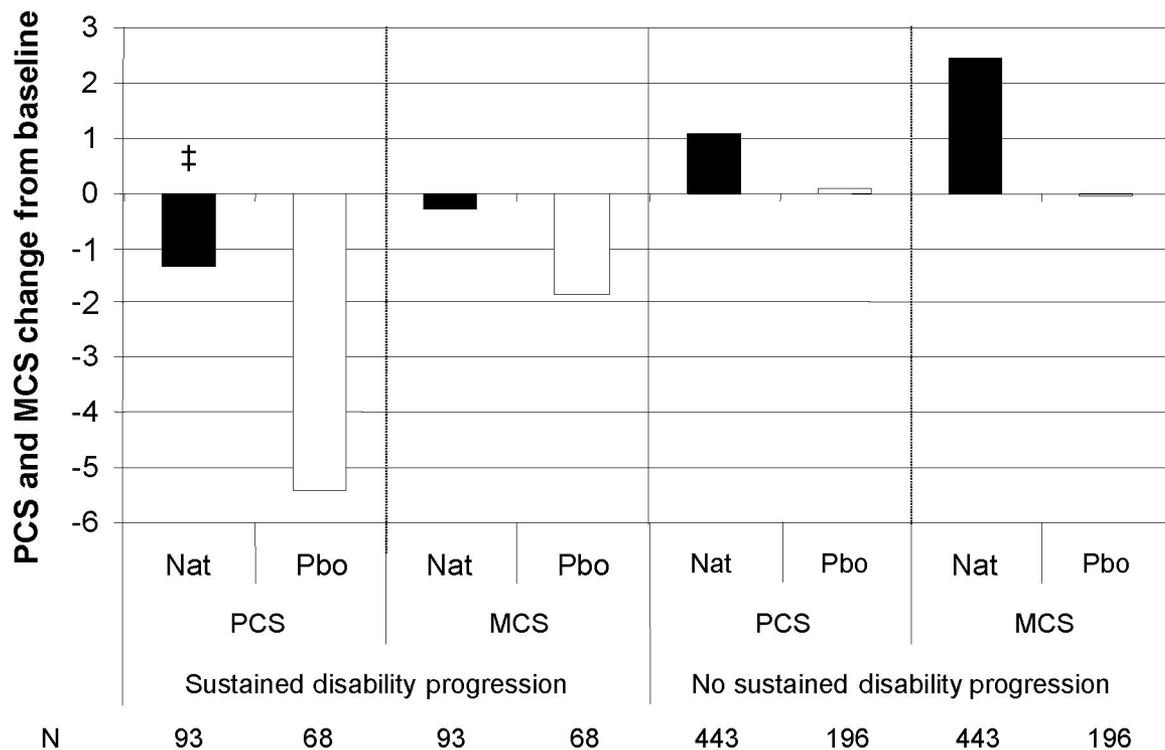
Patients randomized to natalizumab monotherapy had significantly higher changes from baseline scores on 6 of the 8 individual scales of the SF-36 compared with placebo at 2 years ( $p < 0.05$ ). For example, natalizumab-treated patients experienced a mean increase over baseline on the physical function score of 1.21 points compared with a 5.17-point decrease in the placebo group. The role-emotional score showed a 6.81 increase on average for natalizumab-treated patients compared with a 2.73-point mean reduction in the placebo group. Natalizumab therapy resulted in significant HRQoL benefits even among patients who had sustained disability progression or those who relapsed during the study period, suggesting that patients in the active arm had more mild relapses or more mild EDSS progression. All patients with sustained disability progression over the course of the study experienced deterioration in PCS and MCS scores, but patients treated with

**Figure 2** Mean change from baseline scores on the Physical Component Summary (PCS) and Mental Component Summary (MCS) scores over 2 years for natalizumab monotherapy vs placebo in the AFFIRM study<sup>10</sup>



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**Figure 3** Effect of sustained disability progression on the Expanded Disability Status Scale (EDSS) on Physical Component Summary (PCS) and Mental Component Summary (MCS) change scores over 2 years for natalizumab monotherapy vs placebo in the AFFIRM study\*\*10



\*Sustained disability is the prespecified primary clinical end point. †Change from baseline to week 104. ‡ $p < 0.05$  compared with placebo. Nat = natalizumab; Pbo = placebo. Reproduced with permission from Rudick et al. Health-related quality of life in MS: effects of natalizumab. *Ann Neurol* 2007;62:335-346. Copyright John Wiley & Sons, Inc. 2007.

natalizumab monotherapy had more modest reductions in scores compared with placebo ( $p < 0.05$  for PCS scores vs placebo). Patients without sustained disability progression who were randomized to natalizumab monotherapy exhibited improvement on the PCS and MCS compared with placebo, but between-group differences were not statistically significant (figure 3). Reductions in PCS scores occurred for patients who had 1 or more relapses, but placebo-treated patients had greater reductions than patients randomized to natalizumab ( $p < 0.05$ ). In contrast, the mean MCS score increased among relapsing patients in the natalizumab group and decreased in the placebo group, but differences did not reach statistical significance (figure 4). The subjective global assessment visual analogue scale score remained stable at the 1- and 2-year end points in natalizumab-treated patients compared with the placebo group where deterioration was noted ( $p < 0.05$ ).<sup>10</sup>

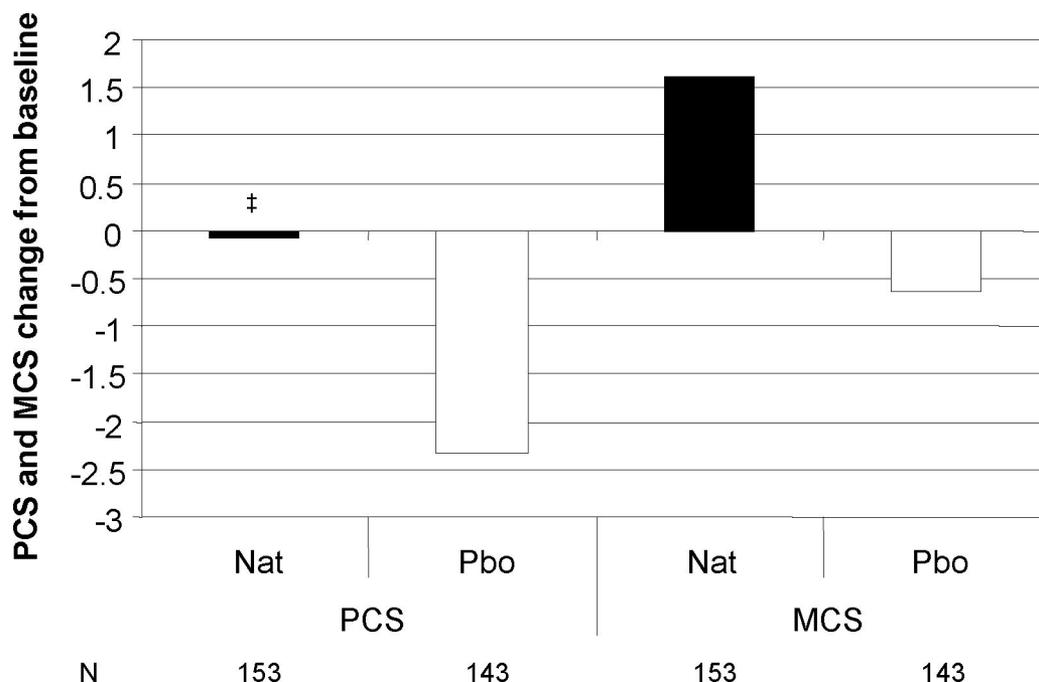
A secondary analysis of data from a subset of AFFIRM patients ( $n = 358$ ) assessed the relationship between baseline disease severity characteristics, response to natalizumab treatment, and pain using the MOS Pain Effects Scale (PES), which is a component

of the MSQOL. The PES is a 6-item scale that evaluates the extent to which pain and unpleasant sensations interfere with mood, ability to walk or move, sleep, work, recreation, and enjoyment of life. Total scores on the PES range from 6 to 30, with higher scores indicating a greater effect of pain on mood or behavior. Disability progression ( $\geq 1$ -point increase in EDSS sustained for 12 weeks) and 2 or more relapses at the 2-year follow-up were significantly associated with increased worsening of pain for patients randomized to placebo treatment ( $p < 0.02$ ). In addition, natalizumab significantly improved PES scores compared with placebo at each postbaseline assessment through year 2 in patients with a baseline PES score  $> 8$  and a baseline EDSS score  $> 1.5$  ( $p \leq 0.023$ ) (figure 5).<sup>40</sup>

Combination therapy with natalizumab and IM IFN $\beta$ -1a in the SENTINEL study also was associated with improvements in PCS and MCS scores as well as significantly improved pain scores over 2 years compared with placebo (Biogen Idec, Inc., data on file).<sup>10,40</sup>

**DISCUSSION** HRQoL is an important consideration when assessing the effects of MS treatment strategies on a patient's self-perception and ability

**Figure 4** Physical Component Summary (PCS) and Mental Component Summary (MCS) change scores for relapsing patients over 2 years in the AFFIRM study\*\*†‡



\*Least square means controlling for age, gender, baseline score, and number of relapses during the study period. †Change from baseline to week 104. ‡p < 0.05 compared with placebo. Nat = natalizumab; Pbo = placebo. Reproduced with permission from Rudick et al. Health-related quality of life in MS: effects of natalizumab. *Ann Neurol* 2007;62:335-346. Copyright John Wiley & Sons, Inc. 2007.

to function in daily life. Traditional measures of MS activity and progression such as the EDSS and MRI studies are essential in evaluating the efficacy of new treatments. However, a more patient-centered approach is necessary to fully understand the benefits or risks associated with treatment. This is especially true for the currently available DMTs, which do not cure MS but rather slow or arrest disease progression and must be administered for many years.

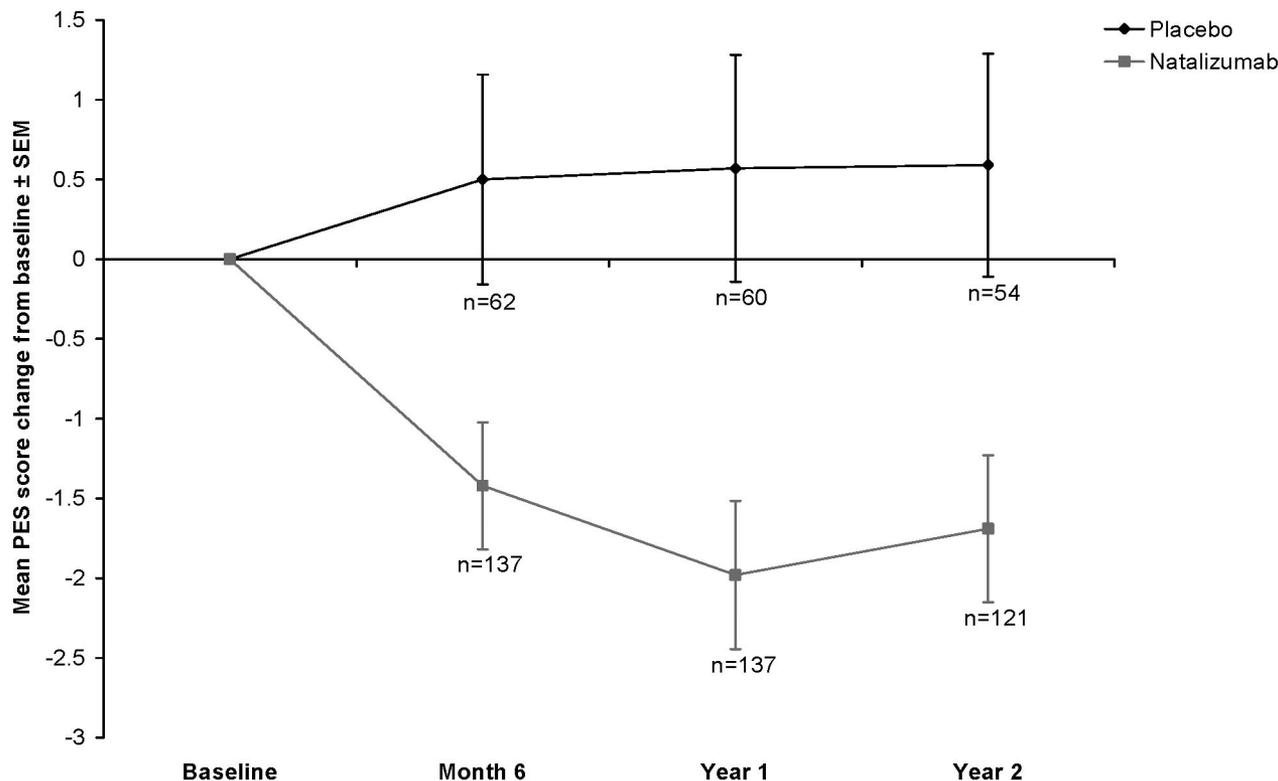
There is evidence that IFN $\beta$ -1a or IFN $\beta$ -1b monotherapy improves HRQoL in patients with SPMS, but data for patients with RRMS is somewhat less conclusive, mainly because HRQoL assessments were not included in the majority of pivotal randomized, controlled trials. There is a marked lack of data on the effects of GA on HRQoL. Moreover, data showing that IFN $\beta$  improves HRQoL outcomes in patients with mild MS more than in patients with more advanced disease in 1 study<sup>33</sup> may be an artifact related to the use of historical controls. Although further research based on well-controlled studies is needed to gain a greater understanding of the effects of IFN $\beta$  and GA on HRQoL in patients with RRMS, it is unlikely to occur given that the pivotal studies now are complete. Future phase 3 randomized, controlled trials with MS treatments should consider including HRQoL as a second-

ary end point to understand how a given therapy affects patients' daily lives.

Although our understanding of HRQoL is limited by the inconsistent use of HRQoL measures across studies of MS and other neurologic conditions, the Neuro-QOL project, a 5-year, multisite, National Institute of Neurological Disorders and Stroke-funded project,<sup>41</sup> promises to relieve these concerns in the future. Initiated in 2004, the main objective of the Neuro-QOL is to develop an HRQoL assessment tool for adults and children with common neurologic conditions, including MS, using item response theory and computer-adaptive testing.<sup>41</sup> This project is designed to assess both common concepts across neurologic conditions and disease-specific concerns. The methodology used in the Neuro-QOL project is in line with the US Food and Drug Administration guidance for the use of patient-reported outcomes in clinical trials.<sup>42</sup> It is anticipated that the availability of this assessment tool will increase the value and willingness to include HRQoL measurements in clinical trials.

To date, natalizumab is the only DMT for which there is class I evidence (i.e., prospectively collected data from large, randomized, double-blinded, placebo-controlled trials with predefined HRQoL outcome assessments) of significant beneficial effects on HRQoL in

**Figure 5** Mean change from baseline in Pain Effects Scale (PES) score over 2 years by treatment group in AFFIRM study patients with baseline Expanded Disability Status Scale (EDSS) scores >1.5 and PES scores >8<sup>40</sup>



patients with RRMS. These HRQoL outcomes amplify and further validate the physician-assessed improvements in disability, relapse, and brain lesions and demonstrate that natalizumab has patient-centered benefits not previously observed in clinical studies of patients with MS. Reported HRQoL improvements with other DMTs in patients with relapsing MS have been more modest, possibly as a result of less robust improvements in neurologic status along with clinically bothersome adverse effects (e.g., fatigue, flu-like symptoms, and depression).<sup>3-5,10</sup>

Clinical research in MS is evolving to include patient-centered outcomes that provide a more comprehensive evaluation of the effects of the disease on patients' lives. Several HRQoL instruments are available for use in MS, and experience of their use is growing. In concert with these developments, incorporating HRQoL outcomes in pivotal studies of MS treatments eventually should become standard practice.

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#### DISCLOSURE

Dr. Miller has served on a scientific advisory board for Expert Medical Education; served as associate editor for the *Journal of Quality of Life Research*; and received research support from Teva and the National Institute of Neurological Disorders and Stroke. Dr. Rudick has served on scientific advisory boards for Bayhill Pharmaceuticals, Genzyme, Novartis Pharmaceuticals, and Wyeth Pharmaceuticals; received compensation for travel/honoraria from Biogen Idec, Genzyme, Novartis, Teva, and Wyeth; received royalties from publishing for the text *Multiple Sclerosis Therapeutics* (Informa Healthcare, UK); and received research funding from the National Institutes of Health. Dr. Hutchinson has received honoraria for speaking from Biogen Idec and received research funding from the Health Research Board of Ireland.

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