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Journal of the Neurological Sciences 413 (2020) 116739

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Evaluation of emotional disorders before and during treatment with interferon beta in patients with multiple sclerosis

Jean-Christophe Ouallet[a,*], Françoise Radat[a], Alain Creange[b], Mohamed Abdellaoui[b], Olivier Heinzlef[c], Claire Giannesini[d], Patrick Hautecoeur[e], Delphine Lamargue Hamel[a], Mathilde Deloire[a], Bruno Brochet[a,f], Anne-Sophie Jean Deleglise[g], Philippe Lehert[h,i]

[a] Service de Neurologie, Centre Hospitalier Universitaire (CHU) de Bordeaux, Bordeaux, France
[b] Service de Neurologie, Groupe Hospitalier Henri Mondor, APHP, Université Paris Est-Créteil, Creteil, France
[c] Service de Neurologie, Centre Hospitalier de Poissy, Poissy, France
[d] Service de Neurologie, Centre Hospitalier Universitaire St Antoine, APHP, Paris, France
[e] Service de Neurologie, Université Catholique de Lille, Lomme, France
[f] NeuroCentre Magendie, INSERM U862, University of Bordeaux, Bordeaux, France
[g] MerckSerono, Lyon, France
[h] Faculty of Economics, Louvain University, Belgium
[i] Faculty of Medicine, University of Melbourne, Australia

ARTICLE INFO

Keywords:
Interferons
Emotions
Affective symptoms
Depression
Multiple sclerosis

ABSTRACT

Background: Domains encompassing emotional disorders in relapsing-remitting MS (RRMS) patients are still unclear.

Methods: We performed a 24-month, multicenter, single-arm, prospective study. RRMS patients started IFN-β treatment at baseline. The primary endpoint was lack of emotional control, measured using the "Echelle d'HumeurDépressive" (EHD) scale three times at baseline and at 10 post-treatment visits. Secondary endpoints were emotional blunting, irritability, fatigue, depression and anxiety. A linear mixed covariance model assessed change from baseline on an intention-to-treat basis, under the assumption of no mood disorder effect (one-sided 97.5% level), in which autoregressive type of autocorrelation was tested.

Results: Out of 79 recruited patients, 70 were analyzed: 80% female; mean (SD) age, 37.0 (11.5) years. Mean (SD) lack of emotional control score at baseline and Month 24 was 12.7 (4.4) and 12.6 (5.5), respectively, versus 10.1 (3.2) in a healthy control population matched for age and sex. Stepwise analysis identified younger age, male sex and antidepressant use as significant predictors of higher lack of emotional control values.

Conclusions: Based on 24 months of prospective follow-up, the results of this study highlights a broad spectrum of emotional disorders in the MS population at the time of disease modifying drugs initiation but no major IFN-β-related emotional disorders (mood dyscontrol, anxiety, depression) were observed. However, sporadic occurrences of severe mood disorders and suicidality cannot be excluded.

1. Introduction

Multiple sclerosis (MS) is a chronic, inflammatory disease that affects both the grey and white matter of the central nervous system (CNS) [1]. Depression is a commonly observed psychiatric symptom in MS [2,3], with an estimated 12-month prevalence of 26% versus 9% among healthy people or patients with other neurological diseases [4]. Several hypotheses have been proposed to explain the origins of depression in MS [5–7], which often manifests in a sub-syndromic manner as emotional instability, including sad mood, irritability and anger [8]. Mood sub-components however have not well been evaluated, especially the lack of emotional control.

Interferon-beta (IFN-β) is a well-established immunomodulating treatment for relapsing-remitting MS (RRMS) that reduces disease activity and progression [9]. While IFN-β is generally well tolerated, with reported adverse events (AEs) including flu-like symptoms (FLS), fatigue and mood changes, in European IFN-β summary product characteristics, it is contraindicated in patients with current severe depression [10]. IFN-β has been associated with depressive symptoms [11,12], and data obtained from administrative claims showed an

* Corresponding author at: Service de Neurologie, Centre Hospitalier Universitaire Pellegrin, Place Raba Leon, 33076 Bordeaux, France.
E-mail address: jean-christophe.ouallet@chu-bordeaux.fr (J.-C. Ouallet).

https://doi.org/10.1016/j.jns.2020.116739
Received 11 June 2019; Received in revised form 14 February 2020; Accepted 15 February 2020
Available online 19 February 2020

incidence ratio for depression of 7.75 [13]. However, other studies have failed to show differences in the development of depression between IFN-β and placebo [14,15]. The effect of interferon-beta (IFN-β) drugs on mood disorders in MS patients still remains unclear.

The methodologies of previous studies have several weaknesses. Depression and anxiety have been evaluated without considering other somatic components, such as fatigue [16]. Furthermore, frequently used scales including the Beck Depression Inventory-Fast Screen [17] and the Hospital Anxiety and Depression Scale [18], are useful for detecting major depression but are less sensitive to differentiate the sub-components of mood disorders.

A new sensitive scale (EHD) has been recently validated investigating affective sub-components of mood disorders in MS [19,20], which seems robust to describe different emotional dimensions and to discriminate from confounding factors. This study prospectively investigated emotional disorders at the time of disease modifying drug initiation and the correlation between IFN-β and the occurrence of emotional changes in RRMS patients using this recent validated scale with categorical assessment that test for specific sub-components of emotional factors.

2. Methods

2.1. Study design

We conducted a single-arm, prospective, multicenter study (Clinicaltrials.gov: NCT01201343, registered retrospectively after study had been completed on September 14, 2010) in RRMS patients who initiated subcutaneous or intramuscular IFN-β-1a, or subcutaneous IFN-β-1b, at baseline and were followed for 2 years. The study was approved by the Ethical Committee of the Hospital Centre of Bordeaux, and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice.

2.2. Patients

Patients were required to be ≥18 years old with MS, have had clinically definite MS and IFN-β indication as described in the European Medicines Agency summary of product characteristics and be eligible for IFN-β as determined by the neurologist. Exclusion criteria were secondary-progressive MS without relapse, on-going acute relapse, pregnancy, previous allergy to IFN-β, current episode of severe depression (in the neurologist investigator opinion) or suicidal thoughts, decompensated liver failure, interruption of IFN-β within 3 months prior to study initiation or corticosteroid treatment during the last 15 days. Patients were recruited from neurologist self-selection during regular outpatient consultations in the MS centers where the data were collected. All participants provided written, informed consent.

2.3. Assessments

The study included 13 neuropsychological and three neurological evaluations (Fig. 1). Three neuropsychological evaluations were performed before IFN-β initiation (Day [D] -15, D-7 and D0) and the others at Months [M] 1–6, M9, M12, M18 and M24; all performed by experienced investigators psychologists. Three neurological evaluations were performed at D-15, M12 and M24. Concomitant medication received during study was left to the investigator and recorded. In case of a Centre for Epidemiologic Studies Depression scale (CES-D) score > 17, the neurologist was informed and an antidepressant could be prescribed depending on his decision.

Lack of emotional control (EHD-EC) and emotional blunting (EHD-EB) were assessed using the self-filled depressive mood scale Echelle d'HumeurDépressive (EHD), an instrument validated in French MS patients, comprising 11 Likert-type, 5-level categorical items and two sum-scores [19,20]. Additional assessments included measures of anxiety, irritability, depression [21] and fatigue, assessed using the instruments summarized in Table S1, and socio-demographic data, medical and disease history. Assessment of safety included AEs and serious AEs (SAEs).

2.4. Statistical analysis

Analysis was performed in the intention-to-treat (ITT) population (all patients who received ≥1 IFN-β dose and had ≥1 evaluation of the primary endpoint pre- and post-baseline). The primary endpoint was the mean change in lack of emotional control from baseline. Secondary endpoints assessed the change in other scales from baseline (Table S1). Baseline score was the mean of the available scores at D-15, D-7 and D0; fatigue and EDSS scores corresponded with the D0 and D-15 evaluations, respectively.

For each endpoint, a non-inferiority test assessed whether the mean change from baseline constantly remained lower than a pre-specified Maximum Tolerable Limit (MTL). Unfortunately no one of these scales (except CES-D) did provide such value that should normally have been identified in previous external validations of these scales. Thus, the MTL had to be conservatively estimated as the lowest value of 30% increase from baseline (corresponding to a minimum significant change) and 50% of the observed standard deviation (SD) of the mean differences (measuring a minimum standardised size effect). For the only scale for which a pre-determined threshold of 17 was existing (CES-D), we checked that the calculated MTL for CES-D was smaller (thus more conservative) than the recommended maximum value. A sample size of 72 was needed to conclude that each scale remains inferior to the previously defined MTL with a power of 0.85 at 97.5% one-sided confidence level.

A supportive covariance analysis featured by a mixed linear model assessed the primary and secondary endpoints using a hypothesized autoregressive autocorrelation. Analyses were adjusted for gender, age, illness duration, elapsed time since diagnosis, initial emotional state and concomitant medication. For patients who withdrew from the study for mood-related reasons, the value that corresponded to the most severe state was attributed during the period after withdrawal. For other missing data not directly related to the primary criterion, the mixed model assumed systematic imputation.

Through a linear model we compared the baseline values found on our MS study sample (EHD, anxiety and fatigue scores) with a reference healthy population (n = 415) described elsewhere [20], by adjusting for age and sex.

For sensitivity purposes, secondary analyses evaluated the number of patients whose EHD-EC and secondary depression (CES-D scale) scores worsened (Score > MTL), improved (score < −MTL), or remained stable (−MTL < score < MTL). Statistical analyses were performed using SAS v9.2 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Patients

Eighty patients were recruited from five centers and 79 entered the study (*Start of Study was January 2005 and completion July 2010)*; 70 were included in the ITT population (Fig. 2). Sixteen patients prematurely withdrew from the study (three before or on the day of IFN-β initiation and 13 after D0) due to AEs (n = 4), patient's decision (n = 3), lack of treatment efficacy (n = 2), AEs and patient's decision, AEs and other reasons, patient's decision and lost to follow-up, lost to follow-up, patient wrongly included (each n = 1), and other reasons (n = 2). Baseline characteristics of the ITT population (mean [SD] age, 37.0 [11.5] years; 80% female) are summarized in Table 1.

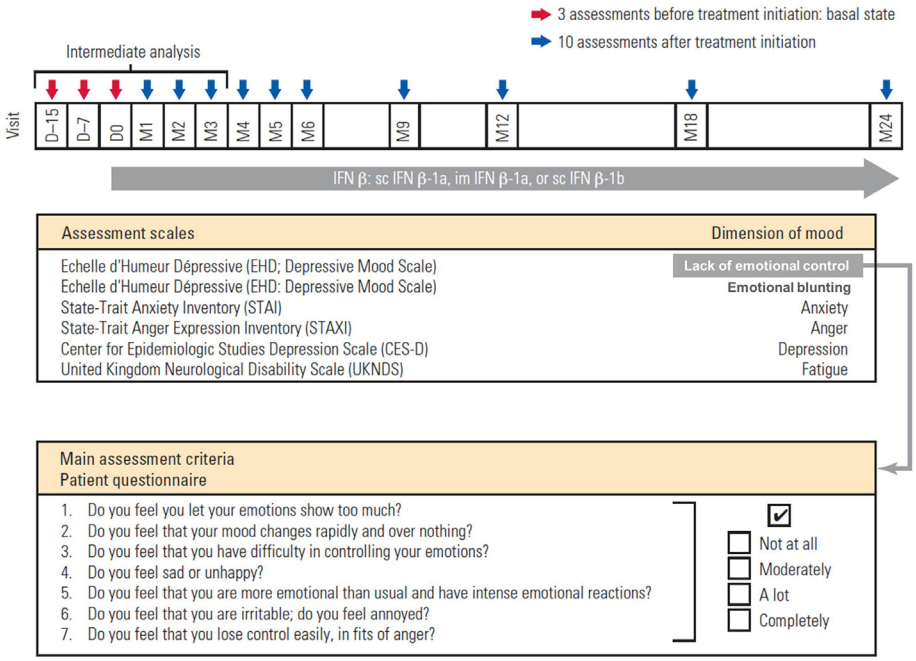

Fig. 1. Design of neuropsychological assessments in the intention-to-treat population. D, day; IFN, interferon; im, intramuscular; M, month; sc, subcutaneous.

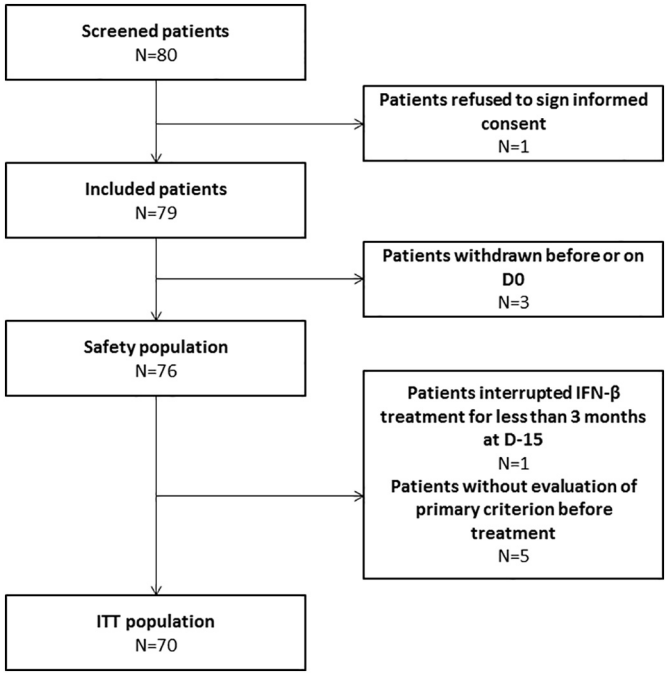

Fig. 2. Disposition of patients. ITT, intention to treat.

3.2. Effects of IFN-β on emotional measures

For all study endpoints, the one-sided 97.5% upper limit of the linear effect in time never exceeded the MTL ($p < .025$ for all tests; Table 2 and Fig. 3). The maximum value was observed for fatigue at Visit 7 ($p = .049$). These results were confirmed by separate unadjusted paired *t*-tests. Only fatigue, which may be a symptom of depression but also related to IFN-β FLS, was mildly increased at different time points during this study (M1, M2 and M6).

For the final mean change of EHD-EC at 24 months, six patients worsened, nine improved and 55 remained stable. For the final mean change of CES-D at 24 months, 12 patients worsened, 14 improved and 44 remained stable. Based on absolute thresholds of the EHD-EC, seven patients worsened, five improved and 58 remained stable; for CES-D, six, six and 58 patients worsened, improved and remained stable, respectively.

Table 1
Baseline patient characteristics (intention-to-treat population).

Characteristic	Patients ($n = 70$)
Age, years	37.0 (11.5)
Female, n (%)	56 (80.0)
Time since diagnosis, years	4.8 (7.7)
Relapses within previous 2 years	2.4 (0.7)
Annualised relapse rate	1.2 (0.3)
Time since last relapse, months	4.2 (3.5)
Expanded Disability Status Scale score	2.06 (1.43)
History of major depressive episode, n (%)[a]	21 (30)
Current[b]	5 (26.3)
Previous[b]	14 (73.7)
Previous mood-stabilizers or antidepressants prescribed, n (%)	
Yes	20 (28.6)
No	50 (71.4)

Values are mean (standard deviation) unless otherwise stated.
[a] Assessed using the Mini International Neuropsychiatric Review at 15 days prior to baseline.
[b] Data missing for two patients.

3.3. Mixed model analysis for effects of time

In the mixed model analysis, baseline covariates significantly associated with a lower final EHD-EC score were lower EHD-EC baseline value (−0.34/unit; 95% CI -0.5, −0.19; $p < .001$), older age (−0.07/year; 95% CI −0.14, −0.01; $p = .029$) and female gender (−1.8; 95% CI -2.8, 0.49; $p = .07$). A higher final (i.e., worse) EHD-EC score was significantly associated with time since diagnosis (0.107/5 years; 95% CI 0.004, 0.21; $p = .043$) and regular use of antidepressants or mood stabilizers (+3.01; 95% CI 1.15, 5.25; $p = .003$). Prior Major Depressive Episodes investigated using the MINI questionnaire, familial mood disorders and neuroticism did not significantly predict the change in lack of emotional control. However, the NEO PI-R was strongly

Table 2
Primary and secondary endpoints.

Endpoints	Range	Baseline	M24	*p*-Value	Mean difference	Adjusted effect	Month	UL	MTL
Lack of emotional control	1–28	12.7 ± 4.4	12.6 ± 5.5	0.007	-0.14 (−1.16, 0.96)	0.26 (−0.96, 1.18)	1	1.07	2.25
Emotional blunting	1–16	5.6 ± 1.6	5.3 ± 1.9	0.010	−0.31 (−0.3, 0.3)	−0.38 (−0.87, 0.09)	1	0.73	0.85
Anxiety	1–80	35.9 ± 11.8	34.4 ± 13.5	< 0.001	−1.45 (−1.7, 0.8)	−1.27 (3.59, 1.03)	1	3.66	5.45
Anger	0–60	16.8 ± 4.1	17.6 ± 6	0.017	0.84 (−0.49, 2.09)	0.75 (−0.47, 1.97)	6	2.19	2.2
Fatigue	0–5	2.1 ± 1.7	2.0 ± 1.7	0.002	−0.16 (−0.59, 0.39)	−0.41 (−0.71, −0.11)	6	0.90	0.93
Depression	0–60	13.5 ± 11.1	13.5 ± 12.3	< 0.001	0.1 (−2.28, 2.48)	−0.22 (−2.19, 1.73)	12	3.94	4.05
Mood Lability	0–10	1.8 ± 0.8	1.9 ± 1.0	< 0.001	0.03 (−0.23, 0.26)	−0.09 (−0.29, 0.22)	1	0.65	0.85
Irritability	0–19	1.9 ± 0.7	2.0 ± 1.0	< 0.001	0.11 (−0.13, 0.34)	−0.03 (−0.16, 0.27)	12	0.71	0.81
Disability	0–7	2.1 ± 1.4	2.0 ± 1.6						

Baseline and Final (M24) values are mean (standard deviation); p-value of the null hypothesis that the score exceed MTL. Mean difference: M24-Baseline (mean [95% CI]); Month column indicates when the largest value was observed. MTL, Maximum Tolerable Limit; UL, largest 95% upper limit of the difference over all the visits.

correlated with baseline values of EHD-EC, State-Trait Anxiety Inventory (STAI), CES-D and EHD-EB with strong mediation along NEO PIR (coefficient correlation $r = 0.61$ for lack of emotional control).

Comparison of baseline values adjusted for age and sex with healthy controls showed significant differences for EHD-EC, EHD-EB, EHD total score, STAI and fatigue (Table 3 and Table S2).

3.4. Adverse events/tolerability

Among the 183 AEs reported, MS relapse (40 events) and FLS (18 events) were most frequent. Thirteen SAEs occurred in nine patients: depression (three events), lung disorder, sudden hearing loss, abortion, anxiety, aggressiveness, headache, neck injury, pleurisy, benzodiazepine dependence and suicide attempt (one event each). Of these, two events (depression and benzodiazepine dependence) were considered by the treating neurologist possibly related to study treatment. This patient had 2 SAEs, depression and dependence on benzodiazepines with a duration of 17 days. Both events were of severe intensity, not intermittent and possibly related to the study treatment. The patient withdrew from the study and the episodes resolved. Another patient had 2 SAEs: aggressiveness and a suicide attempt The events were of severe intensity, not intermittent and probably in relation to the study treatment, which was permanently interrupted. The events resolved. No deaths occurred during the study. Among the AEs that led to permanent discontinuation, four were considered likely related to IFN-β (FLS, depression, suicide attempt and hepatitis).

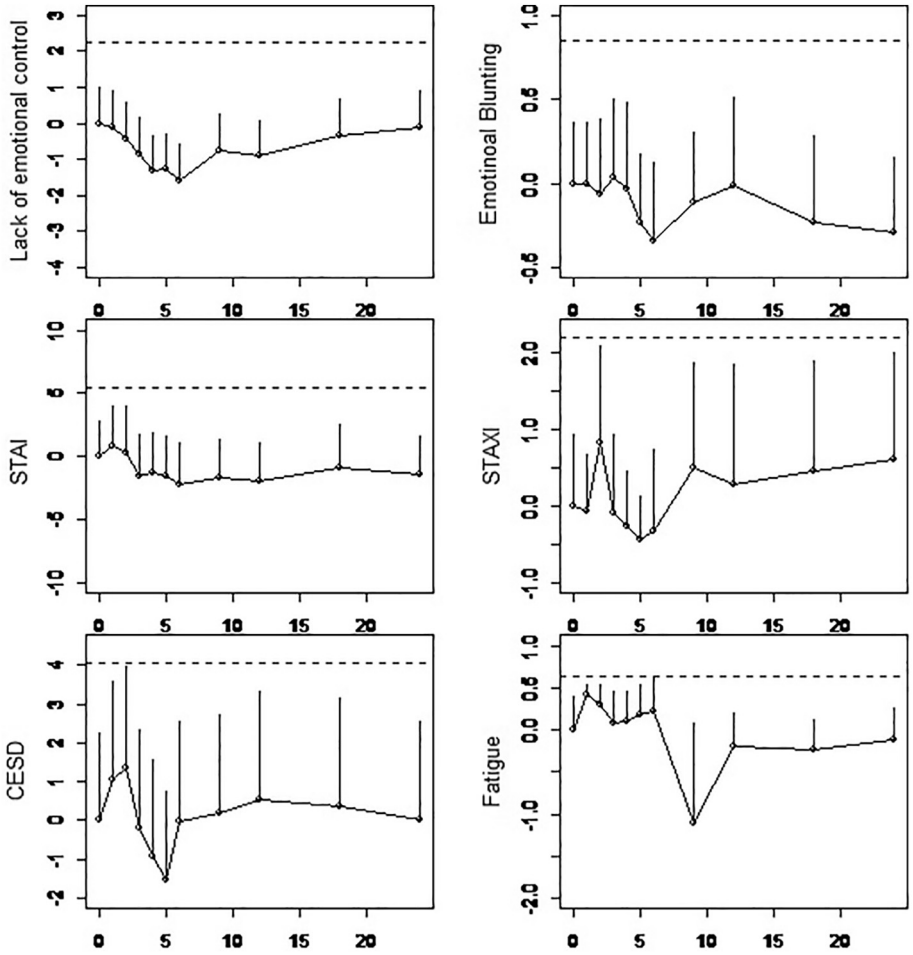

Fig. 3. Mean change in time (X axis in months) compared with baseline for each endpoint. For each endpoint, the horizontal dashed line represents the maximum tolerable limit.

Table 3
Mood endpoints in RRMS patients compared with a reference sample of 415 healthy controls (linear model adjusted for age and sex).

	EHD-EC score			EHD-EB score			Total EHD score			Anxiety (STAI score)			Fatigue (UKNDS score)		
	Value	95% CI	*p*	Value	95% CI	*p*	Value	95% CI	*p*	Value	95% CI	*p*	Value	95% CI	*p*
Intercept	10.1	9.1, 11.239	< 0.001	5.4	5.021, 5.931	< 0.001	15.667	14.413, 16.921	< 0.001	28.491	25.835, 31.146	< 0.001	0.441	0.175, 0.707	0.001
Type	+1.9	1.0, 2.923	< 0.001	+0.54	0.138, 0.953	0.009	+2.530	1.406, 3.653	< 0.001	+5.475	3.012, 7.937	< 0.001	+1.653	1.406, 1.901	< 0.001
Age	−0.004	−0.025, 0.017	0.706	−0.003	−0.012, 0.006	0.494	−0.007	−0.03, 0.018	0.573	+0.006	−0.047, 0.060	0.823	−0.005	−0.01, 0.001	0.085
Gender	+1.3	0.730, 2.045	< 0.001	−0.097	−0.382, 0.189	0.507	+1.290	0.504, 2.077	0.001	+1.978	0.311, 3.645	0.020	+0.248	0.081, 0.415	0.004

Linear model conducted on baseline values (dependent variables). The studied effects (independent covariates) were MS effect (binary variable coded 1 = our study sample and 0 = the healthy control group), age and gender. Intercept: mean healthy control score corresponding to Male patients with age = 30 years; Age effect = effect of age for every incremental year, Female effect: additional female effect.
EHD, Echelle d'HumeurDépressive scale; EHD-EB, EHD emotional blunting sub-score; EHD-EC, EHD lack of emotional control sub-score; CI, confidence interval; RRMS, relapsing-remitting multiple sclerosis; STAI, State-Trait Anxiety Inventory; UKNDS, United Kingdom Neurological Disability Scale.

4. Discussion

This prospective study investigated emotional disorders values in MS patients treated with IFN-β over 2 years. IFN-β did not significantly change major emotional disorder components, such as lack of emotional control, emotional blunting, anxiety and depression. The majority of patients' lack of emotional control and depression scores remained stable, and a similar number of patients either improved or worsened. However, the data confirm the broad spectrum of emotional disorders in RRMS patients compared with healthy controls matched for age and sex. Baseline variables that affected the progression of lack of emotional control included worse baseline value, younger age, longer time since diagnosis, male gender, and regular use of antidepressants and mood stabilizers. The NEO PI-R scale, encompassing neuroticism personality dimensions, predicted the baseline lack of emotional control, emotional blunting, anxiety and depression in MS patients, with strong correlations between the different mood scales. Despite little effect of IFN-β on mood disorders, 30% of the ITT population reported a major depressive episode that lasted for ≥2 weeks either in the past (73.7%) or at the time of evaluation (26.3%), which is higher than that usually reported [3,4] and in the general population [4,22]. 2 patients stopped interferon treatment related to depression for one patient and suicide attempt for the other.

Evidence for whether IFN-β triggers or exacerbates depression or mood disorders in MS is inconclusive to date. IFN-β has been suggested to induce depressive symptomatology, but this was reported without formal assessment using appropriate scales [11,23]. The Controlled High-Risk Subjects Avonex Multiple Sclerosis Prevention Study [23] reported a higher rate of depression among 193 IFN-β-treated patients (20%) versus 190 placebo controls (13%). However, this was not confirmed in the European Study investigating IFN-β-1b in 718 secondary progressive MS (SPMS) patients, in whom depression was evaluated with the Montgomery-Åsberg Depression Rating Scale [24]. Subsequent studies have also failed to show a depressogenic effect [14,25–30]. In the phase III SPECTRIMS study in SPMS patients [4], there were no differences between IFN-β and placebo groups for CES-D, General Health Questionnaire or Beck Hopelessness Scale scores. In a cohort of 13,000 MS patients followed for 3 years, antidepressants were used at the same frequency for glatiramer acetate- or IFN-β-treated patients [29]. It has also been shown that global psychological functioning [25] and anxiety [26] did not significantly worsen following IFN-β treatment. Another study demonstrated no impact on quality of life (MSQoL-54 scale), depression (Hamilton Depression Rating Scale) and fatigue (Fatigue Impact Scale) following subcutaneous IFN β-1a for 3 years [31]. Indeed, studies have shown that pre-treatment depressed mood was found to be the best predictor of subsequent depression [11,27].

Previous studies investigating a correlation between IFN-β and depression are limited by an absence of reliable data on the emotional state or premorbid risk factors of patients before treatment [16], as single pre-therapy evaluation is inadequate to evaluate the basal state. In the current study, we performed three neuropsychological evaluations prior to treatment initiation to establish a reliable determination of baseline emotional state. The time between baseline and post-treatment evaluations in previous studies is often too long [14,26], as the most common IFN-β-related AEs occur early in treatment when they are more likely to influence patients' emotional condition [32]. Given this observation, the absence of any significant changes in these AEs during the first 3 months of this study is notable. Fatigue, which may be a symptom of depression but also related to IFN-β FLS, was mildly increased at different time points (M1, M2 and M6).

The evaluation of depression and anxiety without considering other somatic signs, such as fatigue, further limits previous studies. It is suggested that a formal measure of depressive symptoms, such as the CES-D, is required to ensure that fatigue and asthenia are not mistaken for depression by subjective evaluations. The EHD scale used in this study to measure lack of emotional control and emotional blunting has been validated in a French population of MS patients [19,20], and encompasses emotional disorders not limited to common global depressive aspects investigated with other scales, enabling identification of subjects who lack major depression but who do have significant emotional disturbances [20]. We also used several other distinct scales with specific categorical assessments, assessment of premorbid risk factors and associated somatic factors, and comparison of the basal emotional state with a reference healthy population matched for age and sex.

The main limitation of this study is the open-label design and absence of a control group. However, a placebo-controlled study investigating IFN-β in a similar patient cohort is not any more feasible ethically, and using an active comparator with unknown psychological effects, such as glatiramer acetate, may introduce bias. We did not assess the impact of adverse life events (such as separation or loss of a job), which may be frequent occurrences during the evolution of MS, and we did not assess bipolarity or suicidal ideation. MS is a very heterogeneous disease with many overlapping symptoms (fatigue, pain among others) usually on a relapsing and remitting basis with many social disturbances. It may be difficult in these conditions to sort a signal to noise on emotional disorders. Nevertheless, the current study has several strengths, most notably that this is the first prospective, real-world, 24-month follow-up of patients that included numerous scheduled assessments before and after IFN-β initiation, and included categorical assessment of mood dimensions that have not been previously well evaluated.

5. Conclusion

No major IFN-β-related emotional disorders (mood dyscontrol, anxiety,depression) were observed in RRMS patients. However, sporadic occurrences of severe mood disorders and suicidality cannot be excluded.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2020.116739.

Role of funding source

This study was planned as an academic study at the University of Bordeaux, France, by the first author and funded by Merck Serono S.A.S, France, a subsidiary of Merck KGaA, Darmstadt, Germany as an unconditional grant. Merck was not involved in the study design, choice of outcome or decision to publish.

Declaration of Competing Interest

Dr. JC Ouallet has received consultancy fees, speaker fees, research grants (non-personal), and honoraria from Novartis, Biogen-Idec, Merck, Bayer Schering, Roche, Almirall, Teva and Genzyme Sanofi.

Pr Brochet has received consultancy fees, speaker fees, research grants (non-personal), or honoraria from Novartis, Biogen-Idec, Merck, Bayer Schering, Roche, Medday, Bayer, Actelion, Teva and Genzyme Sanofi.

Prof. P. Lehert is regularly consulted by the pharmaceutical industry and by Merck, for this study in particular.

Dr. Anne-Sophie Jean Deleglise is an employee of Merck Santé SAS, Lyon, France.

Pr A. Créange received departmental research grants from Biogen-Idec, CSL-Behring, GE Neuro, Novartis, Octapharma and expert testimony from Novartis, CSL Behring, Genzyme.

Acknowledgments

Medical writing support was provided by Shaun Foley, in Science Communications, Chester, UK, and funded by Merck KGaA, Darmstadt, Germany. We thank the experienced investigator psychologists for their contribution to the collection of data. We thank Marianne Payet and Kammy Fehrenbacher (Merck Serono S.A.S) for their help in copy-editing this manuscript.

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