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Managing the Adverse Effects of Interferon-β Therapy in Multiple Sclerosis

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Abstract

Interferon-β is an established therapy in relapsing-remitting multiple sclerosis. Recently, it has also been shown that interferon-β-1b is effective in secondary progressive multiple sclerosis. However, adverse effects of interferon-β treatment are common, particularly during the first weeks of treatment, and are a major concern. Flu-like symptoms, injection site reactions and laboratory abnormalities are the most common adverse effects, and may result in reduced compliance or even discontinuation of treatment in a number of patients. Therefore, efforts to minimise these reactions, e.g. appropriate comedication with analgesic/antipyretic drugs, use of correct preparation and injection technique and sometimes modification of the dosage of interferon-β, are of considerable importance.

This article provides an overview of the management of clinically relevant adverse effects related to treatment with interferon-β, based on a literature review and personal experience. Essential aspects of patient information are also stressed. If these recommendations are followed, adverse effects related to interferon-β may be substantially reduced in the majority of patients.

Multiple sclerosis is a chronic inflammatory disease that is restricted to the CNS. There is strong evidence that autoimmune mechanisms against CNS structures play an important role in the course of the disease. Interferon-β has been shown in several trials to have a significant effect on the course of relapsing-remitting multiple sclerosis.

There are currently 3 licensed preparations of interferon-β that have been tested in large multicentre trials. Interferon-β-1b, which is given subcutaneously every other day, was the first interferon licensed by the US Food and Drug Administration (FDA) for multiple sclerosis. It was approved in July 1993 for relapsing-remitting multiple sclerosis because of its significant effect on exacerbation rate and lesion load on cranial magnetic resonance imaging.[1] Interferon-β-1a (Avonex™), administered once weekly by the intramuscular route, was shown to reduce the exacerbation rate as well as the extension of gadolinium enhancing lesions on magnetic resonance imaging, and also significantly reduced sustained disease progression measured by the Expanded Disability Status Scale (EDSS).[2] Finally, another form of interferon-β-1a (Rebif®), given subcutaneously 3 times a week, has shown a significant effect on relapse rate, progression in disability and all magnetic resonance imaging outcome measures.[3] Recently, interferon-β-1b has been shown to be effective in secondary progressive multiple sclerosis. There was delay of sustained disease progression, a reduction of relapse rate and decrease of disease burden on magnetic resonance imaging.[4]

1. Interferon-β–Related Adverse Effects

Despite the encouraging clinical data, the administration of interferon-β bears the risk of a variety of adverse effects. The incidence of adverse effects reported in the trials discussed in the previous section,[1-4] as summarised from the product monographs, is reported in table I. We decided to refer to monographs in the majority, but not all cases, because some of the adverse effects were described in more detail in the monographs compared with the original trials. The most common adverse effects compared with placebo were flu-like symptoms [except in the Prevention of Relapses and Disability by Interferon-β-1a Subcutaneously in Multiple Sclerosis (PRISMS) trial[3]] and injection site reactions in subcutaneously treated patients. The most frequently reported laboratory abnormalities were leucocytopenia and liver enzyme level elevations. In 2 of the trials, different dosages of interferon-β were used.[1,3] In the high dosage groups a number of adverse effects substantially increased compared with the low dosage groups (illustrative values are shown only for interferon-β-1a in table I).[1,6]

Interferon-β–related adverse effects have also been investigated in several postmarketing studies, with injection site reactions and flu-like symptoms belonging to the most common findings.[8-10] Furthermore, there are several reports of rare adverse effects under interferon-β treatment. They include autoimmune hyperthyroidism and hypothyroidism,[11-14] autoimmune hepatitis,[12,14] myasthenia gravis,[15] exacerbation of psoriasis,[16] granulomatous dermatitis with focal sarcoidal features,[17] Raynaud's phenomenon,[18] vasculitis-like skin reaction,[19] cutaneous lupus erythematosus[20] and improvement as well as induction of rheumatoid arthritis or polyarthritis.[21-23] Prospective studies investigating the occurrence of autoimmune events have revealed contrary results concerning the induction of autoantibodies by interferon-β therapy in patients with multiple sclerosis.[13,14,24,25] Therefore a direct causal relationship has not been established.

As a possible molecular basis of a number of the adverse effects related to interferon-β, induction of interferon-γ and tumour necrosis factor-α (TNFα) has been demonstrated in the early phase of treatment.[26,27] Interferon-γ has the ability to provoke exacerbations in multiple sclerosis patients.[28] An increased risk of exacerbations during the early phase of interferon-β treatment by upregulation of interferon-γ has been discussed,[26] but no convincing clinical data are available.

The extent of adverse effects may lead to reduced compliance or even discontinuation of treat-

ment by the patient. In the pivotal trials of interferon-β,[1-4] adverse effects were responsible for the discontinuation of treatment in 4 to 12.5% of actively treated patients (table II). There was a higher rate of discontinuation in the interferon-β-1b trial in secondary progressive multiple sclerosis compared with the trial in relapsing-remitting multiple sclerosis. This may be explained by the enrolment of patients with higher disability grades in the secondary progressive multiple sclerosis trial (EDSS score 3 to 6.5[4] *vs* 0 to 5.5[1]); patients with secondary progressive disease may have reduced ability to tolerate adverse events. The higher rate of discontinuation might also be explained by the

Table I. Frequency of significant adverse effects associated with interferon-β (IFNβ) therapy of multiple sclerosis. Frequencies in placebo recipients are indicated in parentheses

IFNβ-1b 0.25mg (8 MIU) subcutaneously every other day in RRMS[5]	IFNβ-1b 0.25mg (8 MIU) subcutaneously every other day in SPMS[4]	IFNβ-1a (Rebif®) 22 or 44μg subcutaneously thrice weekly in RRMS[6]	IFNβ-1a (Avonex™) 30μg intramuscularly once weekly in RRMS[7]
Flu-like symptoms			
Flu-like symptom complex 76% (56%)	Flu syndrome 59.2% (37.2%)	Fever: 22μg, 24.9%; 44μg, 27.7% (15.5%)	Flu-like symptoms (otherwise unspecified) 61% (40%)
Fever 59% (41%)	Fever 39.4% (13.1%)		Muscle ache 34% (15%)
Chills 46% (19%)	Myalgia 22.8% (8.9%)		Fever 23% (13%)
Myalgia 44% (28%)	Chills 21.9% (7.3%)		Chills 21% (7%)
Sweating 23% (11%)	Chills and fever 3.6% (0.3%)		
Malaise 15% (3%)			
Other systemic adverse effects			
Asthenia 49% (35%)	Hypertonia (nervous system) 37.8% (27.4%)		
Menstrual disorder 17% (8%)	Rash 21.4% (10.6%)		
Palpitations 8% (2%)	Abdominal pain 10.8% (6.4%)		
Dyspnoea 8% (2%)	Hypertension 3.9% (0.8%)		
Injection site reactions			
Injection site reactions 85% (37%)	Injection site inflammation 50% (4.2%)	Injection site inflammation: 22μg, 65.6%; 44μg, 65.8% (15%)	
Injection site necrosis 5% (0%)	Injection site reaction 43.6% (10.3%)		
	Injection site necrosis 4.7% (0%)		
Laboratory abnormalities			
WBC <3000/mm^3 16% (5%)	Leucopenia 10% (5%)	Leucopenia: 22μg, 12.7%; 44μg, 22.3%* (3.7%)	Anaemia 8% (3%)
ANC <1500/mm^3 18% (6%)		Granulocytopenia: 22μg, 11.6%; 44μg, 15.2% (3.7%)	
ALT >5 × baseline 19% (6%)		Lymphopenia: 22μg, 20.1%; 44μg, 28.8% (11.2%)	
AST >5 × baseline 4% (0%)		Thrombocytopenia: 22μg, NS; 44μg, 8.2%* (1.6%)	
		ALT increased: 22μg, 19.6%; 44μg, 27.2% (4.3%)	
		AST increased: 22μg, 10.1%; 44μg, 17.4%* (3.7%)	
		Abnormal liver function: 22μg, NS; 44μg, 9.2%* (1.6%)	

ANC = absolute neutrophil count; **NS** = not significantly increased; **RRMS** = relapsing-remitting multiple sclerosis; **SPMS** = secondary progressive multiple sclerosis; **WBC** = white cell count; * indicates $p < 0.05$ *vs* 22μg dose.

Table II. Proportion of patients discontinuing interferon-β (IFNβ) treatment because of adverse effects

Trial	No. of patients
INFβ-1b in RRMS[1]	15/249 (0.05mg: 5; 0.25mg: 10) [6%] at 2 years
INFβ-1b in SPMS[4]	45/360 (12.5%)
IFNβ-1a (Avonex™) in RRMS[2]	7/158 (4.4%)
IFNβ-1a (Rebif®) in RRMS[3]	15/373 (22μg: 6; 44μg: 9) [4%]

RRMS = relapsing-remitting multiple sclerosis; **SPMS** = secondary progressive multiple sclerosis.

progressive disease course itself. The latter speculation is derived from the results of a nonblind trial with interferon-β-1b.[9] In this study, factors significantly related with treatment discontinuation were fatigue, a fatigue-depression interaction and a chronic progressive course of multiple sclerosis.

Adverse effects subside or even vanish in the majority of patients after the first 6 to 10 weeks of treatment, but a number of individuals may experience continuous problems with the medication. For example, in the interferon-β-1b trial in relapsing-remitting multiple sclerosis,[29] flu-like symptoms in the high dosage group decreased from 52% initially to 8% at the end of year 1, but in 3 to 8% they continued throughout the study. Injection site reactions in this trial decreased rather little, from 80% initially in the group treated with 8 MIU to 44 to 50% at years 4 and 5.[29]

2. Management of Interferon-β–Related Adverse Effects

2.1 General Recommendations

Since interferon-β exerts its effect in a prophylactic manner, usually with a latency of months, individual therapeutic benefit can only be determined over an extended period of time. However, the adverse effects are especially marked in the early phase of treatment. To allow continuation of interferon-β treatment by reducing intolerable adverse events and thus giving the individual a chance of a potentially beneficial treatment, strategies for managing adverse effects are of tremendous importance.

As a first step towards a successful therapy, it is imperative to inform the patient in detail and realistically about the possible adverse effects and the prophylactic nature of the interferon-β treatment. The fact that the frequency and severity of adverse events depend on the duration of treatment, with a maximum during the first weeks, should be emphasised. The possibility of transient worsening of multiple sclerosis symptoms in the early treatment phase should also be discussed. This information alone may increase the patient's compliance and acceptance of adverse effects. Treatment adherence has been demonstrated to be significantly greater in patients with realistic expectations in the pretreatment phase.[30]

2.2 Management of Specific Adverse Effects

In the following sections the management of the important adverse effects of interferon-β are discussed. Recommendations are based on the reviewed literature and on personal clinical experience of interferon–β–treated patients in our department. A synopsis is given in table III.

2.2.1 Flu-Like Symptoms

Flu-like symptoms with a variable combination of fever, chills, sweating and muscle aches belong to the most common adverse events in interferon-β–treated patients. They appear with a variable time-course, usually within 2 to 8 hours after injection and usually resolve within 24 hours. In temperature-sensitive patients, flu-like symptoms may additionally be responsible for the fluctuation of neurological symptoms. Flu-like symptoms occur most frequently during the initiation of treatment. Amelioration of these symptoms can be achieved pharmacologically and by modification of interferon-β administration.

Treatment Modification

Patients should be instructed to administer interferon-β in the evening so that the majority of adverse effects occur during sleep. When starting treatment with interferon-β, the dosage should be increased gradually.[31,32] To achieve a better tolerability of interferon-β-1b during the secondary

Table III. Management of adverse effects related to interferon-β (IFNβ) therapy

Adverse effect	Management	
	pharmacological	nonpharmacological
Flu-like syndrome	NSAIDs or paracetamol (acetaminophen), initially prophylactically, after 6 weeks therapeutically, e.g. ibuprofen 200mg (up to 400mg) or paracetamol 500mg 4 hours before injection, at injection and 4 hours afterwards Prednisone 30 mg/day for 2 weeks, followed by a tapering schedule for not longer than a further 2 weeks Possibly, pentoxifylline 2 × 800 mg/day	Gradual increase in dosage of IFNβ Injection at bedtime Temporary dosage reduction
Injection site reaction	Topical anaesthetics, e.g. 5% lidocaine (lignocaine) Topical corticosteroids, e.g. 1% hydrocortisone Ibuprofen	Correct preparation of prewarmed injection solution at room temperature (check technique regularly) Sterile and proper injection technique (check technique regularly) Regular change of injection sites Precooling injection sites and massaging the skin after injection
Injection site necrosis	Antibacterials if necessary Avoid topical corticosteroids	Temporary IFNβ dosage reduction or discontinuation Surgical therapy, if necessary
Laboratory abnormalities		See table IV for acceptable laboratory values; if they are exceeded, temporary dosage reduction (to 50-25%) or, in severe cases, discontinuation of treatment; careful reintroduction (beginning with 20-25%) after normalisation, with careful monitoring
Depressive symptoms	Antidepressants	Psychiatric evaluation Psychotherapy If necessary, (temporary) discontinuation of treatment
Menstrual disorders	Oral contraceptives may regularise cycle	Gynaecological evaluation Temporary IFNβ dosage reduction or discontinuation

NSAIDs = nonsteroidal anti-inflammatory drugs.

progressive multiple sclerosis trial, patients were treated with 50% of the planned dosage for the first 2 weeks.[4] In the PRISMS trial, 20% of the dosage was given for 2 to 4 weeks, then 50% for the same period before the full dosage was administered.[3] In our experience, treatment may be started with 20 to 25% of the desired dosage for a period of 1 week, followed by 50% in the following week. If treatment is well tolerated the dosage may then be increased to the full amount. If there are major adverse effects despite efforts to ameliorate the symptoms or cotreatment with analgesic/antipyretic drugs, the interferon-β dosage should be reduced or kept at the same level for a longer time until improved drug tolerability allows an increase. In interferon-β-1b–treated patients, flu-like symptoms were more frequent in younger individuals and there was evidence for an inverse relationship between body surface area or bodyweight and adverse effects.[29,33] It was concluded that in future trials the interferon-β dosage should be tailored to bodyweight.[29] It must be emphasised, however, that so far there is no class I evidence[34] for this strategy and that treatment efficacy should be monitored in those patients very closely. Until there are further trials addressing this issue, the aim should be to treat every patient with the licensed dosage that has been shown to be effective.

If pharmacological treatment is required, nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, and paracetamol (acetaminophen), as well as the phosphodiesterase inhibitor pentoxifylline and corticosteroids, have been shown to ameliorate adverse effects.

Analgesics/Antipyretics

In the multicentre interferon-β trials, NSAIDs and paracetamol ameliorated adverse events both prophylactically and therapeutically.[2-4,29] Lublin et al.[33] recommend the use of mild analgesic/antipyretic drugs 4 hours before injection, at injection and 4 hours thereafter. We recommend administering NSAIDs or paracetamol prophylactically for the first 6 weeks of interferon-β treatment, then therapeutically.

Corticosteroids

Since adverse effects and transient worsening of multiple sclerosis symptoms have been attributed to induction of interferon-γ, corticosteroids, which are capable of inhibiting interferon-γ–secreting cells, have been tested for their ability to reduce flu-like symptoms.[35] Patients treated with interferon-β-1b were concomitantly treated either with paracetamol (500mg 4 hours before injection, at injection and 4 hours after injection) or paracetamol plus prednisone (30 mg/day for the first 2 weeks and every day on a tapering schedule for the next 2 weeks). Comedication with prednisone resulted in a significant decrease of flu-like symptoms during the first 15 days of treatment (at week 1, 43 *vs* 80% of patients). After 3 months there was no significant difference between treatment groups, but a trend for fewer exacerbations could be detected in the corticosteroid group (during 3 months 8 patients *vs* 2 patients). To compare flu-like symptoms with the cytokine level, a subsequent study with the same treatment groups (interferon-β-1b + paracetamol *vs* interferon-β-1b + paracetamol + prednisone) was performed.[36] Interferon-β-1b significantly increased the percentage of interleukin-6–producing cells in patients with flu-like symptoms and fever. The percentage of these cells was decreased by treatment with a low dosage of corticosteroid, suggesting that this finding may be related to the reduction of adverse effects.

The effect of corticosteroids on interferon-γ–secreting cells in interferon-β–treated patients was also investigated.[26] The increase of interferon-γ–secreting cells could be prevented by cotreatment with prednisone (3×10 mg/day). Systemic adverse effects in those patients were minimal.

Since pulsed corticosteroids are the established therapy for acute exacerbations, interferon-β therapy can also be started in patients who respond to corticosteroids. Injections may be started when corticosteroids are tapered.

When evaluating the role of corticosteroids in the therapy of flu-like symptoms induced by interferon-β, it must be remembered that the duration of adverse effects and thus the need for concomitant medications is variable. Since longer courses of corticosteroids are themselves accompanied by well known adverse effects, corticosteroids may be a second line alternative to NSAIDs for this indication. If corticosteroids are considered, prednisone 30 mg/day may be given for the first 14 days, followed by a tapering schedule for not longer than 2 further weeks.[35,36]

Pentoxifylline

The phosphodiesterase inhibitor pentoxifylline is also effective in reducing interferon-β–associated flu-like symptoms. Pentoxifylline reduces the production of proinflammatory cytokines and is a potent immunomodulator in multiple sclerosis patients.[37] In a double-blind, placebo-controlled, crossover trial, pentoxifylline 1600 mg/day in patients with relapsing-remitting multiple sclerosis resulted in a significant reduction of the EDSS score during treatment, but the primary end-point of the study (reduction in the composite variable consisting of relapse rate, changes in EDSS, magnetic resonance images or global assessment of the patient) could not be reached. There was even a significant increase of T2-lesion load during therapy.[38] *In vitro* studies with myelin basic protein–specific T cell lines revealed a synergistic suppressive effect of interferon-β-1b and pentoxifylline on TNFα, lymphotoxin and interferon-γ production.[39]

In patients with relapsing-remitting multiple sclerosis, the combination of interferon-β-1b 8 MIU subcutaneously every other day and pentoxifylline 2×800 mg/day during the first 3 months of interferon-β treatment significantly re-

duced adverse effects such as fever, chills and myalgias compared with interferon-β treatment alone.[40] Worsening of multiple sclerosis symptoms occurred only in individuals treated with interferon-β alone, suggesting a positive effect on disease activity. These findings could be confirmed in a subsequent trial with an extended study population.[39] The positive clinical effects could be correlated with changes in the cytokine profile in treated patients. Combination of pentoxifylline and interferon-β-1b significantly suppressed the initial upregulation of mRNA of the proinflammatory cytokines TNFα and interferon-γ that was observed during treatment with interferon-β alone. Additionally, interleukin-10 production (cellular mRNA expression as well as serum concentrations) was higher during combination treatment compared with interferon-β-1b alone.[39] Interleukin-10 at physiological doses has a beneficial effect in experimental autoimmune encephalomyelitis.[41]

Since the numbers of patients treated with a combination of interferon-β-1b and pentoxifylline are small, at the present time we recommend this combination only in those patients who do not obtain sufficient benefit by other symptomatic measures. It is worthwhile mentioning that in several countries the licensed dosage of pentoxifylline is lower than the dosage tested in the above-mentioned trials. With higher dosages, pentoxifylline-related adverse effects, such as tachycardia and hypotension, might increase.

Other Treatments

Some patients notice a deterioration of neurological symptoms after starting interferon-β therapy. The temporal profile of those symptoms will help to delimit them from the underlying disease process. If deterioration appears in combination with flu-like symptoms, the recommendations given above should be followed. In case of increased spasticity, symptomatic antispastic treatment should be introduced or, if pre-existing, temporarily increased.

2.2.2 Injection Site Reactions

Injection site reactions are the most common adverse effect in patients treated with subcutaneous interferon-β, occurring in 50%[4] to 85%[5] of patients in the early phase of treatment. The different clinical presentations of injection site reactions, reaching from mild erythema to severe necrosis, are summarised elsewhere.[33,42,43]. Biopsy findings of the different forms of injection site reactions have also been described.[44] Injection site necrosis was found in up to 5% of patients in the large placebo-controlled trials.[5] There are also several case reports from the postmarketing phase (reviewed in Weinberg et al.[45]) of interferon-β–induced skin necrosis.[46,47] In a nonblind study with interferon-β-1b, ulcerative skin lesions were present in 4 of 200 treated patients.[48] In patients treated with intramuscular interferon-β-1a there was no significant increase of injection site reactions in the treatment group compared with placebo.[2]

To reduce this common adverse effect to a minimum, teaching the patient the correct preparation [necessary with interferon-β-1a (Avonex™) and interferon-β-1b] and injection techniques are of great importance. The procedure should be reviewed regularly by healthcare staff, especially in those patients with major injection site reactions. Precooled solutions should be warmed up gently, and drug preparation should be performed according to the manufacturer‘s recommendations. Recently it has been described that skin ulceration can be reduced by properly prewarmed injection solution.[46] Drug preparation and injection should be performed with different needles. Intradermal injection by mistake has to be avoided. Injection sites have to be changed with every injection, and a patient diary may help for a systematic record. Precooling and regular change of the injection sites, and possibly even topical use of anaesthetics, may be helpful when injections are too painful.[32] After injection the skin should be gently massaged to promote the dispersion of the drug. In more severe injection site reactions ibuprofen and, if necessary, topical corticosteroids (1% hydrocortisone) are recommended.[31]

Circumstances provoking interferon-β–induced skin necrosis are nonsterile injection techniques,

cold injection solutions, failure to change the injection site and exposure of recent injection sites to ultraviolet light.[31] The pathogenic mechanism of skin necrosis is unclear. Among other mechanisms, thrombosis and necrosis of dermal vessels as well as an inflammatory process caused by a hypersensitivity reaction localised to the blood vessels have been proposed.[45,47] In case of skin necrosis, a dosage reduction or temporary discontinuation of interferon-β are recommended.[31] Local treatment of the necrosis should follow standard procedures; if necessary, antibacterials and surgery should be used. Topical corticosteroids are contraindicated in necrosis, since wound healing is prolonged and the risk of infection increased.[31] Interferon-β therapy has been continued after necrosis in a number of patients without recurrence of this type of lesion,[16,45,46], but in general the site of skin necrosis should be spared from further interferon-β injections.

2.2.3 Laboratory Abnormalities

Significant laboratory abnormalities in patients treated with interferon-β are leuco-, lympho- and granulocytopenia, anaemia and elevation of AST and ALT levels (table I). Before starting therapy and regularly during therapy (after 4 to 6 weeks, at 12 weeks and then every 3 months) laboratory values, including complete blood count, serum chemistry, bilirubin, AST, ALT, γ-glutamyl transferase and alkaline phosphatase, should be monitored.[33]

The liver is a catabolic site for interferons, and liver injury under interferon treatment has also been ascribed to directly toxic effects with reduction of cytochrome P450.[14,49,50] Consequently, patients treated with other drugs that are potentially hepatotoxic or metabolised by cytochrome P450 (e.g. a number of antidepressants and anticonvulsants) should be monitored even more closely. Frequent laboratory monitoring is also necessary in patients taking other potentially myelosuppressive drugs.

If there are laboratory abnormalities exceeding the values in table IV,[31] the interferon-β dosage should be reduced to 50 to 25%. Therapy should be interrupted if abnormalities are severe or if AST, ALT, bilirubin and alkaline phosphatase levels are all elevated.[33] Reinstitution of therapy is possible when values return to normal. The dosage should be increased gradually, beginning with 20 to 25% of the normal dosage with careful laboratory monitoring. Recurrence of liver dysfunction is rare. There should be no reintroduction of interferon-β if liver enzyme levels remain abnormal, with AST/ALT >10-fold or bilirubin >5-fold the upper limit of the normal range.[33] For any patient, the extent of acceptable laboratory abnormalities should be decided on an individual basis.

Table IV. Limits of acceptable laboratory values during therapy with interferon-β (after Walther et al.,[31] with permission)

Parameter	Value
Haemoglobin	>94 g/L
White blood cells	$>3 \times 10^9$/L
Absolute neutrophil count	$>1.5 \times 10^9$/L
Lymphocytes	$>1 \times 10^9$/L
Platelets	$>75 \times 10^9$/L
Bilirubin	<2.5 × baseline[a]
Transaminases (AST, ALT)	<5 × baseline[a]
Alkaline phosphatase	<5 × baseline[a]

a Patient's baseline laboratory value.

The development of several autoimmune disorders during interferon-β therapy has been reported (see section 1), and special attention should be paid to symptoms associated with such disorders. If an autoimmune disorder is suspected, organ-specific laboratory values, e.g. thyroid hormones, as well as serum levels of corresponding autoantibodies, should be determined. In cases of autoimmune thyroid dysfunction, interferon-β has been continued with appropriate therapy.[14]

2.2.4 Depressive Symptoms

Patients treated with interferon-β-1b in relapsing-remitting multiple sclerosis had more depressive symptoms than placebo-treated patients.[29] In this study, suicide attempts, of which one was successful, occurred only in interferon-β–treated patients. Increased depression during therapy with interferon-β-1b has also been described by others.[9,51] These findings were not observed in the interferon-β-1b trial in secondary progressive multiple sclerosis, where there was no increased inci-

dence of new or worsened depression in the treatment group, with one suicide in both treatment arms (placebo *vs* interferon-β-1b). In fact, suicide attempts were more frequent in placebo-treated patients.[4] A similar observation was made in both interferon-β-1a trials, with no increase of depressive symptoms, suicide or suicidal attempts in actively treated patients.[2,3]

It is therefore unclear if there is a substantial induction of depression or worsening of pre-existing symptoms by interferon-β therapy. Since there is a high prevalence of mood disorders in multiple sclerosis patients in general,[52,53] and the suicide risk is increased many-fold compared with unaffected individuals,[54,55] every patient should be evaluated regularly for related symptoms. Patients developing depressive symptoms or those with a marked deterioration of pre-existing symptoms under interferon-β therapy should be monitored more closely. Before starting interferon-β therapy, patients should be informed about the possibility of the induction of depression and instructed to report substantial mood changes immediately. Antidepressive treatment should be introduced by a specialist using standard methods, i.e. the use of antidepressants and, if necessary, psychotherapy.

If depression cannot be treated adequately, a temporary discontinuation of interferon-β therapy should be considered. This might also clarify a possible causal relationship if symptoms subside after discontinuation and reoccur after reintroduction of therapy. It has been reported that depressive symptoms do not necessarily reappear after restarting therapy.[31] Careful monitoring of depressive symptoms in a long term follow up of interferon-β–treated patients may help to elucidate whether mood alterations are a substantial adverse effect of interferon-β therapy.

There is a report indicating that treatment of depression improves compliance in patients treated with interferon-β-1b.[51]

2.2.5 Menstrual Disorders

Menstrual disorders were significantly more frequent in interferon-β-1b–treated patients with relapsing-remitting multiple sclerosis compared with placebo-treated patients (28% *vs* 13% of premenopausal women).[5] The reports described disorders of mild to moderate severity, including intermenstrual bleeding and spotting, early or delayed menses, decreased days of menstrual flow and clotting and spotting during menstruation. There is one case report of severe vaginal bleeding associated with interferon-β-1b therapy.[56] In this case, the bleeding stopped within days after interferon-β had been discontinued and hormonal therapy started. The reasons for menstrual disorders related to interferon-β therapy are so far unknown.[56]

If such disorders appear, we recommend a gynaecological evaluation to exclude reasons not related to therapy. To our knowledge, there is no systematic investigation concerning the management of this adverse effect. There is an observation that the concomitant use of oral contraceptives might mask interferon-β-1b–induced menstrual abnormalities.[31] At this time there are only general recommendations for ameliorating this adverse event. Depending on the extent, temporary dosage reduction or treatment discontinuation should be considered.

3. Conclusion

Immunoprophylactic treatment of multiple sclerosis with interferon-β is an effective therapy in patients with relapsing-remitting and secondary progressive multiple sclerosis. With the introduction of interferon-β therapy, adverse effects are a major concern, and result in reduced compliance or discontinuation of treatment in a number of patients. Therefore, substantial efforts to minimise adverse effects are of great importance. They include extensive patient education concerning the possible risks and benefits of the treatment, as well as appropriate prophylactic and symptomatic pharmacological and nonpharmacological measures. By following these recommendations, the number and extent of adverse events, especially in the first weeks of treatment, can be substantially decreased. However, there will probably be a small number of patients who will experience continued severe ad-

verse effects. Keeping this number as low as possible is one of the important challenges of interferon-β treatment in multiple sclerosis.

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