

SHORT REPORT

The effect of immunomodulatory treatment on multiple sclerosis fatigue

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Objective: To assess the effects of glatiramer acetate and β interferon on fatigue in multiple sclerosis.

Methods: Fatigue was measured at baseline and six months using the fatigue impact scale (FIS). Groups (glatiramer acetate and β interferon) were evaluated for the proportion improved, using Fisher's exact test. Logistic regression analysis assessed the relation between treatment group and improvement and controlled for confounding variables.

Results: Six month paired FIS assessments were available for 218 patients (76% female). Ages ranged between 19 and 61 years, with 86% having relapsing-remitting disease. Glatiramer acetate was used by 61% and β interferon by 39%. At baseline, total FIS and subscale scores were comparable in the two groups. More patients improved on glatiramer acetate than on β interferon on total FIS (24.8% v 12.9%, $p=0.033$; adjusted odds ratio=2.36, 95% confidence interval 1.03 to 5.42), and on physical (28.6% v 14.1%, $p=0.013$) and cognitive subscales (21.1% v 10.6%, $p=0.045$). Logistic regression analysis confirmed the association between glatiramer acetate use and improved fatigue, after accounting for baseline group differences.

Conclusions: The odds of reduced multiple sclerosis fatigue were around twice as great with glatiramer acetate treatment as with β interferon. Confirmation of this result is required.

Fatigue is a debilitating symptom that affects the lives of people with multiple sclerosis.^{1–8} Its underlying cause is unknown and current treatments are only modestly effective.^{9–10} Fatigue is often worse during attacks of the disease, when there is active CNS inflammation. We hypothesise that if reduced inflammation is associated with improved fatigue, fatigue may represent a marker of disease activity or an indicator of response to treatment. Even if this association cannot be demonstrated, a reduction in fatigue would be a treatment benefit. Our aim in this study was to determine the impact of immunomodulatory treatment on fatigue over the first six months of treatment, as measured by the fatigue impact scale (FIS).¹¹

METHODS

Population and study design

The Calgary MS Clinic provides population based multidisciplinary care to over 4000 people with multiple sclerosis. In December 1998, the cost of immunomodulating treatment was covered for patients with active relapsing-remitting multiple sclerosis (RRMS). Since January 1999, all treated patients have been asked to participate in a dynamic cohort study, approved by the University of Calgary research ethics board, to evaluate treatment outcomes. Randomisation was

not practical, as many patients had strong ideas about what they would consider acceptable. Treatment choice was usually made by patients after education about all treatments from an MS nurse. Information regarding short term efficacy, dosing frequency, side effects, β interferon dose, and the limited understanding of the relation between magnetic resonance imaging outcomes and long term treatment benefit^{12–15} were provided. Dose escalation over six weeks, along with acetaminophen or ibuprofen for flu-like symptoms, were recommended for β interferon treated patients.

The study cohort consisted of all consenting patients with baseline and six month FIS data available before 30 September 2000. Review of the clinical records confirmed the questionnaire data and detected patients initiating other potential fatigue modulating treatments^{9–10} during the study period.

Outcomes

Demographics, disease features, treatment variables, and fatigue scores were collected at baseline and six months for patients starting their first treatment. Fatigue was measured using the FIS¹¹—a validated scale that differentiates fatigued from non-fatigued populations and detects a treatment effect in people with multiple sclerosis.^{16–18} This 40 item questionnaire comprises three subscales measuring the impact of fatigue on three domains of function: physical, social, and cognitive. Patients rate the impact of their fatigue on a range of daily activities, employing a rating scale from 0 (no problem) to 4 (extreme problem). Total score ranges from 0 to 160, with a higher score indicating a greater fatigue impact.

Data analyses

Data were analysed using computerised statistical software (Stata version 6, Stata Corporation, College Station, Texas, USA). Baseline FIS scores (total and subscale) were square root transformed to fit a normal distribution (possible range 0 to 12.65). Binary variables for age (<41 or \geq 41), sex, extended disability status scale (EDSS) (\leq 3.0 or $>$ 3.0), and disease course (relapsing-remitting or progressive) were defined. Each was evaluated independently for its association with baseline FIS score. Age and EDSS groups were defined by median age and EDSS. FIS change scores, representing change from baseline to six months, were generated by subtracting the six month score from the baseline score. Improvement was predefined as an increase of greater than 1 SD. Worsening was defined as a decrease of greater than 1 SD. No change was defined as any change of 1 SD or less. A binary variable was generated by combining the groups that were unchanged or worse. The proportion of patients within

Abbreviations: EDSS, extended disability status scale; FIS, fatigue impact scale; RRMS, relapsing-remitting multiple sclerosis

each treatment group that improved on each scale or subscale was determined.

Student's *t* tests were used to compare group means when necessary assumptions were met. In other instances, the Wilcoxon rank sum test was used. Proportions were compared using the χ^2 test. Given the non-randomised study design, logistic regression analyses further evaluated the relations between predictive variables and improvement, and provided a means of controlling for potential confounding variables. Predictive variables included in the model were: treatment group (β interferon or glatiramer acetate), age, sex, EDSS scores, disease course, and disease duration. The data were evaluated for interactions and confounding. In all cases, two sided α was set at 0.05.

RESULTS

The study population included 218 patients. Ages ranged between 19 and 61 years (mean (SD), 40 (9.1) years), 76% were female, and 86% had a relapsing-remitting course. The demographic and disease characteristics of the study population were consistent with those of the treated population in our clinic. Sixty one per cent used glatiramer acetate, and 39% used a β interferon (one used interferon beta-1a (Biogen), 24 used interferon beta-1b (Berlex), and 60 used interferon beta-1a (Serono)). Because of the homogeneity of the β interferon treated groups in this study, and the similar biological effects and side effect profiles of the drugs used, the three interferon subgroups were combined to form a single interferon group.

The glatiramer acetate and interferon groups were similar with regard to marital status and education but differed significantly in age, sex, EDSS, and disease course. The interferon group was slightly older (42.8 *v* 38.6 years, $p = 0.004$), contained a smaller proportion of women (68% *v* 80%, $p = 0.040$), had more patients with greater disability (median EDSS, 4.0 *v* 2.5, $p < 0.001$), and had fewer relapsing-remitting patients (81.2% *v* 96.2%, $p < 0.001$). One patient in each treatment group initiated treatment (fluoxetine) that could have affected fatigue scores during the treatment period; both improved. They were not excluded.

Transformed FIS scores (total scores and all subscales) were similar at baseline in the two treatment groups, in men and women, and in relapsing and progressive patients. Mean total transformed FIS scores were 6.89 and 7.07, respectively, in the glatiramer acetate and interferon groups. Total transformed FIS scores were higher at baseline in patients over the age of 40 than in younger patients (7.41 *v* 6.46, $p = 0.005$), and in those with EDSS > 3.0 (7.73 *v* 6.42, $p = 0.001$). In all cases, the subscale scores followed the same pattern as the total FIS scores but significant differences were never detected at baseline on the cognitive subscale. The same patterns were evident when progressive patients were excluded from the analysis (data not shown).

A greater proportion of glatiramer acetate treated than interferon treated patients improved over the first six months of treatment on the total FIS (24.8% *v* 12.9%, $p = 0.033$) and on all subscales (table 1). The difference, however, was not statistically significant on the social subscale. The treatment benefit was similar when progressive patients ($n = 22$) were excluded. No more than 8% of patients worsened on any scale, and there were no treatment group differences.

Logistic regression also indicated that subjects treated with glatiramer acetate were more likely to have improved total FIS scores (crude odds ratio = 2.22; $p = 0.036$; 95% confidence interval (CI), 1.05 to 4.68). The relation between drug exposure and improved FIS scores remained statistically significant after simultaneous adjustment for the other variables (adjusted odds ratio = 2.36; $p = 0.042$; 95% CI, 1.03 to 5.42). None of the other variables was a predictor of

Table 1 Proportion of patients who improved by more than 1 SD

	All patients (n = 218)	RRMS only (n = 196)
Total FIS		
GA	24.8	25.2
IFN	12.9	13.0
	$p = 0.033$	$p = 0.046$
Physical subscale		
GA	28.6	29.1
IFN	14.1	14.5
	$p = 0.013$	$p = 0.022$
Cognitive subscale		
GA	21.1	20.5
IFN	10.6	11.6
	$p = 0.045$	$p = 0.117$
Social subscale		
GA	18.9	19.7
IFN	14.1	15.9
	$p = 0.369$	$p = 0.518$

Proportions compared using χ^2 tests.
FIS, fatigue impact scale; GA, glatiramer acetate; IFN, β interferon;
RRMS, relapsing-remitting multiple sclerosis.

improvement or an effect modifier of the relation between treatment and fatigue.

DISCUSSION

This study provides evidence that multiple sclerosis fatigue may be improved with immune modulating treatment, but given its non-randomised design it does not prove that glatiramer acetate treatment, rather than a feature of the group who chose it, led to better fatigue reduction than β interferon. However, the evidence favouring a treatment effect of glatiramer acetate is strong. At six months the only significant predictor of improved fatigue was treatment with glatiramer acetate. Also, logistic regression analysis showed that factors that varied between the two treatment groups had no effect on the chance of improved fatigue or on the relation between treatment group and improved fatigue.

Interpretation of data from patient based scales is a contentious issue. While the FIS can detect differences between fatigued and non-fatigued patients and can detect a treatment effect,^{11 16-18} it is unknown how much change is clinically significant. We chose 1 SD as the cut off because this is a commonly used limit in psychometrics and because a higher cut off (2 SD) would probably detect only extreme cases, while a lower cut off would probably overestimate the proportion of truly improved patients. Further research is necessary to determine the minimum amount of FIS improvement that represents a clinically meaningful change. Lack of an effect on the psychosocial aspects of fatigue may reflect the short duration of observation. Reduced fatigue would probably improve physical and cognitive function before leading to the behavioural response required to improve the psychosocial aspects of fatigue. This needs to be examined in longer term studies.

It is unclear why glatiramer acetate is more likely to improve fatigue than β interferon, given that both reduce CNS inflammation. Interleukin-6 (IL-6), however, should be considered as a possible mediator of multiple sclerosis fatigue. IL-6 concentrations are raised in multiple sclerosis, especially at times of relapse¹⁹ when fatigue is often worse. Treatment with β interferon also increases IL-6, and dose limiting β interferon side effects (fatigue, fever, chills, and headache) are associated with raised IL-6 concentrations.²⁰

Finally, corticosteroids—which decrease IL-6 in normal individuals—decrease IL-6 levels and reduce flu-like symptoms in patients treated with β interferon.²¹ IL-6 concentrations have not been similarly investigated in patients treated with glatiramer acetate.

Improved fatigue is an important treatment benefit for patients with multiple sclerosis. Our study suggests that the chance of this benefit is more than twofold greater with glatiramer acetate treatment than with β interferon treatment. Confirmation of these results and longer term studies are needed to strengthen these findings.

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