Multiple Sclerosis-Associated Fatigue during Disease-Modifying Treatment with Natalizumab, Interferon-Beta and Glatiramer Acetate

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Dear Sir,

Fatigue is one of the most common symptoms in multiple sclerosis (MS) and can result in severe impairment of quality of life [1]. Fatigue is likely multidimensional but subtle central inflammatory activity may play a role [2]. Disease modifying treatment with interferon- β (IFN) and glatiramer acetate (GA) successfully reduces inflammatory disease activity but does not appear to reduce levels of fatigue [3]. Natalizumab (NTZ) – a monoclonal antibody against Very-Late-Activation-Antigen 4 – reduces leukocyte migration across the blood-brain barrier and thereby unfolds strong effects on central inflammation (i.e. contrast enhancing lesions or new lesions on MRI) [4]. The objective of this study was to compare prevalence and severity of MS-associated fatigue in patients treated with NTZ in comparison to IFN and GA.

This was a cross-sectional case control study. Forty-nine consecutive patients treated with NTZ (all patients treated at our center at the time of study) were compared to 320 MS patients in our database who have been investigated for fatigue before NTZ was licensed. Fifty-three patients met the inclusion criteria (relapsing patients treated with IFN or GA) and were matched for age, gender and disability ($n = 31$ (58.5%) treated with IFN, $n = 22$ (41.5%) treated with GA). The study was conducted

in accordance with requirements of the local Ethics committee. Fatigue was measured with the Modified Fatigue Impact Scale (MFIS) [5] and the Fatigue Severity Scale (FSS) [6]. Mean FSS scores ≥ 5 indicate 'severe fatigue' (FSS ≥ 5) while scores < 4 indicate 'no fatigue' (scores ≥ 4 to < 5 indicate 'borderline fatigue') [7]. The MFIS is a 21-item questionnaire ranging from 0 to 48 (higher scores indicating more fatigue). A cut-off score of 38 discriminates 'severely fatigued' from 'non-fatigued' patients [8]. Means and SDs were used to describe patients' characteristics. Categorical data were compared with the χ^2 test or Fisher's exact test. By means of the Mann-Whitney U test, we compared the nonparametric data. We used logistic regression to investigate the influence of categorical variables on dichotomized (< 4 vs. ≥ 4) FSS scores. All tests have been performed two-sided. $p < 0.05$ was considered statistically significant. Analysis was performed with SPSS 17.0 (Chicago, Ill., USA).

Forty-nine patients were treated with NTZ (mean 37.0 ± 9.9 years, mean disease duration 8.0 ± 4.5 years, 84% females, mean EDSS 2.9 ± 1.2). In the matched control group, 53 patients were treated with IFN/GA (mean age 37.9 ± 8.6 , mean disease duration 8.5 ± 6.4 years, 78% females, mean EDSS 2.6 ± 1.3): $n = 2$ intramuscular IFN- $\beta 1a$ 30 μg once weekly, $n =$

6 s.c. IFN- $\beta 1b$ 250 μg every other day, $n = 11$ s.c. IFN- $\beta 1a$ 22 μg or $n = 13$ IFN- $\beta 1a$ 44 μg three times weekly and $n = 21$ GA 20 mg once daily s.c. Treatment duration was 18.3 ± 8.4 months for NTZ-treated patients and 29.1 ± 15.8 months for IFN/GA. Annualized relapse rate (ARR) was 0.2 in the NTZ group versus 0.5 in the IFN/GA group ($p < 0.001$). Patients were treated before NTZ with: IFN $n = 37$ (75.5%), GA $n = 5$ (10.2%), mitoxantrone $n = 2$ (4.1%), other treatments $n = 2$ (4.1%), no treatment $n = 3$ (6.1%). Mean FSS score was 3.7 ± 1.9 with NTZ versus 4.9 ± 0.8 with IFN/GA ($p = 0.012$) (no differences between IFN and GA). 51% of NTZ patients reported 'no fatigue' versus 13.2% with IFN/GA ($p < 0.001$). Prevalence of severe fatigue was 34.7% in the NTZ group compared to 51% for IFN/GA ($p = 0.041$). 'Borderline fatigue' was 14.3% with NTZ and 35.8% for IFN/GA ($p = 0.029$). Mean total MFIS score was 32.6 ± 20.9 with NTZ and IFN/GA with 47.8 ± 13.7 ($p < 0.001$). There was no significant difference between total MFIS GA 45.8 ± 13.1 and IFN 49.7 ± 14.3 . Fewer patients with NTZ suffered from severe fatigue (50 vs. 71%, $p = 0.04$). Fatigue was less on all subscales of the MFIS for NTZ-treated patients (all $p = 0.001$). See figure 1 for detailed information on the subscales of MFIS. Results for fatigue assessed by means of MFIS corre-

Fig. 1. Mean total MFIS and subscale MFIS scores were compared between NTZ and IFN/GA (all $p < 0.001$).

lated with FSS. Age, gender, disease duration, IFN or GA treatment and EDSS had no influence on fatigue levels as measured with FSS or MFIS.

This cross-sectional case-control study revealed that the prevalence and severity of fatigue during NTZ treatment was lower compared to IFN/GA treatment. Levels of fatigue in IFN/GA-treated patients in the database were comparable in the control group. The literature on a potential effect of IFN or GA on levels of fatigue is controversial [9, 3]. Given the marked re-

duction of clinical and MRI parameters for inflammatory activity in comparison to IFN and GA, this effect could be attributable to a more pronounced decrease of inflammatory CNS activity with NTZ. Our results in longer-term NTZ-treated patients complement results from a previous short-term prospective study [10]. Findings for the control group were similar to previous analyses from the same database [3]. Fatigue was independent from most important patient characteristics, which underlines that we examined a

common construct of fatigue [3, 8–10]. A reduction of fatigue during NTZ treatment represents a relevant, additional treatment benefit for improved quality of life. A randomized controlled trial is necessary to confirm our findings but conduction is currently not feasible due to restrictions for NTZ use.

Disclosure Statement

N.P. is an employee of Biogen Idec.

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