



## Review

Psychiatric side effects of interferon- $\beta$  in multiple sclerosisJ.-L. Goeb<sup>a,\*</sup>, C. Even<sup>b</sup>, G. Nicolas<sup>c</sup>, B. Gohier<sup>d</sup>, F. Dubas<sup>c</sup>, J.B. Garré<sup>d</sup><sup>a</sup> Service de Psychiatrie de l'Enfant et de l'Adolescent, CHRU, 2, avenue Oscar-Lambret, F-59037 Lille, France<sup>b</sup> Clinique des Maladies Mentales et de l'Encéphale, Centre Hospitalier Sainte-Anne, Paris, France<sup>c</sup> Service de Neurologie, CHU, Angers, France<sup>d</sup> Service de Psychiatrie, CHU, Angers, France

Received 19 November 2003; accepted 15 September 2005

**Abstract**

Psychiatric disorders, especially depression, are frequent in patients with multiple sclerosis (MS). They are attributed both to the psychosocial impact of a chronic, usually progressive, disabling illness and to cerebral demyelination. Besides, drugs such as corticosteroids and possibly interferon (IFN) may also have depressogenic effects. Major depressive disorders and/or suicidal ideation are a major concern and efforts to identify and minimize these reactions are of much importance. Psychiatric side effects, particularly depression, are widely reported with IFN- $\alpha$  and have been suspected with IFN- $\beta$  but are not yet fully established. Our review of the literature revealed that most studies discard an association between IFN- $\beta$  and depression or suicide. However, few patients, especially those with a history of depression, might be at higher risk for depression when treated with IFN- $\beta$ . Overall, considering the uncertainty of a link between IFN- $\beta$  and depression and/or suicide, as well as the complete remission of psychiatric complications after IFN discontinuation and/or antidepressant treatment, physicians should closely monitor the psychiatric status of patients, but should not refrain from including them in IFN- $\beta$  treatment programs, even when they have past or present depression.

© 2005 Elsevier SAS. All rights reserved.

*Keywords:* Interferon; Multiple sclerosis; Side effects**1. Introduction**

Psychiatric and particularly affective disorders are frequent in multiple sclerosis (MS) and bear a complex pathogenesis that involves biological and psychosocial factors [16]. In a recent metaanalysis, we showed that the association between MS and depression is frequent and specific, that is not just due to the non specific factors of any chronic disease [14]. Psychiatric side effects of interferon- $\alpha$  (IFN- $\alpha$ ), including symptoms of depression, are widely reported as common adverse events [6,8,17]. But they are still not fully established with IFN- $\beta_{1a}$  and - $\beta_{1b}$ . Since the advent of IFN- $\beta_{1a}$  and - $\beta_{1b}$  treatments in MS, much concern has been raised about potential suicidal and/or depressogenic effects of these treatments.

IFNs are a family of glycoproteins that are naturally secreted in response to viral infection in order to prevent other cells to become infected, a phenomenon referred to as "viral interference". In addition, IFNs also have complex immunomodulatory and antiproliferative properties. Two types of IFNs

have been identified by their functional and molecular characteristics (type I = IFN- $\alpha$  and IFN- $\beta$ ; type II = IFN- $\gamma$ ). IFN- $\alpha$  and IFN- $\beta$  are secreted by lymphocytes and fibroblasts, have similar amino-acid composition, and use the same cell-surface receptor. IFN- $\gamma$  differs from IFN- $\alpha$  and IFN- $\beta$  in its amino-acid composition and cell-surface receptor. IFN- $\alpha$  is widely used for malignancies and chronic viral infections (e.g. hepatitis C virus) but has no significant beneficial effect in MS. The mechanism of action of IFN- $\beta$  in MS is not yet fully understood. It acts at several different levels within the pathways that are involved in the pathological processes of MS. IFN- $\beta$  significantly decreases the T-cell activation [53] and its transmigration through the blood brain barrier [39]. It also decreases the secretion and/or effects of proinflammatory cytokines such as Interleukine II and IFN- $\gamma$  [79]. Finally IFN- $\beta$  impairs antigen presentation and macrophage function mainly via reducing the expression of major histocompatibility complex (MHC) class II molecules on antigen presentation cells [80].

Currently used IFN- $\beta$  products are made by recombinant DNA technology in tissue culture. IFN- $\beta_{1a}$  is a glycosylated recombinant mammalian product with an amino acid sequence identical to that of natural IFN- $\beta$ . IFN- $\beta_{1b}$  is a non glycosylated

\* Corresponding author.

E-mail address: jlgoeb@wanadoo.fr (J.-L. Goeb).

recombinant bacterial product in which serine is substituted for cysteine at position 17. Both forms were subjected to investigation in large clinical trials and are considered as appropriate treatments for patients with relapsing remitting multiple sclerosis (RRMS) or secondary progressive multiple sclerosis (SPMS) [27]. Although the structural differences may impact on the level of biological activity exhibited by these two molecules (the *in vitro* antiviral activity of IFN- $\beta_{1a}$  being higher than that of IFN- $\beta_{1b}$ ) and possibly on the level of clinical efficacy, there is no evidence that they differ from one another in terms of their mechanism of action.

## 2. Method

In order to review the psychiatric side effects of IFN- $\beta$  in MS, we searched the electronic databases Medline<sup>®</sup>, Embase<sup>®</sup>, and Pascal<sup>®</sup> up to January 2005. The search words “MS”, “IFN”, “Psychiatry”, “Psychological”, “Depression” “Suicide”, “Psychosis”, and “Side effects” were used and were crossed in different ways. The abstracts initially found were examined to identify the articles that provide data about psychiatric side effects under IFN. The reference lists of the articles selected were also searched.

## 3. Results

### 3.1. MS and psychiatric disorders

The most common psychiatric manifestations in MS are depressed mood and major depressive disorder (MDD) [3,18,20,22,45]. MDD occurs in a quarter to a half of patients with MS during their lifetime [48,74]. The whole literature shows the complex interplay between biological and psychosocial factors in affective disorders in association with MS. Acute major depressive and manic episodes may be psychiatric manifestations of demyelinating lesions and may represent the initial symptoms of MS [24], sometimes with delusional paranoid ideas [28]. Neurological signs of MS may be misdiagnosed as lithium or neuroleptic toxicity or dismissed as psychogenic, and treatment of manic symptoms in these patients may require anti-inflammatory agents [24,42,60]. We described earlier a patient with concomitant depression and MS relapse which both dramatically improved with intravenous methylprednisolone pulse therapy under lithium coverage [16]. An association between MS and bipolar affective disorders has been suggested by the epidemiological study performed by Schiffer et al. [65]. These authors advanced several explanations referring to neurogenetic, neuroanatomic, and psychodynamic mechanisms, but they were unable to identify a pattern of hemispheric or midline damage that would be correlated with the type of affective disturbance.

Psychotic symptoms in association with MS are rare [22]. A recent study reported that, when this association occurs, the onset of neurological symptoms comes first in most cases, and suggested that psychotic symptoms may be associated to temporal lobe pathology [63]. Ten MS patients who experienced psychotic symptoms [22], presented a higher total lesion score in comparison with matched MS controls. The lesions

were located in the periventricular areas (left temporal horn and adjacent left trigone area). Psychotic symptoms arose on average at 36 years of age, 8 years after MS, and without neurological exacerbation in 60% of the cases. The treatment of psychosis in MS with neuroleptics suggests a particular vulnerability to extrapyramidal symptoms, and clozapine should be preferred, but at lower doses than for schizophrenia [14].

### 3.2. IFN- $\beta$ and mood disorders

Thanks to the bibliographic search described above, we screened more than 150 abstracts and finally identified 16 studies (Table 1) that yield specific data about the occurrence of depression and/or suicide in MS patients treated with IFN- $\beta_{1a/1b}$ . With these compounds, side effects mainly occur in the early phase of treatment and are responsible for the discontinuation of treatment in 2–12.5% of patients [17,31,38,61,69,74,82]. IFN- $\beta_{1a/1b}$  psychiatric side effects are not yet fully established, but might be similar to IFN- $\alpha$  ones, which are acknowledged and frequent at any time throughout treatment. Depression has been suspected with IFN- $\beta_{1a}$  and  $\beta_{1b}$  in MS. In fact, although this association may be only casual, many patients with MS who are initially depressed are regrettably not treated with IFN due to the purported risks of increased depression or induced psychiatric complications [10].

Concerns that IFN- $\beta$  may cause depression in patients with MS followed the report of a suicide and attempted suicides during the first clinical trial of IFN- $\beta_{1b}$  in RRMS [36]. In the study led by the IFNB Multiple Sclerosis Study Group and the University of British Columbia MS/MRI Analysis Group [68], a higher ratio of depressive symptoms and suicide attempts (including one completed suicide) was reported in both arms treated with IFN- $\beta_{1b}$ , while no suicide attempt and fewer depressive symptoms were observed in the placebo group. A recent clinical trial of IFN- $\beta_{1a}$  initiated after the first demyelinating event reported that depression was more frequently reported as a side effect in the active treatment (20%) than in the placebo group (13%) [30], but a formal measure of depression was not used in this study. A validated diagnostic instrument for depression would have ensured that depression had not been mistaken for fatigue, asthenia or unspecific emotional disturbances. As Bayas and Rieckman [4] noted, there was a higher rate of discontinuation in the IFN- $\beta_{1b}$  trial in secondary progressive MS compared with the trial in RRMS. This may be explained by the enrolment of patients with higher disability grades in the secondary progressive MS trial. Besides, the patients with a secondary progressive disease may have a reduced tolerance to adverse events. Mohr et al. [47,48] have reported an increase in self-reported symptoms of depression 6 months after the first injection, together with an increase in adherence to IFN- $\beta_{1b}$  treatment when patients are treated for depression.

On the other hand, Borrás et al. [10] studied the emotional state of 90 patients with RRMS with a follow-up period of 2 years after the introduction of IFN- $\beta_{1b}$ . They found no increase of depression or anxiety in patients with MS during the first and second years of IFN- $\beta_{1a}$  treatment. They even

Table 1  
Depression and/or suicide under IFN- $\beta$  in MS

Study	Number of patients Sex ratio (M/F)	Age (years)	Treatment regimen	MS subtype	Treatment duration	Psychiatric assessment	Psychiatric outcome
IFNB-MS Study Group 1995 [68]	125 124 123	35.5	IFN- $\beta$ 1b 1.6 MIU IFN- $\beta$ 1b 8 MIU Placebo	RRMS	5 years		IFN 1.6 MIU: 3 SA IFN 8 MIU: 1 SA Placebo: 0 SA
Jacobs et al., 1996 [31]	158 (40/118) 143 (40/103)	18–55	IFN- $\beta$ 1a 30 $\mu$ g 1 per week Placebo	RRMS	2 years	BDI	Placebo: 1 SA IFN: 0 SA
Mohr et al., 1997 [46]	85 (27/58)	–	IFN- $\beta$ 1b	MS	6 months		New or increased depression within 6 months of initiating IFN
PRISMS, 1998 [61]	189 (62/127) 184 (63/121) 187 (47/140)	23–43	IFN- $\beta$ 1a 22 $\mu$ g 3 per week IFN- $\beta$ 1a 44 $\mu$ g 3 per week Placebo	RRMS	2 years	CES-D BHS	No increased depression in the IFN group. Depression reported in 21–28% of all groups. Placebo: 1 S, 3 SA or ST IFN: 3 SA or ST
Muraoka et al., 1999 [51]	56 (9/47)	43.3 $\pm$ 9.5	IFN- $\beta$ 1a	RRMS	2 months	PMS	Increases in depression are related to levels of depression 2 weeks before initiation of treatment.
Borras et al., 1999 [10]	90 (37/53)	18–53	IFN- $\beta$ 1b 8MIU 1/2d	RRMS	2 years	HDRS BDI STAI	Significant improvement in depression symptoms.
OWIMS Study Group 1999 [55]	95 (26/69) 98 (28/70) 100 (26/74)	35.5 $\pm$ 7.4	IFN- $\beta$ 1a 22 $\mu$ g 1 per week IFN- $\beta$ 1a 44 $\mu$ g 1 per week Placebo	RRMS	48 weeks		No increase of depression in the IFN group
Jacobs et al., 2000 [30]	193 (52/141) 190 (50/148)	33 $\pm$ 7	IFN- $\beta$ 1a 30 $\mu$ g 1 per week Placebo	First demyelinating event	3 years		More depression in the IFN group (20% vs. 13%, $P = 0.05$ )
Leon et al., 2000 [38]	25 (7/18)	29.8 $\pm$ 6.7	IFN- $\beta$ 1a 6MIU 3 per week	RRMS	2 years		Depressed mood has been reported.
Kappos et al., 2001 [34]	360 (151/209) 358 (128/230)	18–55	IFN- $\beta$ 1b 8MIU 1/2d Placebo	SPMS	3 years	MADRS	No increase of depression in the IFN group. Placebo: 1 S, 5 SA IFN: 1 S, 3 SA
Patten and Metz, 2002 [59]	104 98 104	19–55	IFN- $\beta$ 1a 22 $\mu$ g 3 per week IFN- $\beta$ 1a 44 $\mu$ g 3 per week Placebo	SPMS	3 years	CES-D BHS	No increase of depression in the IFN group.
Feinstein et al., 2002 [23]	42 (12/30)	39.8 $\pm$ 10.5	IFN- $\beta$ 1b 8MIU 1/2d	RRMS	12 months	SCID	Threefold decline in depression rates under IFN- $\beta$ .
Vermersch et al., 2002 [74]	188 (58/130)	36.6 $\pm$ 8	IFN- $\beta$ 1a 30 $\mu$ g 1 per week	RRMS	18 months		Severe depression in 3 cases (1.6%).
Zivadnov et al., 2003 [83]	27 (9/18)	18–55	IFN- $\beta$ 1a 30 $\mu$ g 1 per week	RRMS	18 months	HADRS MADRS	No change in psychological and cognitive functions.
Zephir et al., 2003 [82]	106 (38/68)	36 $\pm$ 9	IFN- $\beta$ 1a	RRMS	12 months	BDI	No influence of IFN- $\beta$ on the depression status.
Patten et al., 2003 [57]	4 (1/4) 13 (1/12) 32 (12/20) 17 (5/12) 97 (12/85)	40.4	IM IFN- $\beta$ 1a SC IFN- $\beta$ 1b SC IFN- $\beta$ 1a 6MU SC IFN- $\beta$ 1a 12MU Glatiramer acetate	RRMS	3 months	CES-D	No influence of IFN- $\beta$ on the incidence of depression

RRMS: relapsing relapsing multiple sclerosis; SPMS: secondary progressive multiple sclerosis. SA: suicidal attempts; ST: suicidal thoughts; S: suicide. BDI: Beck Depression Inventory; BHS: Beck Hopelessness Scale; CES-D: Center for Epidemiological Studies Depression Scale; HDRS: Hamilton Depression Rating Scale; MADRS: Montgomery Asberg Depression Rating Scale; MMSE: mini mental state examination; PMS: Depression-detection Scale of the Profile of Mood States; SCID: structured clinical interview for axis 1 DSM-IV disorders; STAI: state-trait anxiety inventory.

found a significant improvement in the emotional state of the patients during IFN- $\beta$ <sub>1a</sub> treatment. These inconsistent results compared with previous studies may be due to positive treatment expectations and to the good response to the drug in these patients. It also suggests that depressive symptoms may be MS-related rather than IFN-related.

Subsequent studies showed no association between IFN- $\beta$ <sub>1a/1b</sub> and depressive symptoms or suicidal attempts [1,17,31,61]. Jacobs et al. [31] reported the effects of IFN- $\beta$ <sub>1a</sub> vs. placebo in 301 patients with relapsing MS. There were no major adverse events related to treatment. In both treatment arms, depression has been noted in 10–15% of patients. There was

no evidence of increased depression in patients treated with IFN. Mean scores on the Beck Depression Inventory [5] did not differ significantly between the two treatment arms at any time during the study, nor did they change significantly from baseline to the second year in either group. There was one suicide attempt in the placebo group and none in the IFN- $\beta_{1a}$  group.

The SPECTRIMS study [59] evaluated the possible association between IFN- $\beta_{1a}$  and depression in 365 subjects treated either with IFN- $\beta_{1a}$  or placebo. No significant difference between groups emerged in terms of psychiatric events over the 3-year follow-up period. These data suggest that depression may not be a side effect of IFN- $\beta_{1a}$  and supports the psychiatric safety of treatment with IFN- $\beta_{1a}$  in MS.

In the PRISMS trial [61], which included 560 subjects, there was no significant difference among the three groups in any of the measures of psychiatric status at any time of the study. Depression was reported by 28% of the placebo-treated patients, by 21% of the patients receiving 22  $\mu\text{g}$  IFN- $\beta_{1a}$ , and by 24% of the patients with 44  $\mu\text{g}$  IFN- $\beta_{1a}$ . One placebo-treated patient committed suicide during the study, and three patients in each group attempted suicide or reported suicidal thoughts.

In the European Study Group on IFN- $\beta_{1b}$  in Secondary Progressive MS [17,34], two out of 718 patients committed suicide (one on placebo, one on IFN- $\beta_{1b}$ ). The patients under IFN had no more depression, neither as a spontaneously reported adverse event nor in the quarterly monitoring with the Montgomery Asberg Depression Rating Scale (MADRS) [50]. Suicides or suicide attempts were reported in five patients on placebo and three on IFN- $\beta_{1b}$ .

In a study by Feinstein et al. [23], 42 patients with RRMS were assessed with a structured interview prior to starting IFN- $\beta_{1b}$  and thereafter at 3, 6 and 12 months. The prevalence rates for major depression declined threefold over the course of a year suggesting a possible beneficial effect of IFN- $\beta_{1b}$  on mood.

In a recent work [25], we found that the French database *Système National de Pharmacovigilance* indicated only a dozen of unpublished reports of psychiatric complications during IFN- $\beta_{1a}$  treatment. On average, they occurred 7 months after treatment outset (range from 1 to 18 months). However, these side effects may be underreported.

Zephir et al. [82] also found that IFN- $\beta_{1a}$  did not significantly influence the depression status in a sample of 106 consecutive patients with RRMS, even in those with disability progression. There were no correlations between age, gender, duration of illness or disability and depression scores. Patients with disability progression after 1 year of IFN- $\beta_{1a}$  treatment had a significantly higher depression score at baseline than patients without disability progression. However, this study excluded patients with evidence of severe depression.

Finally, Patten et al. [57] conducted an observational study to assess whether the absence of a significant association between IFN- $\beta$  and depression was generalizable to “real world” settings. They observed no increase in depression scores after 1 year in patients treated with IFN- $\beta$  compared to those treated with glatiramer acetate.

### 3.3. IFN- $\alpha$ and mood disorders

Manic symptoms and bipolar disorder have been reported in patients treated with IFN- $\alpha$  for several diseases [29]. These neurotoxic effects of IFN are generally acute and typically resolve with treatment discontinuation. However, chronic IFN- $\alpha$  therapy may also be associated with manic symptoms. Some cases of manic episodes are reported years after IFN- $\alpha$  was started, despite good tolerance of neurotoxic effects, high levels of functioning in daily life and no history of psychiatric illness [66].

Depression may be mistaken for lethargy and/or may not be adequately linked to IFN therapy [76] but is frequently reported with IFN- $\alpha$  in hepatitis C patients [15,41]. The reported rates of depressive symptoms associated with IFN- $\alpha$  range from 3% to 57% of the patients [16,26,69]. Such wide variations remain unclear. They are partly due to differences in dosage, disease and length of treatment. In spite of these rather high rates of depression, suicidal attempts appear rare, and suicidal ideations consistently remit after discontinuation of IFN treatment [32]. In a large multicenter retrospective study, among 11,241 consecutive patients with viral hepatitis under IFN- $\alpha$  treatment, only two patients attempted suicide [21].

### 3.4. IFN and psychotic disorders

Psychotic symptoms seem very rare during IFN- $\alpha$  therapies. In their wide retrospective study on 11,241 consecutive patients who underwent IFN- $\alpha$  treatment, Fattovich et al. [21] reported only 10 patients who developed psychosis during treatment. A case has been reported [36] of a patient who had been treated for almost 3 years with IFN- $\alpha$  for a chronic myelogenous leukemia and who presented an acute confusional episode with delusions, following the resumption of IFN- $\alpha$  after a 2-week discontinuation. Clinical improvement occurred rapidly after IFN was discontinued. Three cases of psychotic episodes have been described after 4–12 weeks of IFN- $\alpha$  treatment [62]. Manic and delirious episodes, with persecution and complex thought disorder, have also been described after several weeks or months of IFN- $\alpha$  therapy [33,51,62,64,66].

Among IFN- $\beta_{1a/1b}$  adverse effects, psychotic manifestations are very rare [16,25,43,70] and causality is uncertain. We recently reported [25] the case of a patient with RRMS treated with IFN- $\beta_{1a}$  for 8 months. He presented with an acute delirium with psychotic characteristics associated with a MDD with mood congruent psychotic features and delusion. He dramatically remitted after 10 days haloperidol therapy and IFN discontinuation. It suggests that patients with a prior history of psychosis should be carefully monitored for psychotic symptoms when they receive IFN- $\beta_{1a}$  therapy. Among the reports of psychiatric complications during IFN- $\beta_{1a}$  treatment noted in the French Database *Système National de Pharmacovigilance*, only one described a delirium with such psychotic features [25]. However a close collaboration between medical and psychiatric staffs is needed to allow patients with MS, including those suffering from a psychiatric illness [72] to receive and benefit from IFN treatment.

## 4. Discussion

### 4.1. Depression and suicide under IFN- $\beta$ therapy

The assessment of depression in MS is hampered by the overlap between the somatic symptoms of depression and the symptoms of MS (insomnia, fatigue, poor concentration). The somatic items included in depression scales may therefore artificially raise the rates and/or severity ratings of depression in MS. Different methods have been proposed to overcome this potential bias and to increase the specificity of the instruments used to assess depression in MS. Some authors have suggested to suppress or modify the somatic items of the depression scales [44,46]. Alternatively, one may use separate subscales for vegetative, mood and cognitive components of depression as can be done with the Chicago Multiscale Inventory [54]. It has also been proposed to perform an additional statistical analysis without the somatic symptoms to check whether they influenced the results or not [45]. These methods may be necessary for self-reports such as the Beck Depression Inventory [46,54], but as regards structured interviews, recent evidence showed that suppressing the “fatigue or loss of energy” item or the “diminished ability to think or concentrate” item of the DSM IV criteria does not modify the number of depression cases [58]. Besides, some self-report instruments such as the Center for Epidemiologic Studies-Depression (CES-D), used in three of the studies in Table 1 [57,59,61] emphasize psychological symptoms of depression as opposed to somatic ones. CES-D is widely used in medical/surgical populations and has proved valid and reliable to screen for depression in MS [73,7].

The studies listed in Table 1 have not straightforwardly dealt with the problem of the overlap of symptoms. It could have led to overdiagnosing depression, but on the contrary, relatively low rates of depression were found. The bias linked to the overlap of depressive and MS symptoms has therefore probably not had much impact on the results of the studies in Table 1.

Clinical trial participants recruited in academic centers, such as the settings of the studies in Table 1, do not necessarily reflect larger clinical populations of patients with MS. However randomization is expected to ensure that any particular characteristic of the population studied is equally distributed between the treatment groups. Besides, there is no data available for patients who are not followed in academic centers or who refuse to participate in clinical trials.

As summarized in Table 1, most studies (14 studies out of 16) discard an association between IFN- $\beta$  and depression or suicide. This finding may be true “on average” but does not mean that IFN- $\beta$  can never precipitate depression and its inherent risks in few vulnerable patients. For instance, a case has recently been reported about a young MS adult without any history of affective disorders who experienced depression and suicidal ideation in coincidence with increased doses of IFN- $\beta_{1a}$  and who completely remitted after treatment discontinuation [37]. Thus, few patients may be more vulnerable to de-

pression when treated with IFN- $\beta$ . Indeed, patients with a recent history of depression may be at higher risk for depression within 2 months after starting IFN- $\beta_{1a}$  treatment, even if they are not depressed at treatment initiation [49]. Moreover, in the study by Feinstein et al. [23], most of the depressed subjects had a history of psychiatric illness prior to the treatment with IFN- $\beta_{1b}$ . Besides, the incidence of depression may have been reduced by the exclusion of patients prone to depression in subsequent trials after the IFNB-MSSG study had shown high rates of suicide attempts under IFN- $\beta_{1b}$  [69]. Hence, physicians should assess history of depression for all patients in whom IFN- $\beta$  treatment is initiated. The patients should always be informed about the possibility of the induction of a depression and instructed to report substantial mood changes immediately. But overall, although rare cases of IFN- $\beta$  induced depressions may exist and raise concerns, it does not offset the expected benefits of this treatment. Therefore a past or present depression should prompt a careful monitoring of mood when IFN- $\beta$  is prescribed but does not appear sufficient to contra-indicate this treatment.

### 4.2. Pathophysiology of IFN induced depression

Most of the data on the pathophysiology of IFN-induced depression refer to IFN- $\alpha$ . Given that psychiatric side effects have been identified in a variety of diseases, at different dosages, and in patients of varying ages, Trask et al. [70], who pooled data from both IFN- $\alpha$  and IFN- $\beta$  treatments, have suggested that the mechanisms responsible for the development of the symptoms was neither disease-, dose-, nor behavioral or demographically related. Instead, they stated that the side effects result from the action of IFNs on basic biological mechanism. A direct action of IFNs on the brain is not the only mechanism, since IFNs do not readily cross the blood-brain barrier when it is intact. In fact, a number of central and peripheral neurochemical and endocrine effects have been proposed for IFN- $\alpha$  induced depression. They involve a hypothalamic-pituitary-adrenal (HPA) activation, immunoregulatory actions [6] and serotonin depletion [9].

Evidence shows a frequent association between a hyperactive HPA axis and depression [35,78]. A relation between HPA axis response to IFN- $\alpha$  therapy and the occurrence of depression under this therapy has been reported by Capuron et al. [11]. In 14 patients with malignant melanoma, they found significantly higher adreno-corticotrophic hormone and cortisol responses to an initial administration of IFN- $\alpha$  in the patients who subsequently developed depression under IFN- $\alpha$  therapy.

Some hypotheses involve serotonin in the pathophysiology of both IFN- $\alpha$  and - $\beta$  induced depression. Although there is less consensus for IFN- $\alpha$  and IFN- $\beta$  than for IFN- $\gamma$ , it seems that all classes of IFNs have an effect on serotonin metabolism mainly by inducing the enzyme indoleamine 2,3 dioxygenase (IDO), which leads to a depletion of tryptophan, the precursor of serotonin [2,13,67,77,81]. In a recent study, the administration of IFN- $\beta$  in patients with MS significantly increased the serum kynurenine concentration and the kynurenine/tryptophan

ratio, a quotient that estimates the activity of IDO [19]. As the synthesis of serotonin is largely dependant upon the availability of tryptophan, an activation of IDO leads to a decrease in the central serotonergic neurotransmission level. These mechanisms are consistent with the general link between serotonin depletion and depression. Besides, Capuron et al. [12] found a significant correlation between depressive symptoms and the decrease in tryptophan plasma level in 16 cancer patients treated with IFN- $\alpha$ . Finally, despite a lack of controlled clinical trials, serotonin selective reuptake inhibitors (SSRI) are used in clinical settings to treat IFN-induced depression [72].

#### 4.3. Management of psychiatric side effects

The recognition of the complex pathogenesis of affective disorder in association with MS and/or its treatments has several practical implications. As recommended by Garland and Zis [24], an acute affective disorder in a patient with MS should first lead to careful neurological assessment to determine whether the symptomatology is due to an acute demyelination. Cerebral imaging is required to detect neurologically silent but psychiatrically manifested demyelinations. Anti-inflammatory agents may therefore be specifically indicated in the presence of acute psychiatric symptoms, but coverage with lithium, neuroleptics or antidepressants is suggested, as well as psychiatric hospitalization when necessary. Second, psychodynamic and psychosocial factors need to be assessed in order to reduce depressive symptoms of a reactive nature. Finally, the occurrence of transient, unexplained neurological disturbances in a patient with bipolar affective disorder or psychotic depression should prompt a neurological examination to rule out MS.

As IFN-induced side-effects mechanisms remain unclear, it is difficult to design strategies to reduce them. However, clinicians should focus their attention on psychiatric symptoms that may be serious, but may also be improved with well tolerated medication as SSRI in IFN-induced depression, allowing the patients to benefit from IFN. It is necessary to inform the patients in detail about the possibility of general and psychiatric adverse effects and the prophylactic nature of IFN- $\beta$  treatment. Besides, considering that most patients have overly optimistic expectations regarding the effect of IFN- $\beta$  [47], the clinician has to give appropriate and realistic information on the reduction of attack rate that may be expected. Otherwise unrealistic expectations can lead to poor compliance and possibly trigger depressive episodes [47,75]. The possibility of transient worsening of MS symptoms in the early treatment phase should also be discussed to increase the patient's compliance and acceptance of adverse effects, and to minimize his anxiety [4,47]. Some assessment procedures (self-rating scales such as the Beck Depression Inventory, or standardized psychiatric interviews) have been recommended to identify these effects [71]. A close cooperation between neurologic and psychiatric staffs is required before, during (especially during the first 4 months) and after IFN therapy. If depression occurs under IFN- $\beta$ , selective serotonin reuptake inhibitors will be the preferred compounds. Indeed, a double-blind clinical trial

showed the prophylactic efficacy of paroxetine to minimize depression induced by IFN- $\alpha$  in patients with malignant melanoma [52]. Besides a case report showed the efficacy of citalopram in a woman who developed depression after receiving IFN- $\beta_{1a}$  for MS [56]. When depression cannot be treated adequately with antidepressants, a temporary discontinuation of IFN- $\beta$  therapy should be considered. This may also clarify a possible causal relationship if symptoms subside after discontinuation and reoccur after the reintroduction of therapy. The patients with RRMS for whom IFN- $\beta$  is discontinued may be treated with copolymer, which seems to have the same magnitude of clinical effect as IFN- $\beta$  [40].

#### 5. Conclusion

The psychiatric side effects of IFN- $\beta$  are not as well established as those of IFN- $\alpha$ . In MS, affective disorders have a complex pathogenesis and neurological, psychological and iatrogenic factors are difficult to disentangle. Most studies have ruled out an association between IFN- $\beta$  and depression or suicide in MS patients. However, it cannot be ruled out that few patients, especially those with a psychiatric history, may develop depression when treated with IFN- $\beta$ . Overall, we recommend that: 1) no patient, even with past or present depression, should be denied treatment with IFN- $\beta$ ; 2) those with past or present depression should receive cautious psychiatric monitoring; 3) in case depression occurs or worsens under IFN- $\beta$ , antidepressant treatment and/or IFN discontinuation must be considered.

#### References

- [1] Alarcia R, Ara JR, Martin J, Bertol V. Factores predictores de depression en la esclerosis multiple. *Neurologia* 2004;19:364–8.
- [2] Amirkhani A, Rajda C, Arvidsson B, Bencsik K, Boda K, Seres E, et al. Interferon-beta affects the tryptophan metabolism in multiple sclerosis patients. *Eur J Neurol* 2005;12:625–31.
- [3] Arias Bal MA, Vazquez-Barquero JL, Pena C, Miro J, Berciano JA. Psychiatric effects of multiple sclerosis. *Acta Psychiatr Scand* 1991;83:292–329.
- [4] Bayas A, Rieckmann P. Managing the adverse effects of interferon-beta therapy in multiple sclerosis. *Drug Saf* 2000;22:149–59.
- [5] Beck AT, Steer RA. Beck Depression Inventory (BDI) manual. San Antonio: Psychological Corporation; 1987.
- [6] Billiau A, Kieseier BC, Hartung HP. Biologic role of interferon beta in multiple sclerosis. *J Neurol* 2004;251(Suppl 2):II10–II14.
- [7] Blalock SJ, DeVellis RF, Brown GK, Wallston KA. Validity of the Center for Epidemiological Studies Depression Scale in arthritis populations. *Arthritis Rheum* 1989;32:991–7.
- [8] Bonaccorso S, Marino V, Biondi M, Grimaldi F, Ippoliti F, Maes M. Depression induced by treatment with interferon-alpha in patients affected by hepatitis C virus. *J Affect Disord* 2002;72:237–341.
- [9] Bonaccorso S, Marino V, Puzella A, Pasquini M, Biondi M, Artini M, et al. Increased depressive ratings in patients with hepatitis C receiving interferon-alpha-based immunotherapy are related to interferon-alpha-induced changes in the serotonergic system. *J Clin Psychopharmacol* 2002; 22:86–90.
- [10] Borrás C, Rio J, Porcel J, Barrios M, Tintore M, Montalban X. Emotional state of patients with relapsing–remitting MS treated with interferon beta-1b. *Neurology* 1999;52:1636–9.

- [11] Capuron L, Raison CL, Musselman DL, Lawson DH, Nemeroff CB, Miller AH. Association of exaggerated HPA axis response to the initial injection of interferon-alpha with development of depression during interferon-alpha therapy. *Am J Psychiatry* 2003;160:1342–5.
- [12] Capuron L, Ravaud A, Neveu PJ, Miller AH, Maes M, Dantzer R. Association between decreased serum tryptophan concentrations and depressive symptoms in cancer patients undergoing cytokine therapy. *Mol Psychiatry* 2002;7:468–73.
- [13] Carlin JM, Borden EC, Byrne GI. Enhancement of indoleamine 2,3-dioxygenase activity in cancer patients receiving interferon-beta. *Interferon Res* 1989;9:167–73.
- [14] Chong SA, Ko SM. Clozapine treatment of psychosis associated with multiple sclerosis. *Can J Psychiatry* 1997;42:90–1.
- [15] Davidson K, Bradley CR. Schizophrenia-like psychoses associated with organic disorders of the central nervous system: a review of the literature. In: Harrington RN, editor. *Current problems in neuropsychiatry*. Ashford: Kent: Headley; 1969. p. 113–84.
- [16] Dieperink E, Willenbring M, Ho SB. Neuropsychiatric symptoms associated with hepatitis C and interferon Alpha: a review. *Am J Psychiatry* 2000;157:867–76.
- [17] European Study Group on Interferon beta-1b in Secondary Progressive MS. Placebo-controlled multicentre randomized trial of Interferon beta-1b in treatment of secondary progressive multiple sclerosis. *Lancet* 1998;352:1491–7.
- [18] Even C, Friedman S, Dardennes R, Zuber M, Guelfi JD. Prevalence of depression in multiple sclerosis: a review and meta-analysis. *Rev Neurol* 2004;160:917–25.
- [19] Even C, Goeb JL, Taussig D, Dardennes R, Haguenu M, Hakim-Kreis CM. Depression and multiple sclerosis. *Eur Psychiatry* 1997;12:425–6.
- [20] Even C, Lafitte C, Etain B, Dardennes R. Les déterminants de la dépression dans la sclérose en plaques. *Encephale* 1999;25:78–85.
- [21] Fattovich G, Giustina G, Favarato S, Azzario F, Donato F, Giustina G, Fasola M, Pantalena M, Portera G, Tagger A. A survey of adverse events in 11 241 patients with chronic viral hepatitis treated with Alpha interferon. *J Hepatol* 1996;24:38–47.
- [22] Feinstein A, du Boulay G, Ron MA. Psychotic illness in multiple sclerosis. *Br J Psychiatry* 1992;161:680–5.
- [23] Feinstein A, O'Connor P, Feinstein K. Multiple sclerosis, interferon beta-1b and depression. A prospective investigation. *J Neurol* 2002;249:815–20.
- [24] Garland EJ, Zis AP. Multiple sclerosis and affective disorders. *Can J Psychiatry* 1991;36:112–7.
- [25] Goeb JL, Cailleau A, Lainé P, Etcharry-Bouy F, Maugin D, Duverger P, Gohier B, Rannou-Dubas K, Dubas F, Garre JB. Acute delirium, delusion and depression during IFN- $\beta$ -1a therapy for multiple sclerosis: a case report. *Clin Neuropharmacol* 2003;26:5–7.
- [26] Gohier B, Goeb JL, Rannou-Dubas K, Fouchard I, Cales P, Garre JB. Hepatitis C, alpha interferon, anxiety and depression disorders: a prospective study of 71 patients. *World J Biol Psychiatry* 2003;4:115–9.
- [27] Goodin DS, Frohman EM, Garmany Jr. GP, Halper J, Likosky WH, Lublin FD, et al. Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the MS Council for Clinical Practice Guidelines. Disease modifying therapies in multiple sclerosis: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the MS Council for Clinical Practice Guidelines. *Neurology* 2002;22(58):169–78.
- [28] Heila H, Turpeinen P, Erkinjuntti T. Case study: mania associated with multiple sclerosis. *J Am Acad Child Adolesc Psychiatry* 1995;34:1591–5.
- [29] Iancu I, Sverdlik A, Dannon PN, Lepkifker E. Bipolar disorder associated with interferon-alpha treatment. *Postgrad Med J* 1997;73:834–5.
- [30] Jacobs LD, Beck RY, Simon JH, Kinkel RP, Brownschidle CM, Murray TS, Simonian NA, Slasor PJ, Sandrock AW. Intramuscular Interferon beta-1a therapy initiated during a first demyelinating event in multiple sclerosis. *N Engl J Med* 2000;343:898–904.
- [31] Jacobs LD, Cookfair DL, Rudick RA, Herndon RM, Richert JR, Salazar AM, Fisher JS, Goodkin DE, Granger CV, Simon JH. Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. *Ann Neurol* 1996;39:285–94.
- [32] Janssen H, Brouwer J, Van der Mast R, Van Der Mast RC, Schalm SW. Suicide associated with alpha-interferon therapy for chronic viral hepatitis. *J Hepatol* 1994;21:241–3.
- [33] Kanno A, Yamada M, Abe M, Okamoto Y. A case of interferon Alpha-induced manic psychosis in chronic hepatitis C. *Tohoku J Exp Med* 1999;187:79–82.
- [34] Kappos L, Polman C, Pozzilli C, Thompson A, Beckmann NK, Dahlke F, European Study Group in Interferon beta-1b in Secondary MS. Final analysis of the European multicenter trial on IFN beta 1b in secondary progressive MS. *Neurology* 2001;57:1969–75.
- [35] Kathol RG, Jaekle RS, Lopez JF, Meller WH. Pathophysiology of HPA axis abnormalities in patients with major depression: an update. *Am J Psychiatry* 1989;146:311–7.
- [36] Kayser N, Louiz H, Guillin O. Syndrome confusodépressif sous IFN Alpha. *Encephale* 2001;27:585–7.
- [37] Lana-Peixoto MA, Teixeira Jr. AL, Haase VG. Interferon beta-1a-induced depression and suicidal ideation in multiple sclerosis. *Arq Neuropsiquiatr* 2002;60:721–4.
- [38] Leon C, Violante A, Arriada N, Santana HR, Corona T. Interferon-beta 1a in relapsing-remitting multiple sclerosis. First report of a Mexican population. *Rev Neurol* 2000;31:1019–22.
- [39] Leppert D, Waubant E, Burk MR, Oksenberg JR, Hauser SL. Interferon beta-1b inhibits gelatinase secretion and in vitro migration of human T cells: a possible mechanism for treatment efficacy in multiple sclerosis. *Ann Neurol* 1996;40:846–52.
- [40] Lubetzki C. Treatment of remitting forms of multiple sclerosis. *Rev Neurol* 2001;157:996–1000.
- [41] Malaguama M, Laurino A, Di Fazio I, et al. Neuropsychiatric effects and type of IFN-alpha in chronic hepatitis C. *J Interferon Cytokine Res* 2001;21:273–8.
- [42] Mapelli G, Ramelli E. Manic symptoms associated with multiple sclerosis: secondary mania? *Acta Psychiatr Belg* 1981;81:337–49.
- [43] McDonald EM, Mann AH, Thomas HC. Interferons as mediators of psychiatric morbidity. *Lancet* 1987;330(8569):1175–7.
- [44] Minden SL, Orav J, Reich P. Depression in multiple sclerosis. *Gen Hosp Psychiatry* 1987;9:426–34.
- [45] Minden SL, Schiffer RB. Affective disorders in multiple sclerosis. Review and recommendations for clinical research. *Arch Neurol* 1990;47:98–104.
- [46] Mohr DC, Goodkin DE, Likosky W, Beutler L, Gatto N, Langan MK. Identification of Beck Depression Inventory items related to multiple sclerosis. *J Behav Med* 1997;20:407–14.
- [47] Mohr DC, Goodkin DE, Likosky W, Gatto N, Neilley LK, Griffin C, Stiebling B. Therapeutic expectations of patients with multiple sclerosis upon initiating interferon beta-1b: relationship to adherence to treatment. *Mult Scler* 1996;2:222–6.
- [48] Mohr DC, Goodkin DE, Likosky W, Gatto N, Baumann KA, Rudick RA. Treatment of depression improves adherence to interferon beta-1b therapy for multiple sclerosis. *Arch Neurol* 1997;54:531–3.
- [49] Mohr DC, Likosky W, Dwyer P, Van Den Wende J, Boudewyn AC, Goodkin DE. Course of depression during the initiation of interferon beta-1a treatment for multiple sclerosis. *Arch Neurol* 1999;56:1263–5.
- [50] Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry* 1979;134:382–9.
- [51] Muraoka H, Sanefuji T, Keida R, Tsuji R, Abe H, Uchimura Y, Sata M, Tanikawa K, Nose I, Uchimura N, Nakazawa Y. A patient with chronic hepatitis C and a history of abuse of analeptic drugs, who showed hallucinations and delusion with interferon administration. *Kurume Med J* 1996;43:73–7.
- [52] Musselman DL, Lawson DH, Gumnick JF, Manatunga AK, Penna S, Goodkin RS, et al. Paroxetine for the prevention of depression induced by high-dose interferon alfa. *N Engl J Med* 2001;344:961–6.
- [53] Noronha A, Tosca A, Jensen MA. Interferon beta decreases T cell activation and interferon gamma production in multiple sclerosis. *J Neuroimmunol* 1993;46:145–53.

- [54] Nyenhuis DL, Rao SM, Zajecka JM, Luchetta T, Bernardin L, Garron DC. Mood disturbance versus other symptoms of depression in multiple sclerosis. *J Int Neuropsychol Soc* 1995;1:291–6.
- [55] OWIMS Study group. Evidence of interferon beta-1a dose response in relapsing–remitting MS: the OWIMS Study. The Once Weekly Interferon for MS Study Group. *Neurology* 1999;53:679–86.
- [56] Pandya R, Patten S. Depression in multiple sclerosis associated with interferon beta-1a (Rebif). *Can J Psychiatry* 2002;47:686.
- [57] Patten SB, Fridhandler S, Beck CA, Metz LM. Depressive symptoms in a treated multiple sclerosis cohort. *Mult Scler* 2003;9:616–20.
- [58] Patten SB, Metz LM, Reimer MA. Biopsychosocial correlates of lifetime major depression in a multiple sclerosis population. *Mult Scler* 2000;6:115–20.
- [59] Patten SB, Metz LM. Interferon beta-1a and depression in secondary progressive multiple sclerosis: data from the Spectrims trial. *Neurology* 2002;59:744–6.
- [60] Peselow ED, Deutsch SI, Fieve RR, Gulbenkian G, Deutsch SI, Kaufmann M. Coexistent manic symptoms and multiple sclerosis. *Psychosomatics* 1981;22:824–5.
- [61] PRISMS Study Group. Randomized double-blind placebo-controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis. *Lancet* 1998;352:1498–504.
- [62] Renault PF, Hoofnagie JH, Park Y, et al. Psychiatric complications of long-term interferon Alpha therapy. *Arch Intern Med* 1987;147:1577–80.
- [63] Ron MA, Logsdail SJ. Psychiatric morbidity in multiple sclerosis: a clinical and MRI study. *Psychol Med* 1989;19:887–95.
- [64] Schafer M, Boetsch T, Laakman G. Psychosis in a methadone-substituted patient during interferon Alpha treatment of hepatitis C. *Addiction* 2000;95:1101–4.
- [65] Schiffer RB, Wineman NM, Weitkamp LR. Association between bipolar affective disorder and multiple sclerosis. *Am J Psychiatry* 1986;143:94–5.
- [66] Strite D, Valentine AD, Meyers CA. Manic episodes in two patients treated with interferon Alpha. *J Neuropsychiatry Clin Neurosci* 1997;9:273–6.
- [67] Taylor MW, Feng GS. Relationship between interferon-gamma, indoleamine 2,3-dioxygenase, and tryptophan catabolism. *FASEB J* 1991;5:2516–22.
- [68] The IFNB Multiple Sclerosis Study Group and the University of British Columbia MS/MRI Analysis Group. Interferon beta-1b in the treatment of multiple sclerosis: final outcome of the randomized control trial. *Neurology* 1995;45:1277–85.
- [69] The IFNB Multiple Sclerosis Study Group. Interferon beta-1b is effective in relapsing–remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. *Neurology* 1993;43:655–61.
- [70] Trask PC, Esper P, Riba M, Redman B. Psychiatric side effects of interferon therapy: prevalence, proposed mechanisms and future directions. *J Clin Oncol* 2000;18:2316–26.
- [71] Valentine AD, Meyers CA, Kling MA, Richelson E, Hauser P. Mood and cognitive side effects of interferon-alpha therapy. *Semin Oncol* 1998;25(Suppl 1):39–47.
- [72] Van Thiel DH, Friedlander L, Molloy PJ, Fagioli S, Kania RJ, Caraceni P. Interferon Alpha can be used successfully in patients with hepatitis C virus-positive chronic hepatitis who have a psychiatric illness. *Eur J Gastroenterol Hepatol* 1995;7:165–8.
- [73] Verdier-Taillefer MH, Gourlet V, Fuhrer R, Alperovitch A. Psychometric properties of the Center for Epidemiologic Studies–Depression scale in multiple sclerosis. *Neuroepidemiology* 2001;20:262–7.
- [74] Vermersch P, de Seze J, Stojkovic T, Hauteceur P. Interferon beta 1a (Avonex<sup>®</sup>) treatment in multiple sclerosis: similarity of effects on progression of disability in patients with mild and moderate disability. *J Neurol* 2002;249:184–7.
- [75] Walther EU, Dietrich E, Hohlfeld R. Therapy of multiple sclerosis with interferon-beta-1b. Educating the patient and managing side-effects. *Nervenarzt* 1996;67:452–6.
- [76] Weiss K. Safety profile of Interferon Alpha therapy. *Semin Oncol* 1998;25(Suppl 1):9–13.
- [77] Werner-Felmayer G, Werner ER, Fuchs D, Hausen A, Reibnegger G, Wachter H. Tumour necrosis factor-alpha and lipopolysaccharide enhance interferon-induced tryptophan degradation and pteridine synthesis in human cells. *Biol Chem Hoppe Seyler* 1989;370:1063–9.
- [78] West van D, Maes M. Activation of the inflammatory response system: a new look at the etiopathogenesis of major depression. *Neuroendocrinol Lett* 1999;20:11–7.
- [79] Yong VW, Chabot S, Stuve O, Williams G. Interferon beta in the treatment of multiple sclerosis: mechanisms of action. *Neurology* 1998;51:682–9.
- [80] Yong VW. Differential mechanisms of action of interferon-beta and glatiramer acetate in MS. *Neurology* 2002;59:802–8.
- [81] Yoshida R, Urade Y, Tokuda M, Hayaishi O. Induction of indoleamine 2,3-dioxygenase in mouse lung during virus infection. *Proc Natl Acad Sci USA* 1979;76:4084–6.
- [82] Zephir H, De Seze J, Stojkovic T, Delisse B, Ferriby D, Cabaret M, Vermersch P. Multiple sclerosis and depression: influence of interferon beta therapy. *Mult Scler* 2003;9:284–8.
- [83] Zivadinov R, Zorzon M, Tommasi MA, Nasuelli D, Bernardi M, Monti-Bragadin L, Cazzato G. A longitudinal study of quality of life and side effects in patients with multiple sclerosis treated with interferon beta-1a. *J Neurol Sci* 2003;216:113–8.