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Interferon-beta (INF-b) antibodies in interferon-b1a- and interferon-b1b-treated multiple sclerosis patients. Prevalence, kinetics, cross-reactivity, and factors enhancing interferon-b immunogenicity in vivo.

Abstract

We analysed the role of dosage, route and frequency of administration of clinical grade interferon-beta (IFN-b) preparations in inducing anti-IFN-b antibodies

(IFN-b-Abs) in 5 groups of relapsing-remitting multiple sclerosis (RRMS) patients who were respectively treated as follows: 1) weekly intramuscular (i.m.) injections of 30 mg of recombinant IFN-b1a (Avonex™), 2) subcutis (s.c.) injections of 250 mg IFN-b1b (Betaferon®) every other day, 3) weekly i.m. injections of 250 mg IFN-b1b (Betaferon®), 4) s.c. injections of 22 mg of IFN-b1a (Rebif®) three times a week, and 5) i.m. injections of 22 mg of IFN-b1a (Rebif®) twice a week. IFN-b-Abs were determined by ELISA. IFN-b1b was more immunogenic than IFN-b1a not only when administered s.c. every other day, but also when administered i.m. at a lower weekly dose; i.m. injection, however, significantly delayed the appearance, and induced lower serum levels of IFN-b-Abs. In patients treated with s.c. IFN-b1b, Ab levels peaked 3 to 9 months after therapy initiation, and then slowly, but progressively, declined to pre-therapy levels that in some patients were reached after three years. Patients treated with i.m. or s.c. IFN-b1a only rarely developed IFN-b-Abs, and then at very low titers. Overall, the i.m. weekly administration of IFN-b1a was the less immunogenic treatment. In IFN-b1b-treated patients, a wash-out period of two/three months was sufficient to bring the IFN-b-Ab levels below the cut-off. Our findings suggest that the immunogenicity of IFN-b1a is low, regardless of the route of administration and the dosage, while that of IFN-b1b is high, and is significantly, but not completely reduced by i.m. administration. As IFN-b-Abs are cross-reactive, a wash-out period is suggested when the preparation is changed from IFN-b1b to IFN-b1a in order to maintain the clinical benefits of the therapy.

Full text

INTRODUCTION

A complex, but still undefined network of naturally occurring soluble factors, including cytokines, soluble cytokine receptors, cytokine receptor antagonists, and anti-cytokine antibodies regulates the activation of the immune system. Autoantibodies to cytokines are only occasionally found in the serum of normal healthy individuals, but they are frequently detected at high titers in the serum of patients with autoimmune and inflammatory diseases [1-3]. It was suggested that these antibodies down-regulate cytokine activity in pathological situations, and thereby prevent/reduce dangerous tissue damage due to cytokine excess [4, 5]. Two types of anti-cytokine antibodies have been recognized, *binding* (BAb) and *neutralizing* (NAb). It is recognized that NAbs are directed against the

receptor binding sequence of the cytokine molecule, and neutralize its action on target cells. The biological role of BAb, which bind to other molecule epitopes, is still debated. However, these antibodies may also play an immunoregulatory role by forming immune-complexes which are rapidly absorbed by the reticular-endothelial system, thus reducing cytokine bioavailability [6]. Moreover, the literature data suggest that some immunogenic epitopes of IFNs reside in distinct domains that mediate different biological activities [7].

Type I IFNs (IFN-alpha/beta) are used to treat a variety of infectious, neoplastic and autoimmune diseases, including the relapsing-remitting form of multiple sclerosis (RRMS) [8-11]. However, long-term administration of IFN-alpha/beta may evoke the appearance of anti-IFN-Abs that are often associated with therapy failure [12-14]. It follows that all factors that increase IFN-beta immunogenicity *in vivo* should be carefully evaluated when long-term therapies are contemplated. We studied the role of the route of administration and the weekly dosage of two commercially available IFN-beta preparations in inducing IFN-beta-Abs *in vivo* in RRMS patients.

MATERIALS AND METHODS

Patients

All the patients included in this study were randomly selected from MS patients having the following clinical features: clinically defined RRMS, age range 18-50 years, a baseline Expanded Disability Status Scale (EDSS) score of 1.0 to 3.5 inclusive, and at least two documented clinical exacerbations in the preceding two years. None had ever received immunosuppressive drugs, or treatment with corticosteroids in the month prior to study entry. All were exacerbation-free when IFN-beta therapy was initiated. According to the treatment modality, the RRMS patients could be divided into 5 groups, as follows:

1) 24 patients treated with 8 million international units (MIU) of IFN-beta1b (Betaferon®) sub cutis (s.c.) every other day (*i.e.*, 750-1,000 mug per week);

2) 30 patients treated with weekly intramuscular (i.m.) injections of 30 mug (6 MIU) IFN-beta1a (Avonex▒);

3) 15 patients *unconventionally* treated with weekly i.m. injections of 8 MIU (250 mug) IFN-beta1b (Betaferon®). These patients were included in a clinical trial aimed at studying the safety and the clinical efficacy of weekly i.m. injections of IFN-beta1b; accordingly, their informed consent was obtained, and the study was approved by the local Ethics Committee (A.R.M. and D.D.P., Institute of Neurology, Catholic University, Rome);

4) 16 patients treated with s.c. injections of 22 mug IFN-beta1a (Rebif®) three time a week;

5) 10 patients *unconventionally* treated with i.m. injections of 22 mug IFN-beta1a (Rebif®) twice a week, following their informed consent. These patients were included in a pre-marketing clinical trial aimed at defining the efficacy of i.m. administered Rebif. This study was approved by the local Ethics Committee (A.B., Multiple Sclerosis Center, Clinical Neurology, S. Luigi Hospital, Orbassano).

No significant difference in age range, gender distribution, age at disease onset, mean disease duration, and number of relapses in the two years before therapy initiation was observed among the five groups of patients.

Peripheral blood was collected at 8.00 a.m. before treatment (T0), at one (T1), and three (T3) months, and then every three months (T6, T9, ect.) after treatment initiation, and allowed to clot at room temperature for one hour before centrifugation. Serum samples were stored at - 40° C in small aliquots, and thawed just before testing. All tests were performed in one laboratory (Padova), and in a blind fashion.

*Demonstration of IFN-*beta*-Abs*

To detect IFN-beta-Abs, a standard indirect immunoenzymatic assay (ELISA) was used [15]. Briefly, flat-bottomed microtiter plates (Immulon I, Dynathec) were coated with 200 mul/well of 1 mug/ml diluted IFN-beta1a or IFN-beta1b overnight at + 4° C. After washing and blocking (0.5% BSA in PBS-Tween), two-fold dilutions (starting from 1:10 diluted specimens) of serum samples were added in triplicate, and incubated for 1 hour at room temperature. After further washing, 150 mul of 1:4.500 diluted peroxidase-conjugated goat anti-human IgG antiserum (Cappel Laboratories) were added for 1 hour at room temperature. After further washing, 150 mul of chromogen substrate mixture (0.025% ABTS,

pH 4.0) were added, and incubated at 37° C for 1 hour. Absorbance was determined at 415 nm (Titertek, Flow). Cut-off for positive samples was 0.180 OD, corresponding to the mean + 3 SD of the OD of 20 sera from healthy subjects (blood donors). A very similar OD mean value (0.190) was obtained at T0 from the sera of the RRMS patients included in the present study.

Statistical methods

Mean, standard deviation (SD), and standard error (SEM) were calculated at every time-point. Student's *t*-test or Anova were applyed when appropriate.

RESULTS

Patients treated with 250 mug (8 MIU) of IFN-beta1b s.c. (group 1) showed a rapid increase in serum IFN-beta-Ab levels (Figure 1). The IFN-beta-Abs were almost exclusively IgG (trace amounts of IgM were rarely found), and detectable in up to 60% of the patients as early as one month after treatment initiation. At T3, 90% of these patients were IFN-beta-Ab positive ($p = 0.000$), and this percentage did not change during the first year of therapy. However, at T18 and T24, the percentage of positive patients fell to 65 and 50% ($p = 0.01$), respectively. Highest IFN-beta-Ab levels were reached after three to nine months and then, in the majority of the patients who continued the treatment, slowly but progressively declined (Figure 2,); at T36, IFN-beta-Ab levels were still detectable in some patients (2 positive out of 6 tested; T36 *versus* T0: $p = 0.09$).

Of the 30 patients treated with i.m. IFN-beta1a (group 2), none showed increased IFN-beta-Ab levels after one month, only one (3.3%) and two (6.6%) showed a mild positivity at T3 and T6, respectively, and 10% were slightly positive at T9, T12 and T15; after two years of therapy, however, only one of 20 tested patients had detectable IFN-beta-Abs. IFN-beta-Ab levels in these patients (Figure 2,) were much lower than those observed in IFN-beta1b-treated patients. In the small group of patients treated with two weekly i.m. injections of IFN-beta1a (group 5), IFN-beta-Ab levels were very similar to those observed in patients treated once a week (data not shown). No correlation was found between time of appearance and titers of IFN-beta-Abs, patient's age and gender, disease duration, and relapse rate before therapy.

In one center (A.R.M. & D.D.P., Rome), 15 RRMS patients were treated with weekly i.m. injection of 8 MIU of IFN-beta1b (group 3). This *unconventional* treatment gave us the unique opportunity to evaluate the role played by the route of administration and the IFN-beta1b dosage in inducing IFNbeta-Abs. Interestingly, IFNbeta-Ab levels increased more gradually compared to conventionally treated (*i.e.*, s.c. every other day) patients: at T3 *only* 1/3 of the patients had IFN Abs, and at T6 50% were positive (Figure 2,). In these patients, IFN-beta-Abs peaked at T12 with OD levels usually lower than those observed in patients treated with s.c. IFN-beta1b; thereafter, they declined slowly and progressively, and at T21 all the tested patients were negative. Therefore, the i.m. and less frequent administration of IFN-beta1b delayed the appearance and reduced the levels of IFN-beta-Abs.

In patients treated with s.c. IFN-beta1a three time a week (group 4), IFN-beta-Ab behavior was similar to that observed in patients treated with i.m. injection (Figure 2,): only 4 patients (25%) developed antibodies, but only two showed high OD values from T6 to T15. Therefore, the route of IFN-beta1a administration did not significantly influence the appearance of IFN-beta-Abs.

Longitudinal analysis of IFNbeta-Ab levels in patients whose treatment was changed from s.c. IFN-beta1b to i.m. IFN-beta1a definitely confirmed the latter's lower immunogenicity. Indeed, in three patients previously treated with IFN-beta1b, we observed that treatment with weekly i.m. IFN-beta1a after a wash-out period of two/three months, during which IFN-Ab levels fell below the cut-off value, did not induce antibody reappearance in the subsequent observation period (up to 18 months) (two of these patients are reported in Figure 3, A and B). In 4 patients who underwent a change in therapy without a wash-out period, we observed a very slow decline in IFN-Ab titers, but antibodies were still detectable more than one year later (two representative patients - C and D - are shown in Figure 3). IFN-beta-Abs were clearly cross-reactive, and sera from IFN-beta1b-treated patients displayed the same or even higher antibody titers when tested against IFN-beta1a (Figure 4).

DISCUSSION

Our study confirms that IFN-beta1b is highly immunogenic when administered s.c. every other day [16,17], and demonstrates that its weekly i.m. administration significantly delays the appearance of IFN-Abs and reduces their levels, thus

confirming observations in experimental models [18]. On the other hand, in s.c. or i.m. IFN-beta1a-treated patients IFN-beta-Abs develop less frequently and at lower levels. This indicates that the s.c. route does not play a crucial role in inducing IFN-Abs when patients are treated with the "natural" form of the molecule (glycosylated, with no amino acid substitution/deletion). Our findings are unique and particularly interesting because they demonstrate that IFN-beta1a and IFN-beta1b immunogenicity significantly differs even when both preparations are administered i.m. once a week. Therefore, neither the route of administration, nor the weekly dose of IFN-beta1b are sufficient to explain the strong Ab response to the "mutein" form of the IFN-beta molecule (unglycosylated, with amino acid substitution and deletion). As suggested by pre-clinical studies, the structure of the molecule and, probably, the presence of aggregates in the final solution might play a crucial role in determining IFN type I immunogenicity [19, 20]. Indeed, glycosylation was demonstrated to be important for the creation of structurally stable glycoproteins [21], and de-glycosylation was found to diminish the biological activity of IFN-beta due to the formation of soluble aggregates [22]. Following Dresser's study (1962), it is well known that the aggregated form of protein antigens induces a complete antibody response, while the deaggregated soluble form induces tolerance [23].

We confirm that IFN-beta-Abs produced in RRMS patients during therapy are cross-reactive [24-26]; indeed, when tested against IFN-beta1b or IFN-beta1a, sera from IFN-beta1b-treated patients displayed very similar patterns of reactivity. This cross-reactivity was also confirmed *in vivo* by the IFN-beta-Ab kinetics observed in patients who changed treatment from s.c. IFN-beta1b to i.m. IFN-beta1a without a wash-out period; in these patients, the non-immunogenic IFN-beta1a maintained a long lasting IFN-beta-Ab response, whose longitudinal behavior resembled that observed in patients treated for three years with IFN-beta1b. Considering also that IFN-betaAbs completely disappeared after a short wash-out period, these kinetics indicate that the continuous administration of the antigen maintains the Ab response, but is unable to trigger the differentiation of additional Ab-forming cell precursors over time; if IFN-beta-Abs disappearance after a short wash-out period is due to Ag tolerance, then similar results should be expected in IFN-beta1b-treated patients who start IFN-beta1b treatment again after the wash-out. In any case, the IFN-beta-Ab cross-reactivity suggests that in patients who develop high antibody levels, switching from the immunogenic IFN-beta1b to the non-immunogenic IFN-beta1a may not

be clinically beneficial, and that a wash-out period of two/three months is appropriate before starting a second IFN-beta-based treatment.

CONCLUSION

In conclusion, our study suggests that the structure of the molecule is relevant to the immunogenicity of IFN-beta, and demonstrates that the i.m. route of administration delays/reduces, but does not abolish the IFN-beta-Ab response to IFN-beta1b *in vivo* in RRMS patients. Therefore, the "natural" form of the molecule would preferred when IFN-beta-based, long-term treatment is initiated in patients with chronic autoimmune diseases, such as MS, in order to avoid/reduce the production of high IFN-beta-Ab levels that may bind to immunologically relevant epitopes of the molecule.

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Figures

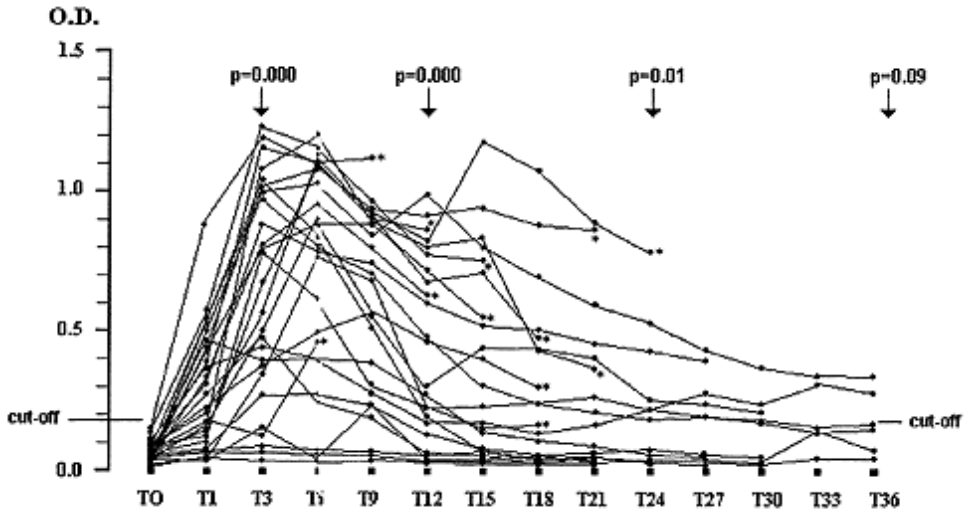


Figure 1

Time-course of IFN-beta-Abs in RRMS patients treated with s.c. injections of 250 mug IFN-beta1b (Betaferon) every other day.

Connecting lines refer to individual patients examined every three months (T0-T36) for up to three years.

* Indicates drop-out patients.

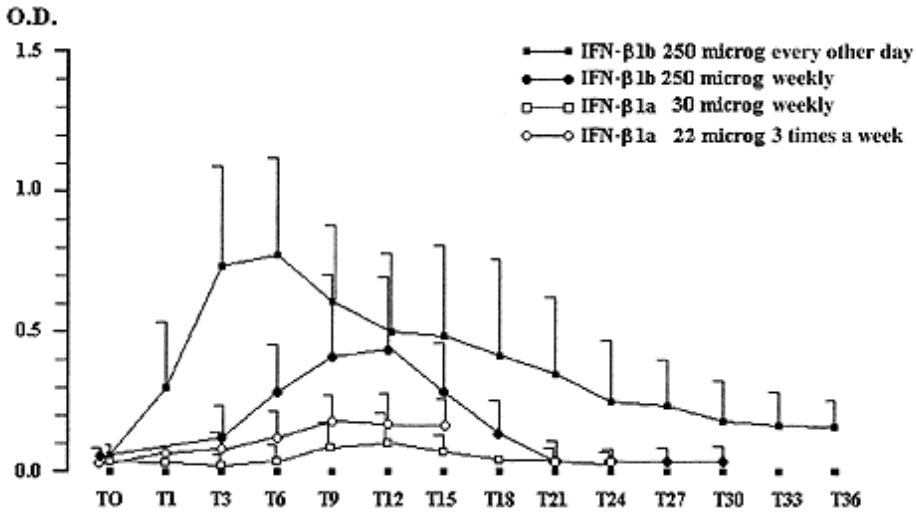


Figure 2

Time-course of IFN-beta-Abs in four groups of RRMS patients treated with : s.c. injections of 250 mug IFN-beta1b (Betaferon®) every other day, weekly i.m. injections of 250 mug IFN-beta1b (Beta-feron®), s.c. injection of 22 mug IFN-beta1a (Rebif) three times a week, and weekly i.m. injection of 30 mug IFN-beta1a (Avonex).

Means and standard deviations for all the patients studied (both antibody positive and negative) are reported. IFN-beta-Abs were analysed every three months (T0-T36).

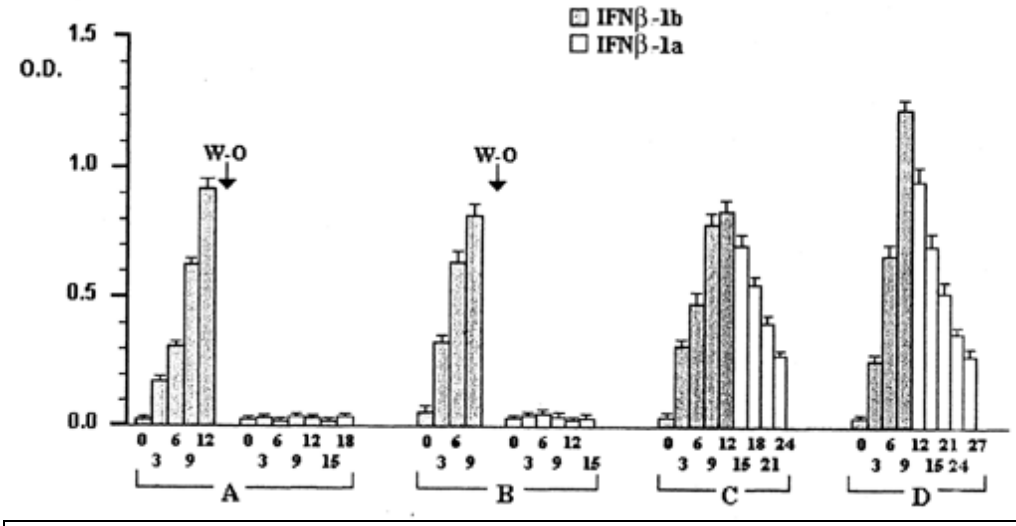


Figure 3

Effect of a wash-out pe-riod of two/three months on IFN-beta-Abs levels.

Grey and white bars show IFN-beta-Ab levels during treatment with IFN-beta1b (Betaferon) and IFN-beta1a (Avonex), respectively. Four representative patients are shown (A, B, C, D). In patients A and B, the initiation of the second IFN-beta treatment followed a wash-out period of three months, while in patients C and D treatment was changed without an intervening wash-out period.

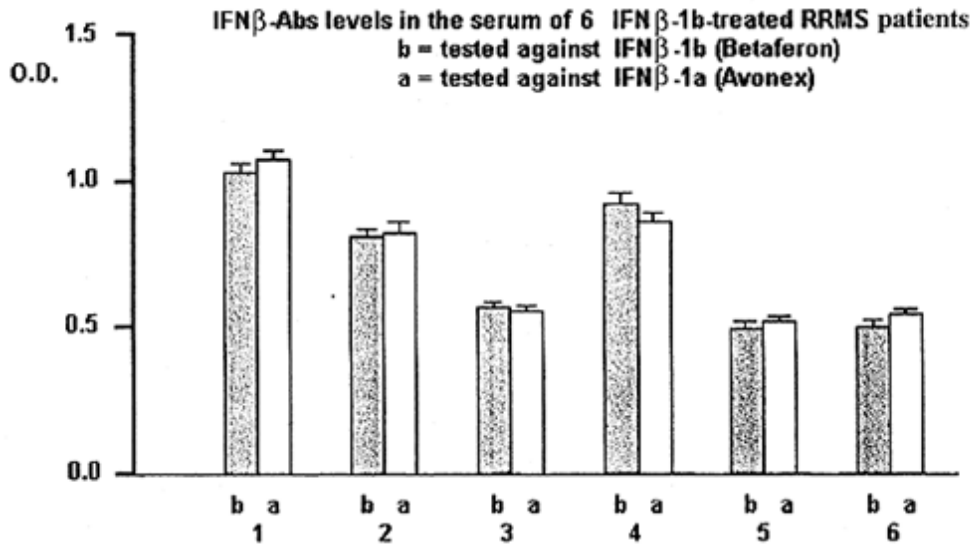


Figure 4

IFN-beta-Abs are cross-reactive.

Serum samples from RRMS patients treated with s.c. injections of 250 mug
IFN-beta1b (Betaferon) were tested by ELISA against IFN-beta1b (grey bars) or IFN-beta1a (white bars). Six representative patients are shown.

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neuroblastoma, immunotherapy, gene therapy, cytokine, IL-1b, TNF-a.

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intestinal mucosa, Crohn's disease, interleukin-18, caspase-1/ICE, immunohistochemistry, reverse transcription polymerase chain reaction.

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TNF, cytokine, LPS.

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apoptosis, caspases, Hsp27, Hsp70, T lymphocytes.

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MHC class II antigens, murine macrophages, c-Fos.

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transforming growth factor-b1, interleukin-10, U. 937 cells.

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IL-10, recombinant, rat, cytokines.

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