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Quality of life for veterans with multiple sclerosis on disease-modifying agents: Relationship to disability

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Abstract—Our objective was to compare self-reported health-related quality of life (HRQOL) for U.S. veterans with multiple sclerosis (MS) on disease-modifying agents with provider reports of HRQOL from standard disability measures. We conducted a 3-year prospective observational study of 204 subjects who used interferon beta or glatiramer acetate and compared subjects' responses on the Veterans Short-Form 36 (VSF-36) (36-item short-form functional status assessment for veterans) with the Kurtzke Expanded Disability Status Scale (EDSS) and the Functional System (FS) scales, which are standard MS disability scales. EDSS and FS scores were significantly correlated with some VSF-36 domains (physical function [$r = -0.57$], role physical [$r = -0.37$], and physical component summary [$r = -0.40$]) and weakly correlated with other domains. HRQOL scores did not predict disability or compliance with therapy. We observed decrements in HRQOL at relatively low disability levels. HRQOL measures directly associated with physical function were correlated with standard MS disability scales. Researchers need to clarify the role of HRQOL in clinical outcomes assessment, as shown by the lack of outcome sensitivity and predictive value of the VSF-36.

Key words: clinical outcome assessment, disability, disease-modifying agents, Expanded Disability Status Scale, functional status, Functional System scales, health-related quality of life, multiple sclerosis, outcome sensitivity, Veterans Short-Form 36.

INTRODUCTION

Multiple sclerosis (MS) is one of the most common diseases of the central nervous system (CNS) in young adults. The pathophysiology of MS is that of an inflammatory process directed primarily at the myelin in the CNS [1–2]. The most common clinical subtype is relapsing-remitting MS (RRMS), which is characterized by acute neurological symptoms followed by partial or complete remissions. Progressive forms of MS (e.g., secondary or primary progressive MS) are characterized by

Abbreviations: CNS = central nervous system, DMA = disease- modifying agent, EDSS = Expanded Disability Status Scale, FDA = Food and Drug Administration, FS = Functional System, HRQOL = health-related quality of life, MCS = medical component summary, MOS SF-36 = Medical Outcomes Study 36-item short form, MS = multiple sclerosis, PCS = physical component summary, RRMS = relapsing-remitting MS, SAS = Statistical Analysis Software, SD = standard deviation, VA = Department of Veterans Affairs, VAMC = VA medical center, VSF-36 = Veterans Short-Form 36.

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chronic neurological deterioration in the interval between attacks or in the absence of attacks. While the cause of MS is unknown, a leading hypothesis is that it is an autoimmune process directed at the myelin in the CNS.

While MS has no cure, to date, five medications approved by the U.S. Food and Drug Administration (FDA) are in use for MS. Marketing of a sixth FDA-approved medication, natalizumab (Tysabri®), has been suspended pending investigation of serious adverse results in a clinical trial of natalizumab. These medications reduce attack rates, modestly slow progression, and inhibit lesion formation in the brain, as detected by magnetic resonance imaging [3–6]. The five FDA-approved agents that are immunomodulators include interferon β (Avonex®, Betaseron®, and Rebif®), glatiramer acetate (Copaxone®), and natalizumab (Tysabri®). Mitoxantrone (Novantrone®) is an antineoplastic drug approved for patients with rapidly progressive disease.

Because these medications offer only partial control of the disease, researchers have conducted studies to demonstrate the utility of some of these treatments in clinical practice using cost effectiveness analyses [7–9]. The significant expense, partial efficacy, side effects, and requirement for self-injection of these medications have made their effectiveness in clinical practice difficult for researchers to determine.

We used patient-derived outcome assessments to measure the effectiveness of these medications in clinical practice [10–12]. These outcome instruments measure health-related quality of life (HRQOL) and are used for assessing the effect of chronic disease on various health-related functions; they may also provide standardized comparisons between different chronic diseases.

We conducted this study to assess the effectiveness of disease-modifying agents (DMAs) for MS in terms of HRQOL in U.S. veterans. The Veterans Short-Form 36 (VSF-36) (36-item short-form functional status assessment for veterans) was administered serially to subjects who were starting therapy for MS and followed for up to 3 years [13]. We also compared participants' self-reported outcome measures with provider responses to standard neurological scales for MS impairment and disability.

METHODS

Background and Subjects

We conducted a 3-year prospective observational study of 204 U.S. veterans with MS who were treated with interferon β or glatiramer acetate by the Department of Veterans Affairs (VA) between 1993 and 2000. The 204 subjects were recruited from 34 VA clinics. Most clinics recruited between 1 and 10 participants. A single center had 30 participants, and three centers had 11 to 15 participants. Follow-up ranged from 1 to 3 years. All veterans who started treatment were eligible and participation was voluntary. The study began in 1993 after the approval of interferon β-1b (Betaseron®) and later included subjects who started treatment with interferon β-1a (Avonex®) and glatiramer acetate (Copaxone®), which were approved in 1996 and 1997, respectively.

Treatment recommendations for subjects were made at the local level and beyond the scope of this study. Treating physicians or other healthcare providers, subject to approval by local VA Pharmacy and Therapeutics Committees, made these recommendations. Subjects were recruited through local VA medical center (VAMC) Neurology Departments and MS clinics. Each participating VAMC obtained local institutional review board approval.

Outcome Measures

The assessments we conducted included baseline and follow-up Kurtzke Expanded Disability Status Scale (EDSS), Functional System (FS) scales, and VSF-36. Baseline evaluation also included a medical status questionnaire, symptoms checklist, and the Folstein Mini-Mental State Examination. At each visit, subjects were asked to report adverse drug effects, reasons for discontinuing drug therapy, new symptoms, or exacerbations of MS. Treating physicians and healthcare providers performed these assessments prior to the start of therapy, at 3 months posttreatment, and every 6 months for 3 years thereafter.

Kurtzke Expanded Disability Status Scale and Functional System Scales

EDSS and FS are the standard MS impairment and disability scales [14]. The EDSS is an ordinal scale of half-point steps, which ranges from 0 (no physical disability) to 10 (death as a result of MS). Scores of 1.0 to 3.5 indicate slight-to-mild disability, 4.0 to 5.5 mild-to-moderate disability (independent ambulation), 6.0 moderate disability (unilateral assistance, cane or crutch, required to ambulate 100 m), 6.5 moderate-to-severe disability (bilateral assistance, crutches or walker, required to ambulate at least 20 m), and 7.0 severe disability (nonambulatory). The FS scale is composed of seven neurological subscales: motor, cerebellar, brain stem, sensory, bowel/bladder, visual, and

cognitive. The EDSS is based in part on the FS for EDSS scores ≤ 5.0. Both intrarater and interrater variability exist in the scoring of the EDSS, but this variation is consistent with general clinical practice [15].

Veterans Short-Form 36

The VSF-36 is a 36-item self-report questionnaire that measures eight health categories: physical function, role physical, pain, general health, vitality, social function, emotional role, and mental health [16–18] (**Appendix, available online only at www.rehab.research.va.gov**). These eight domains are scored from 0 (worst) to 100 (best). Two additional summary domains exist: the physical component summary (PCS) and the mental component summary (MCS). The scores are linear transformed *t*-tests, with 50 as the mean and 10 as the standard deviation (SD) based on a normally distributed population. The VSF-36 was modified from the Medical Outcomes Study 36-item short form (MOS SF-36) in domains that cover "role limitations due to physical and emotional problems" by replacement of dichotomized yes/no choices with a 5-point ordinal scale that ranges from "no, none of the time" to "yes, all of the time." These changes increase the precision and discriminatory validity of the role scales, PCS, and MCS. Validated conversion formulas for the VSF-36 allow for direct comparison with MOS SF-36 benchmark scores [19].

Data Collection and Analysis

The VA Cooperative Studies Program Center in West Haven, Connecticut, coordinated data collection and analysis and provided other administrative support. We performed the analyses using Statistical Analysis Software (SAS) (version 8.2, SAS Institute Inc, Cary, North Carolina) and S-PLUS 2000 (Insightful Corp, Seattle, Washington). We scored the VSF-36 according to published VA algorithms [18].

We used summary statistics (frequency and mean) to analyze sociodemographic variables such as age, age at diagnosis, sex, race/ethnicity, marital status, and education. Descriptive statistics (mean, SD) were also obtained for EDSS and VSF-36 scores at baseline, 1, 2, and 3 years. We used paired *t*-tests to test the mean differences between EDSS and VSF-36 scores at baseline versus 1, 2, and 3 years. We used the Pearson's correlation coefficient (r) to evaluate correlations between EDSS and VSF-36 scores. For the Pearson's correlation coefficient, the null hypothesis was that no correlation existed between two variables. An r value of 0 indicates no correlation, while an r value of 1 indicates perfect correlation. Values between 0 and 1 have somewhat subjective interpretations; i.e., values greater than 0 and less than 0.50 could be considered poor to fair correlation, while values between 0.50 and 0.90 could be considered good to very good correlation. Tests were considered significant at $p < 0.05$.

We used logistic regression to investigate the relationship between baseline variables and the change between baseline and subsequent follow-up EDSS scores. This analysis predicts the logarithmic odds of an event (improvement or no change versus worsening between EDSS at baseline and EDSS at follow-up). Missing outcomes were omitted from the regression.

Initially, we used a model with demographic variables and VSF-36 variables that were not highly correlated with EDSS scores or with each other (e.g., physical component summary vs physical function or mental component summary vs mental health) to obtain a final model for year 1. Variables were removed from the model one at a time based on their having a higher p-value ($p \geq 0.10$) than other variables. We also included in the final model a binary variable that indicated whether or not subjects had remained on Betaseron® through year 1. A similar procedure was followed for years 2 and 3, except that the "on Betaseron® through year 1" variable was removed.

RESULTS

Subject Demographics

The cohort originally comprised 259 subjects, of which 204 completed baseline assessments and started therapy. Of the 204 initial participants, 145 started interferon β-1b, 54 started interferon β-1a, and 5 started glatiramer acetate. **Table 1** shows subject demographics. Compared with participants in the interferon β-1b pivotal phase III trial, which led to the FDA approval of interferon β-1b [3], four times as many males as females participated in the current study; average age in the current study was 42 years, or 6 years older than participants in the Betaseron® trial. In the current study, 79 percent of the participants were white/non-Hispanic, and in the Betaseron® phase III trial, 93 percent of participants were Caucasian [3]. Average EDSS scores were greater for veterans in the current study than participants in the Betaseron® trial, 4.1 versus 2.8 to 3.0, respectively. This comparison is useful because it indicates that compared with the Betaseron® phase III trial cohort, the veterans in the current study were predominantly male, older, and more disabled.

Table 1.
Baseline characteristics (mean ± standard deviation or percentage) for subjects in current study of veterans with multiple sclerosis.

Characteristic	*n*	Value
Age (yr)	198	41.9 ± 9.2
Sex Ratio (male:female)	203	4:1
Age at Diagnosis (yr)	116	34.3 ± 8.6
Range (yr)	—	20 to 62
Education (yr)	111	14.3 ± 2.5
Range (yr)	—	4 to 20
Race/Ethnicity	188	—
White (non-Hispanic)	149	79%
White (Hispanic)	15	8%
Black (non-Hispanic)	22	12%
Black (Hispanic)	1	—
Marital Status	153	—
Married	90	59%
Divorced	23	15%
Separated	2	—
Widowed	1	—
Never Married	25	16%
Other	12	8%
Expanded Disability Status Scale	204	4.1 ± 1.8

Change in Drug Therapy

Forty-three percent of subjects (87/204) switched or discontinued drug therapy or left the study. The subjects switched drugs or discontinued drug use for the following reasons: side effects, convenience of administration, perceived therapeutic advantage, increase in disability, noncompliance, other, no longer followed at VAMC, increase in relapses, cost or availability on formulary, death, none, and neutralizing antibodies (**Table 2)**.

Baseline Veterans Short-Form 36 Comparisons with Expanded Disability Status Scale and Functional System Scales

Baseline impairment and disability measured by healthcare providers were compared with subject self-assessment of HRQOL (**Table 3**). Self-assessed physical limitations reported on the VSF-36 (a higher score indicates better health) were highly correlated with EDSS scores (a higher score indicates worse health): physical function (r = –0.57), role physical (r = –0.37), and PCS (r = –0.40). By contrast, EDSS scores were not highly correlated with vitality (r = –0.15), social function (r = –0.28), mental health (r = –0.13), and role emotional (r = –0.25). Similarly, little or no correlation existed between the EDSS and general health, bodily pain, and MCS.

Table 2.
Reason and frequency for participants who switched or discontinued therapies or left study. Of 204 subjects who started therapy, 87 reported ≥ 1 therapy changes or discontinuations: 57 subjects reported one change, 24 two changes, 4 three changes, and 2 four changes. Total of 194 reasons for switch or discontinuation were cited.

Reason	Number (%)
Side Effects	49 (25)
Convenience of Administration	25 (13)
Perceived Therapeutic Advantage*	24 (12)
Increase in Disability	24 (12)
Noncompliance	21 (11)
Other	18 (9.3)
No Longer Followed at VAMC	14 (7.2)
Increase in Relapses	9 (4.6)
Cost or Availability on Formulary	5 (2.6)
Death	2 (1.0)
None	2 (1.0)
Neutralizing Antibodies	1 (<1.0)

*Switched from Betaseron® to Avonex® or Copaxone® based on perception that alternate therapies would be more effective.
VAMC = Department of Veterans Affairs medical center.

Table 3.
Pearson's correlation coefficient (r) between participants' self-assessments (Veterans Short-Form 36 [VSF-36]) and provider assessments (Expanded Disability Status Scale) on VSF-36 domains.

VSF-36 Domain	*n*	*r*	*p*-Value
Physical Function	178	–0.57	<0.001
Role Physical	186	–0.37	<0.001
Bodily Pain	178	–0.06	0.46
General Health	177	–0.15	0.05
Vitality	176	–0.15	0.04
Social Function	186	–0.28	<0.001
Role Emotional	185	–0.25	<0.001
Mental Health	176	–0.13	0.08
Physical Component Summary	172	–0.40	<0.001
Mental Component Summary	172	–0.10	0.22

These trends were also observed after subjects were grouped by categorical EDSS scores (**Table 4**). Mild, moderate, and severe impairment groups were defined as EDSS scores of < 3.5, 3.5 to 5.5, and > 6.0, respectively. Significant decreasing trends and group differences were observed for physical function. However, role physical, role emotional, social function, and mental health were significantly different only between subjects with mild versus moderate and severe impairment. No significant differences existed between subjects with moderate versus severe impairment.

Therefore, VSF-36 scores are more sensitive to change at milder levels of impairment, with the exception of bodily pain, general health, and vitality. We compared the seven subscales of the FS with VSF-36 domains to determine the relationship between category of impairment (e.g., motor dysfunction [pyramidal functional system]), and HRQOL (**Table 5**). As would be expected, pyramidal system scores had the greatest association with physical function, role physical, and PCS. However, bowel/bladder FS scores were also significantly correlated with physical function (r = –0.46) and more weakly with role physical, social function, and PCS (r = –0.31, –0.24, and –0.32, respectively). Cerebellar FS (coordination) scores were mildly correlated with physical function, role physical, social function, and role emotional (r = –0.29, –0.29, –0.21, and –0.23, respectively). By contrast, other FS subscales, including brain stem, sensory, visual, and cerebral, were not correlated or had minimal correlation with VSF-36 scales.

Expanded Disability Status Scale and Veterans Short-Form 36 Changes over Time with Disease-Modifying Agent Use

One of our main goals in this study was to determine whether treatment with immunomodulating DMAs for MS affect impairment and disability and health-related function. **Table 6** compares EDSS scores and VSF-36 scores between baseline and years 1, 2, and 3, respectively, in individual subjects with the use of paired t-tests. Slight

Table 4.
Summary statistics (mean ± standard deviation) and significant differences (two-sample t-test) by Expanded Disability Status Scale (EDSS) group within each Veterans Short-Form 36 (VSF-36) domain. Group 1 defined as EDSS score < 3.5, Group 2 as EDSS score 3.5 to 5.5, and Group 3 as EDSS score > 6.

VSF-36 Domain	Group 1 (n = 88)	Group 2 (n = 37)	Group 3 (n = 61)	Significant Differences Between Groups ($p < 0.05$)
Physical Function	55.3 ± 26	42.7 ± 25	19.0 ± 19	1 & 2, 1 & 3, 2 & 3
Role Physical	48.5 ± 27	35.6 ± 25	28.3 ± 27	1 & 2, 1 & 3
Bodily Pain	59.9 ± 28	62.9 ± 33	54.1 ± 27	—
General Health	52.2 ± 19	45.6 ± 22	45.7 ± 23	—
Vitality	38.6 ± 24	29.9 ± 20	32.1 ± 21	—
Social Function	62.4 ± 23	53.4 ± 27	46.7 ± 29	1 & 3
Role Emotional	68.4 ± 23	58.1 ± 30	56.3 ± 30	1 & 2, 1 & 3
Mental Health	70.0 ± 17	61.1 ± 20	66.3 ± 18	1 & 2
Physical Component Summary	36.7 ± 9	33.7 ± 9	27.5 ± 8	1 & 3, 2 & 3
Mental Component Summary	45.9 ± 9	41.6 ± 11	44.9 ± 10	1 & 2

Table 5.
Pearson's correlation coefficient (r) between Veterans Short-Form 36 (VSF-36) domains and Functional System subscales (correlations shown for $p < 0.05$).

VSF-36 Domain	Functional System Subscales						
	Pyramidal	Cerebellar	Brain Stem	Sensory	Bowel/ Bladder	Visual	Cerebral
Physical Function	–0.57	–0.29	–0.19	–0.16	–0.46	—	—
Role Physical	–0.32	–0.29	–0.19	–0.18	–0.31	—	—
Bodily Pain	—	—	—	—	—	—	—
General Health	–0.16	—	—	—	–0.17	—	—
Vitality	–0.18	—	—	—	—	—	—
Social Function	–0.28	–0.21	–0.15	–0.17	–0.24	–0.17	—
Role Emotional	–0.21	–0.23	–0.19	–0.17	–0.19	—	—
Mental Health	–0.16	–0.16	—	—	–0.15	—	–0.20
Physical Component Summary	–0.40	—	—	—	–0.32	—	—
Mental Component Summary	—	—	—	—	—	—	–0.19

worsening in mean EDSS scores was observed in years 1, 2, and 3 compared with baseline (0.33, 0.37, and 0.38, respectively), which were statistically significant ($p < 0.05$) in years 1 and 2. Similar declines in mean physical function (decrease in scores indicates worsening of condition) also occurred in each follow-up year (1, 2, and 3) compared with baseline (–3.76, –7.90, and –5.84 [$p < 0.1$, $p < 0.01$, and $p < 0.05$, respectively]). No other VSF-36 domain scores were significantly different in individuals in follow-up years.

Baseline Variables Associated with Improvement

We used a logistic regression analysis model to determine whether any variables at baseline predicted clinical outcome (**Table 7**). This analysis models the relationship among baseline demographic characteristics, functional variables (i.e., EDSS and VSF-36 scores and compliance with interferon β-1b therapy at 1 year), and the probability of change in EDSS in years 1, 2, and 3 compared with baseline. A favorable outcome in EDSS was defined as a change in score of <1.0, i.e., improvement or stability,

Table 6.
Subject 1-, 2-, and 3-year follow-up mean Expanded Disability Status Scale (EDSS) and Veterans Short-Form 36 (VSF-36). Worsening impairment indicated by positive mean difference EDSS and negative mean difference VSF-36. Mean of individual differences compared by paired *t*-test.

Assessment Instrument	1-Year Mean	Mean Difference Baseline to 1 Year	2-Year Mean	Mean Difference Baseline to 2 Years	3-Year Mean	Mean Difference Baseline to 3 Years
	n = 114		*n* = 57		*n* = 43	
EDSS Score	4.4	0.33*	4.2	0.37*	4.9	0.38
VSF-36 Domain						
Physical Function	39.4	–3.76*	39.6	–7.90†	39.2	–5.84*
Role Physical	42.6	0.64	50.4	1.23	45.0	0.99
Bodily Pain	60.1	2.58	60.2	1.31	61.4	4.30
General Health	46.7	–1.98	51.2	–3.22	52.3	0.41
Vitality	34.5	–2.33	41.9	1.05	36.6	–0.48
Social Function	56.6	0.34	64.3	2.70	58.8	–4.28
Role Emotional	58.3	–6.56*	65.6	–3.30	57.2	–6.76
Mental Health	65.3	–3.75‡	69.0	1.32	69.5	0.39
Physical Component Summary	34.1	0.60	35.1	1.16	34.6	0.48
Mental Component Summary	43.5	–1.99	46.8	–0.10	45.0	–0.62

*$p < 0.05$.
†$p < 0.01$.
‡$p < 0.1$.

Table 7.
Logistic regression results for prediction of improvement or stability at years 1, 2, and 3* compared with baseline. Missing values were omitted.

Parameter	First-Year Prediction		Second-Year Prediction		Third-Year Prediction	
	p-Value	Odds Ratio Estimate	*p*-Value	Odds Ratio Estimate	*p*-Value	Odds Ratio Estimate
Intercept	0.13	—	0.19	—	0.64	—
EDSS Baseline	0.07	1.29	0.01	1.71	0.03	1.65
VSF-36 Domain						
Bodily Pain	0.06	0.98	0.55	0.99	0.58	0.99
Vitality	0.003	1.04	0.36	1.01	—	—
Mental Health	0.03	0.97	—	—	—	—
Remained on Betaseron® Through Year 1	0.06	2.58	—	—	—	—

Note: Area under receiver operating characteristic curve > 0.71 in each situation.
*n = 104, 53, and 38 for first-, second-, and third-year predictions, respectively.
EDSS = Expanded Disability Status Scale, VSF-36 = Veterans Short-Form 36.

while an unfavorable change was defined as 1.0. This analysis showed that for every increase of 1 point in baseline EDSS score, a 29, 71, and 65 percent increase in the odds for stable or improved EDSS scores existed at years 1, 2, and 3, respectively. Therefore, in terms of EDSS, the more disabled the subject at baseline, the better the chance for stability or improvement in the subsequent years. Conversely, better scores for vitality on the VSF-36 at baseline were associated with slightly better odds for improvement or stability in EDSS at 1 year. At years 2 and 3, the only variable that was statistically significant in explaining the odds for improvement or stability was the baseline EDSS score. Subjects who remained on Betaseron® through year 1 were also significantly more likely to be stable (odds ratio 2.58). However, adherence to therapy did not predict stability in years 2 and 3.

DISCUSSION

This 3-year, nonrandomized, nonblinded prospective cohort study of U.S. veterans with MS on immunomodulating DMAs failed to establish significant changes in HRQOL. The VSF-36 domain physical function declined each year from baseline, and role emotional declined in the first year. This was associated with small, but significant, worsening of EDSS scores in years 1 and 2. Other VSF-36 domains showed nonsignificant changes in either direction, i.e., worsening or improvement. The magnitude of the change from baseline in the VSF-36 and EDSS scores was not greater in the third follow-up year compared with the first follow-up year, which suggests that the subjects in this study who remained on therapy were stable. The generalizability of these findings, however, is tempered by the fact that a high attrition rate existed in each of the 3 years of the study. Furthermore, the only factor that predicted stability in terms of EDSS was a higher EDSS score (more disabled) at baseline. This is likely an artifact of the EDSS scale itself, a nonparametric interval scale that has a bimodal distribution [20]. Patients tend to spend more time at each step at the higher end of the scale because relatively greater changes in disability are required for EDSS scores to change. In addition, subjects who remained on Betaseron® therapy for 1 year were more likely to have favorable outcomes. While this study was not designed to test efficacy of the drug, one explanation is that the drug had a therapeutic effect on subjects. Another explanation is that subjects who tended to be stable remained on Betaseron®, while those not stable switched or discontinued the medication. More than 27 percent of reasons given for switching or discontinuing therapy were related to efficacy, including perceived therapeutic advantage, increase in disability, or an increase in relapse rate (**Table 2**).

Therefore, conclusions regarding the effectiveness of immunomodulating therapy for MS from this study are limited by the (1) absence of an untreated control group, (2) high attrition rate, and (3) lack of follow-up data on subjects who either discontinued therapy or dropped out of the study. As stated earlier, the decision not to maintain an untreated cohort of patients was based on the ethics of withholding a therapy that might benefit subjects. The high attrition rate in this study reflects the general experience of treating MS patients with these therapies.* In this study, 40 percent of subjects reported one or more changes in drugs or discontinued drug treatment, while 25 percent cited side effects from the therapy as at least one of their reasons for changing or discontinuing treatment. Other studies suggest that interferon β does result in improved quality of life during the early period of treatment [21–23].

Despite its limitations, this study provides data on a subgroup of MS patients that are distinctly different from the cohorts on which these immunomodulating therapies were originally tested in randomized, controlled clinical trials. The veterans group is predominantly male, older, and more disabled at baseline than the participants in the Betaseron® pivotal phase III trial. The veteran cohort has characteristics that are more commonly associated with progressive MS than with RRMS. Changes in relapse rate were not an outcome measure for this study, so statements regarding the efficacy of therapy in this cohort compared with other reported cohorts cannot be made.

The use of a generic HRQOL scale, the VSF-36, in this study for determining whether a treatment for MS is effective raises several issues. Since the VSF-36 failed to show consistent changes over time, except in the one domain of physical function, the scale may lack sensitivity for longitudinal MS studies of a duration that is typical for MS clinical trials. This lack of sensitivity may be due to smaller sample sizes at follow-up and inadequate power for detecting significant change in the cohort data. The survivors might be apt to show no change or diminished worsening over time because of a cohort effect.

*Consortium of MS Centers. North American Research Committee on Multiple Sclerosis (NARCOMS) Project. Barrow Neurological Institute; Phoenix, Arizona.

Differing opinions exist on whether HRQOL assessments in MS might be made more sensitive by a disease-specific, rather than generic, rating scale [24–28]. This study was not specifically designed to answer that question. However, the VSF-36 was strongly correlated with the EDSS, which is an MS-specific scale, in the physical function domain. This demonstrates that the VSF-36 is a reliable indicator of physical impairment and disability in persons with MS. Other VSF-36 domains were not strongly correlated with physical disability as measured by EDSS scores, which indicates that the VSF-36 measures other aspects of disability that are not directly related to motor function, such as energy and vitality, social interaction, and emotional and mental health. The EDSS measurement is heavily weighted toward ambulation and is insensitive to pain, fatigue, mental health, and cognitive dysfunction, which are often the major sources of disability for persons with MS.

In this MS veterans cohort, VSF-36 domain scores generally worsened with increasing disability (**Tables 3–4**); however, even at mild levels of disability, when ambulation was normal, low scores were observed in several domains, including vitality. Many of these domain scores show significant decreases at the transition from EDSS scores that indicate mild-to-moderate disability, where ambulation was still independent, albeit restricted. Changes noted on the VSF-36 for subjects with minimal disability suggest that the EDSS does not adequately capture the full range of disabling symptoms, since it is primarily a measure of gait. This confirms what is commonly observed in clinical practice (i.e., that patients may report significant limitations in daily function despite a relatively normal neurological examination) and suggests that therapeutic interventions need to be started early in the disease course to have a meaningful impact on disability and impairment.

In summary, this study suggests that while a HRQOL instrument, such as the VSF-36, might provide meaningful data on health-related function as an adjunct to more traditional outcome measurements, more clarification as to the sensitivity of the instrument to specific clinical end points and the relative value of disease-specific versus generic instruments is required for demonstration of its usefulness in health outcomes assessment in MS.

CONCLUSION

In summary, this study validates the use of the VSF-36 as an outcome measure for assessing health-related functional status of veterans with MS on DMAs and shows that it has good agreement with standard neurological measures. In a cohort of patients in a nonrandomized study, who differed significantly from MS subjects who were enrolled in pivotal clinical trials of these drugs, no definite effect on quality of life or neurological function was observed. The high rate of switching or discontinuation of therapy implies that studies of therapies in targeted cohorts may be beneficial, and patient-reported outcome measures might have validity in assessing these cohorts.

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