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Fatigue evaluation in fingolimod treated patients: An observational study

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ABSTRACT

Background: Fatigue is one of the most disabling symptoms in Multiple Sclerosis (MS) patients and is associated with a low quality of life. Fingolimod (Fg), a sphingosine 1-phosphate receptor modulator, is the first oral MS disease modifying treatment. Little is known about its effect on fatigue. To assess the impact of Fg on fatigue within the first 6 months of treatment in MS patients, we conducted a prospective, open label study, in real life setting.

Methods: Change of Modified Fatigue Impact Scale (MFIS) between Fg treatment start and at 6 months was used as a first outcome. Secondary outcomes were changes of MFIS subscales, Fatigue severity scale (FSS) and Visual Analogic Scale of Fatigue (VAS-F) scores,

Results: 54 completed the study at M6. No significant change was noted in global MFIS (and neither in sub analysis of MFIS), FSS or VAS-F at M6. Patients with high level of fatigue (MFIS or ≥38) had a higher EDSS score than patients with lower level of fatigue (MFIS < 38), (mean 3.3, [SD 1.6] versus 1.6 [SD1.1], p = 0.0002) but showed no significant difference in MFIS evolution at M6. There was no significant statistical difference in fatigue parameters evolution at M6 within patients Nz+ or Nz-.

Conclusion: There is no significant impact of Fg on fatigue after 6 months of treatment.

1. Introduction

Multiple sclerosis (MS) is a chronic dysimmune demyelinating central nervous system disease with various clinical manifestations. Cognitive impairment and fatigue are invisible symptoms that take place in patient's handicap. Fatigue can be one of the most disabling symptoms and is often associated with a low quality of life because of its negative impact on daily work, family life, and social activities (Hadjimichael et al., 2008). Fatigue can affect 50 to more than 75% of MS patients (Tabrizi and Radfar, 2015; Krupp et al., 1988; Fisk et al., 1994). Little is known about its underlying cause. Some studies suggest that the subjective feeling of fatigue is related to inflammation (Hanken et al., 2014) and increased levels of cytokines; others suggest that a dopamine imbalance could be involved (Dobryakova et al., 2015). Factors like sleep disorders, depression, cognitive impairment, chronic infections and adverse effects of medications presumably also contribute to the clinical picture. Several pharmacological and non-pharmacological treatment approaches have been investigated, but evidence regarding their effectiveness is limited (Tur, 2016; Stankoff et al., 2005).

Fingolimod (Fg), acts as a sphingosine 1-phosphate receptor modulator, allowing to selectively retain autoreactive lymphocytes in lymph nodes thereby reducing damaging infiltration into the central nervous system (Groves et al., 2013). It is the first oral disease-modifying treatment approved for relapsing forms of multiple sclerosis (Novartis Pharmaceuticals, 2014; European Medicines Agency, 2014; Kappos et al., 2010; Cohen et al., 2010).

It is well known to have cardiovascular and immunodepletion-related adverse effects but little is known about its effect on fatigue. Contrary to other MS treatments, few studies have been conducted on the impact of Fg on fatigue (Wilken et al., 2013; Putzki et al., 2009). Because of its impact on CNS inflammation with a highly potent action on MS disease evolution and because CNS inflammation is one of the potential causes of fatigue, Fg could have an action on MS-associated fatigue.

Previous works on fatigue, particularly in MS, have used the Modified Fatigue Impact Scale (MFIS), the Fatigue severity scale

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(FSS) and a Visual Analogic Scale of Fatigue (VAS-F). MFIS is a scale able to differentiate MS fatigue from depression and to assess the impact of fatigue on daily life. FSS scale and VAS-F are simple, reliable and rapid tests (Wilken et al., 2013; Putzki et al., 2009; Téllez et al., 2005; Larson, 2013; Krupp et al., 1989; Valko et al., 2008; Whitehead, 2209; Kos et al., 2005; Iaffaldano et al., 2012).

This study aims to investigate, in real life setting, the impact of Fg on fatigue within the first 6 months of treatment in MS patients.

2. Materials and methods

2.1. Study design and patients

This is a prospective bicentric open-label study. MS patients were included consecutively between February 2014 and June 2015 in the Pitié-Salpêtrière MS clinic, France and the Neurology Department of Liège Hospital, Belgium.

Informed consent was obtained from all patients prior to entering the study.

The study included relapsing-remitting (RR) MS patients aged ≥18 years beginning Fg. Patients were either treatment naïve or had been on disease modifying treatment (DMT): interferon β1a and β1b (IFN), glatiramer acetate (GA) and natalizumab (Nz) before Fg switch. To avoid rebound after Nz, a bridging therapy with intravenous methylprednisolone (IVMP) 1 g per month was initiated during the wash-out period. This IVMP regimen was maintained during the first 3 months of Fg due to the action delay of Fg. No bridging therapy was given during the wash-out period of the other drugs. The use of antidepressant or anti fatigue drugs was allowed and was recorded. No specific assessing scale for depression was scheduled during the study.

Patients were asked to complete two fatigue self- report questionnaires and a visual scale.

Modified Fatigue Impact Scale (MFIS) (derived from the original 40-item Fatigue Impact Scale), a self questionnaire, is a 21-item scale with physical (range 0–36), cognitive (range 0–40) and psychosocial items (range 0–8) (Téllez et al., 2005). The maximum score is 84, with higher scores indicating a greater impact on quality of life. MFIS has been widely used as a measure of fatigue in MS patients and is recommended by the American Multiple Sclerosis Council for clinical practice guidelines (Multiple Sclerosis Council, 1998). In this study, patients were divided in two groups at baseline evaluation: patients with low or moderate fatigue (MFIS < 38) and with severe fatigue (MFIS ≥38), the cut-off of 38 for severe fatigue was chosen accordingly to previous published studies (Téllez et al., 2005; Larson, 2013).

Fatigue severity scale (FSS), a self-questionnaire, is a short 9-item scale rated from 1 to 7, higher scores indicating more severity, frequency, and impact of fatigue (Krupp et al., 1989). It has been chosen because it's a simple and practical tool for evaluation of fatigue and it had been validated for clinical and research purposes (Valko et al., 2008; Whitehead, 2209).

Visual Analogic Scale of Fatigue (VAS-F) is a visual scale graded from 0 to 10 with 10 being the worst possible fatigue.

The FSS was implemented 2 months after the start of the study because this simple questionnaire is complementary and is used in fatigue studies.

MFIS, FSS and the VAS-F were delivered by a neurologist at the initiation of treatment (M0) in the day care unit and 6 months later (M6) during an outpatient consultation.

Baseline demographic and disease characteristics including age, gender, disease duration, EDSS score annualized relapse rate in the previous year and then during Fg treatment, therapy prior to enrollment and reason of switch to Fg, as well as anti-fatigue such amantadine or antidepressant, either selective or non-selective serotonin reuptake inhibitors, concomitant treatments were summarized using descriptive statistics. All patients had a brain MRI no more than 3 months prior to and after 6 months of Fg treatment onset and data (number of new T2 or gadolinium-enhancing lesions) were recorded.

Change in the MFIS score between M0 and M6 was chosen as the primary outcome to assess the impact of fatigue on functioning or quality of life. MFIS covers wider aspects (cognitive and physical) than FSS and can be more representative than FSS for patients with higher levels of fatigue (Antmann et al., 2012).

Secondary endpoints included the change in 1) MFIS sub-scales, FSS and VAS-F scores between M0 and M6, 2) analysis of subgroups of patients with patients with MFIS < or ≥38 and 3) because of possible Nz rebound effect, another sub-analysis was done among patients previously treated by Nz (Nz+) or not (Nz-).

2.2. Statistical analysis

First the general characteristics of the sample at baseline and at M6 were summarized in term of percentage and number for categorical variables and in terms of mean and standard deviation for continuous variables. Mean fatigue scale scores were calculated for the whole sample. Changes between baseline and M6 were compared with Chi^2 for categorical variables and t-test for continuous variables.

Analysis was then performed in subgroups: patients with MFIS < or ≥38 at baseline and according to use of NZ prior to Fg.

2.3. Analytical sample

Overall, 74 patients were included. Among them, 54 completed the study at M6. Two interrupted the treatment because of inefficiency (n=1) or contraindication due to brain surgery (n=1), 3 moved to another country and 15 did not complete the questionnaires at M6. There was no significant difference in the clinical characteristics between the 74 and the 54 patients and thus detailed analysis was only calculated for the 54 patients that completed the study.

3. Results

3.1. Patients' overall characteristics

Clinical characteristics of the 54 patients are shown in Table 1.

MFIS, which was the primary endpoint, was available at M0 and M6 for all 54 patients; FSS was available for 33 patients at M0 and 37 patients at M6, and VAS-F available for 54 patients at M0 and 52 at M6. Mean age was 35.1 (standard deviation=9.3) years old with a majority of women (78%). Mean disease duration was 9.9 (6.5) years and mean annualized relapse rate was of 1 (1) during the year preceding Fg onset. At least, one Gd-enhancing lesion was observed in 47.8% of patients on the baseline brain MRI. Fg was introduced as first treatment in 5 patients, as a switch from Nz in 40.4% (n=21) of patients, from IFN in 34.6% (n=18) and from GA in 15.4% (n=8). Reasons for switching were inefficacy in 55% of patients. Among the patients previously treated by Nz, 90% stopped Nz because of PML risk. The wash-out period between Nz and Fg was 3–4 months in 10 patients, 1–2 months in 10 patients and 17 months in one patient.

Among the 54 patients, 19.5% (n=8) were treated by anti-depressant drugs prior to Fg introduction, and 2 started anti-depressants during the 6 months follow-up.

At M6, 23% (11/48) of patients had at least one relapse during the 6 month follow-up (Table 2), among them 7 were switched from Nz. New T2 lesions and Gd enhancing lesions were respectively observed in 23.2% and 24.4%. No significant change in EDSS score was noted between M0 and M6.

3.2. Fatigue within 6 months after Fg Start

Concerning fatigue evaluation, no significant change was noted in global MFIS (and neither in any sub scales of MFIS), FSS or VAS-F (Table 3).