INTRODUCTION

Biological drugs that have a protein or peptide structure provide new and highly effective therapies for a number of conditions and diseases, but their prolonged use in patients gives rise to new problems and questions, amongst them the possible occurrence of neutralizing antibodies (Nabs).

We discuss some aspects of this particular problem in relation to interferon-beta therapy of multiple sclerosis (MS).

Interferon beta-1b is the first effective long-term therapy for MS. It has been shown to reduce in a significant way the number and severity of MS attacks both in relapsing-remitting and in secondary-progressive MS and to postpone motor and other forms of disability – as expressed in the extended disability status score (EDSS) – as well as to delay, in the more advanced progressive form of the disease, the point at which a patient becomes wheelchair-bound. It also has a strong impact on the “burden of disease” and on the occurrence of new CNS lesions, as evidenced by MRI, which indicates an impressive suppression of the acute inflammatory process in MS. Interferon beta is a human cytokine with non-specific anti-viral and anti-proliferative effects; it is also

NEUTRALIZING ANTIBODIES (NABS) AND INTERFERON BETA-1B THERAPY OF MULTIPLE SCLEROSIS

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part of a complex cytokine network involved in immune responses. As far as is known today, it suppresses acute inflammation by inhibiting some actions of interferon gamma, TNFα and other inflammatory cytokines, and by switching the T cell immune response towards the production of Th2 cytokines. On the other hand, it may also generate IL-6, a potential polyclonal B-cell activator (1). Under normal conditions, beta-interferons act on T cells in a paracrine way (cell-to-cell interaction) via receptors that are specific for type-I-interferons (α and β). This results in non-specific induction of the MxA cellular proteins as an early rapid response, but with postreceptorial signalling mechanisms different from those of the alpha-interferons.

The local effect of interferon beta and its modifications can be amplified by induction of its own synthesis (“cascade reaction”) and can be propagated by activated cells. Early biological markers of beta-interferon activity such as neopterin, 2′-5′-oligoadenylate-synthetase or β2-microglobulin (shed from macrophages) – correlation with the clinical efficacy of these molecules in MS is unknown – are elevated in a dose-dependent way for about 2-4 days in volunteers and patients after a single application of interferon-beta and its modifications (2-4). Beta-interferon plasma levels are rather high after i.v. and low or undetectable after s.c. or i.m injection but they are associated with very similar biological effects over time, as estimated by assays using these biological markers (5).

The exact mechanism of the therapeutic effect of interferon beta-1b in MS is unknown, although numerous different mechanisms of action are being proposed (for review, see 6): they include a restoration of T-cell suppressor function and normalization of beta-interferon activity, both of which are reported to be deficient in MS (6,7), an inhibition of pro-inflammatory reactions such as iNOS induction (8) and of cytokine effects (including inhibitory effects on the synthesis of TNFα, β, and interferon γ), an elevation of anti-inflammatory cytokines (e.g. IL-10, TGFβ) and, last but not least, a stabilization of the impaired blood-brain-barrier function in acute MS attacks. This effect can be demonstrated in patients within days of beginning interferon beta-1b therapy, by the disappearance of gadolinium-positive lesions in brain MRI, possibly due to an effect of interferon beta-1b on adhesion molecules, e.g. VCAM and sICAM (9,10) or metalloproteases (11).

As mentioned, interferon beta-1b constitutes the first effective long-term treatment of MS (subsequently, efficacy in MS has also been shown, but only in part, for interferon beta-1a modifications); however, as from the first pivotal study (12), there has been some concern that these beneficial effects might be jeopardized by the occurrence of neutralizing antibodies (Nabs) against these drugs after prolonged administration, at least in patients with high Nab titers.

Here, we discuss some of the biological aspects of Nabs to beta-interferons, and the methodological problems and difficulties related to their detection and quantification (which, for a number of reasons, are far from being standardized). Subsequently, the clinical data are reviewed and illustrated with some new examples from the most recent large multicenter study of interferon beta-1b in secondary-progressive MS (13), also in the light of the conclusions of an earlier expert workshop (14). We attempt to draw some tentative conclusions regarding current therapy as well as further research. At the present time, most experts in the field will concur with the view, reiterated in a recent review on Nabs (15), that quantitative comparisons between different drugs and their dosing and administration are not yet possible and that therapeutic decision-making must continue to be based on the clinical situation.

**BIOLOGICAL ASPECTS OF NABs**

Given the unknown etiology and pathogenesis of MS and its highly unpredictable and vari-
able course, studying the occurrence and the impact of antibodies arising during beta-interferon therapy is inevitably difficult and, indeed, no easy and clear picture has emerged so far. This is even less surprising if one looks at possible precedents: in fact, all protein-based biological drug therapies appear to be associated with the development of antibodies in at least some patients and at least for some time. This could be of clinical significance especially in cases where blood levels of biological drugs (and, thus, their possible neutralization by antibodies present in the serum) obviously must be taken into account (e.g. in the case of blood-borne hormones, such as insulin or growth hormone therapy, or of alpha-interferons acting on viremia in the case of hepatitis). It is reassuring that the occurrence of antibodies in these and other forms of biological therapy apparently appears only in a small percentage of susceptible patients and also that it seems to be a phenomenon that is limited in time. Furthermore, it can often be overcome, e.g. by a dose increase or other measures and, finally, we are not aware – beyond the possibility of reduced or abolished biological effects of the biological drugs and factors themselves – of any additional untoward consequences of the occurrence of antibodies to biological drugs (such as, e.g., induction of autoimmunity).

Indeed, in the case of natural and recombinant human peptide or protein therapies, we are not confronted with the strong reactions to foreign antigens that we see, for example, in microbiological disease, vaccination or organ transplantation. The patients’ condition and reactivity, but also other factors, seem to be much more important, and no uniform and strong biological reaction is to be expected. We also have to consider that MS patients per se show an increased incidence of auto-antibodies, e.g. to liver and thyroid antigens, usually in the absence of clinical manifestations (15,16). Furthermore, there are some animal data showing that under certain circumstances, not only may antibodies to cytokines not always reduce efficacy, they can even enhance the effects of these molecules, possibly by changing their kinetics and slowing down their clearance. This has been clearly shown by the work of Billiau’s group where the effects of gamma-interferon in animal models were enhanced and not reduced by specific antibodies to this cytokine (17). In children with cerebral malaria, treatment with monoclonal antibodies to TNF resulted in higher TNFα plasma levels over time (18). More recently, intravenous application of a TNFα-receptor molecule linked to the immunoglobulin Fc-fragment (lenercept) supposed to “neutralize” TNFα has, indeed, in a pilot-study, resulted in a dose-dependent worsening of MS-pathology in patients, and one interpretation could be that there is an enhancement of TNFα effects due to altered kinetics of the cytokine (alternatively we will have to revise our former view (6) that TNFα is one of the molecules that worsens MS and helps to trigger attacks).

METHODOLOGICAL PROBLEMS

Testing for antibodies is complicated by the observation that endogenous inhibitors, including Nabs to endogenous cytokines, can occur in the human body, although usually at low frequency, even without previous exposure to any biological drug of this type (19). Methods solely investigating the presence of any antibodies, e.g. ELISA or testing for antibody-producing cells (20), have not yet been validated, and in the case of binding antibodies, which may leave the biological function of the cytokine unaffected, may even be misleading when it comes to detecting possible interactions with drug therapy (15). Thus, neutralization of beta-interferon effects needs to be demonstrated in biological tests. Theoretically, biological assays of interferon activity can assess anti-viral, anti-proliferative or immunomodulatory effects in vitro or in vivo, but in view of the considerable problems as regards methodology and standardization, in vitro assays...
of inhibition of viral effects (e.g. inhibition of plaque-forming units by human stomatitis virus) or of MxA production by leucocytes are the preferred assays for Nabs because they are the most convenient and reproducible. However, it should be emphasized that these biological response markers are very likely not to be amongst the main mechanisms of action of beta-interferons in MS. The antiviral assay is performed by quantifying possible inhibitory effects of test sera and their dilutions on the protective effects of a standard amount of exogenous beta-interferon (or of one of its modifications) against virus-induced cell pathology in vitro. We thus have to deal a) with the variability of the virus-induced cytotoxic effects, b) with the variability of the inhibitory effect of the exogenous standard interferon and finally c), with the variability of the sera containing the Nabs we want to quantify (15). Furthermore, studies with monoclonal antibodies to alpha- and beta-interferons indicate that both affinity and neutralizing efficacy are of possible importance and that some Nabs, even in great excess, will not fully inhibit interferon efficacy; thus, antibodies cannot always simply be labelled “neutralizing” in an all-or-none fashion (21). Titers should be expressed as a dilution of serum which reduces 10 Laboratory Units of a given cytokine to 1 (Kawade’s method, as recommended by WHO; 22). Eventually, the relevance of any biological assay needs to be validated by clinical data documenting potential consequences on the clinical efficacy. In the case of beta-interferons in the treatment of MS patients, this has been done only to a limited extent so far and only the dataset of the relapsing-remitting study with interferon beta-1b has been intensively evaluated using statistical cross-sectional and longitudinal analysis methods (12,23).

Although various other anti-viral assays have been used by other groups in the case of interferon beta-1a, only very few comprehensive, peer-reviewed results from large long-term clinical trials are available (24,25). Differences in patient population, assay methodology and definition of a positive titer, but also in the frequency and in the technique of sampling (e.g. how long after the last injection), make any comparison between those assays, and therefore also between the different preparations of beta-interferons, quite difficult, although there is cross-reactivity of Nabs against different beta-interferon modifications (26). They all appear to react with the same antigenic epitope of the beta-interferon molecule (aminoacids 39-48, (27)). All this was underlined at a workshop devoted exclusively to Nabs and their effects on interferons (14). As with other interferons in therapeutic use so far, no generally accepted common reference standard and methodology for defining biological activity of the different forms of beta-interferon exists, to say nothing of a standardized and generally accepted assay for testing Nabs, even though methodological standardization and other improvements are clearly needed (15,28).

In view of the rather cumbersome and time-consuming virus inhibition assay – which might also be influenced by other inhibitory factors including heme structures, heparins or endogenous interferon-inhibiting activity – an assay based upon the rapid induction of the MxA protein on leukocytes under the influence of beta-interferons has been developed and validated against the originally used anti-viral assay (29,30). This test is currently being offered as a service to clinicians and has also provided the basis for general recommendations (31). It has to be stressed, however, that little is known about how MxA induction is related to subsequent biological effects (antiviral, antiproliferative, immunomodulatory) and how this ultimately translates into activity in MS patients (biological markers, clinical and MRI effects in various conditions as well as side effects). There appear, indeed, to be differences between these effects: in a recent study on Nabs to alpha-interferons, clear discrepancies between their influence on antiviral and antiproliferative effects were reported (32) and this is also in line with theoretical considerations (21).
In the case of a supposed autoimmune disease such as MS and its treatment by beta-interferons, a number of hypotheses (or even their combination) regarding the effect of Nabs on the pharmacokinetics (33) or biological effects of beta-interferons can be advanced:

1. Nabs do indeed reduce or abolish the anti-MS effects of beta-interferons, although the following questions remain unanswered:

   - are these effects dose- and time-dependent (i.e. what is a relevant titer, and how long must it remain elevated to achieve clinical significance?)
   - can the effect be overcome by higher drug dose or concomitant therapies?
   - are these effects similar for all indicators of disease activity and progression? (results of the longitudinal analyses of the betaferon beta-1b trial in relapsing-remitting MS do not support this assumption)
   - are these effects persistent or reversible?
   - is there cross-reactivity between different types and brands of beta-interferons, and are there differences between drugs?

2. There is no influence whatsoever.

3. Nabs enhance therapeutic effects in MS.

Finally, Nabs to beta-interferons could be an integral part of the known association between MS and increased incidence of various autoantibodies.

CLINICAL RESULTS AND CORRELATIONS

There are still insufficient clinical data on Nabs, as the primary concern of most therapeutic studies of beta-interferons so far has been to establish therapeutic efficacy in MS, formerly an orphan disease. Investigation of Nabs and their possible implications, considered a minor topic, was restricted mainly to retrospective and cross-sectional analyses of clinical trials. In the meantime, however, it has become clear that a prospective longitudinal analysis is the method of choice (23), as Nab patients seem to differ, even in baseline conditions, from patients who eventually become intermittently or persistently positive. In one interferon beta-1a study, MRI revealed a higher burden of disease at baseline in those who subsequently did develop Nabs (34), and a similar observation seems possible in one secondary-progressive study with interferon beta-1a (J. Petkau, pers. comm.).

However, as mentioned, the first peer-reviewed published attempt at establishing a correlation with the clinical situation was that of the IFNB MS Study Group (12). These authors tried to find, in a retrospective analysis, correlations with clinical effects or side effects of a high and low dose of interferon beta-1b compared to placebo in a cross-sectional data analysis. Patients were defined as Nab-positive if two tests (repeated at a 3-month interval) had at least resulted in the lowest detectable anti-interferon activity of 20 neutralizing units/ml (using the human stomatitis virus inhibition test). Patients were labelled as positive according to the idea “once Nab-positive, always Nab-positive”, even when they were actually Nab-negative again. Nabs were found in 35% of the patients with the majority of patients showing low Nab titers (below 296 neutralizing units which was the highest titer found in untreated patients). Using this cross-sectional approach for comparing Nab-negative and Nab-positive treatment periods the investigators noted for the clinical results obtained during the 6 different periods of the study of the 2 different dosages, a total of three significant differences between Nab-positive and negative treatment periods (p values of < 0.05: better effect on relapse rate at 19-24 months in the low-dose group, worse results (close to placebo) in the periods 19-24 months and 25-30 months in the high-dose group). MRI revealed larger or new lesions in the second and third years of therapy compared to Nab-negative patients, although these were still clearly fewer than in the placebo group. Other MRI parameters revealed only trends and quite surprisingly the therapeutic effect on the EDSS fa-
vored Nab-positive patients. It is worth mentioning that out of the 24% of the patients who stayed relapse-free over three years of treatment, one third were Nab-positive. This multiple-testing retrospective cross-sectional analysis had been published as a kind of worst-case scenario, and in the published guidelines the authors emphasized the preliminary aspect of the correlation attempts and stressed the importance of the clinical parameters (31). Petkau and White (23) have since strongly advocated longitudinal analysis of these same data which should also take into account the fact that Nab-positivity as defined in the study (with the minimum titer as defined by the HSV virus inhibition test occurring in 35% of treated patients), already reverted to negative titers within the 3-year study period in 60% of the positive cases (50% of these remaining negative). This kind of longitudinal analysis, which also takes into account possible differences in the baseline characteristics of the individual patient, demonstrates a certain impact of the presence of Nabs on the number of attacks but not on the disability score, EDSS, or MRI parameters. Significant results were only found in the low-dose group, especially in the case of very high titers (23). The impact of Nabs appears to be limited over time. Also, these patients, who eventually became negative again, appeared to have a sustained long-term efficacy similar to those who never had Nabs at all.

Eventually all or almost all patients may become Nab-negative again, as suggested by two cohorts of patients followed up for up to 102 months (34,35), and similar observations are known from the use of alpha-interferons (36). These findings explain why it is not possible to draw conclusions when patients treated with one product (e.g. interferon beta-1b) then have a lower incidence of Nabs in subsequent therapy with another interferon beta (e.g. one of the interferon beta-1a modifications (24)) because the patients could be expected to experience a similar decline without any change of treatment (i.e. continuing on interferon beta-1b). Furthermore, the findings of a clearly higher impact of Nabs on the relapse rate in the low-dose IFN beta-1b group support the idea that higher doses/concentrations of interferon can overcome at least part of the neutralizing activity of Nab (see also the results of the PRISMS study).

The published results thus indicate that the presence of Nabs to interferon beta-1b in MS patients appears to be a temporary phenomenon whose impact on the disease course is still unclear. Although some statistical correlations have been reported with regard to the reduction of the relapse rate, no clear predictions are possible for individual patients: Nab-positive patients might continue to remain free from new MRI lesions and clinical relapses (about one third) whilst some antibody-negative patients, for unknown reasons, can again develop frequent relapses (37). It has also been suggested that Nabs to beta-interferons occur more frequently or even exclusively in the treatment of MS but not in other conditions treated with beta-interferons (15,16). As mentioned, it has indeed been proposed that patients who develop Nabs had a more active disease before interferon beta-1b therapy was started (37) or had higher IgG levels at baseline (in an in vitro assay using peripheral blood cells; 38); however there is as yet no consensus on risk factors for developing Nabs except the disease itself.

From meetings devoted to this issue (14,39), a preliminary consensus has emerged that the decision to suspend any interferon-beta treatment in patients with MS must continue to be made on clinical grounds, and that testing for Nabs might in fact support this clinical decision-making more than other paraclinical parameters such as MRI. It also emerges that it may not be the mere presence of neutralizing activity that is important but that there could be a very small subgroup of patients with very high titers in whom an interference with clinical efficacy is perhaps possible; however, so far it is not clear what is the cut-off point that could improve the
predictive value of a positive titer for Nabs (21,40). This obviously holds true for other beta-interferon modifications. The situation regarding Nabs and different brands of recombinant interferon beta-1a is even less clear as the duration of the trials was shorter (1½ to 2 years). It is difficult to evaluate the i.m. study of a special brand of interferon beta-1a (due to some unusual patients’ characteristics and to too short a duration of therapy). In the PRISMS study of another s.c. interferon beta-1a modification tested at two different dose levels (41), Nabs did appear at 6-24 months, but sera were studied only at 6-month intervals. According to the definitions used in this study, 24% of patients had developed Nabs after 2 years in the low-dose group and 16% in the high-dose group but only 4/49 in the low- (6 MIU 3x s.c./week) as opposed to 9/32 patients in the high-dose group (12 MIU 3x s.c./week) became negative again. The lower incidence in the higher dose group seems surprising; as discussed by the investigators, this might indicate some “neutralization” of Nabs in serum by higher circulating antigen levels.

The same drug was also tested in a once-a-week s.c. schedule (in a similar way as another brand of interferon beta-1a is also used with this schedule, although on an i.m. basis in relapsing-remitting MS). The authors (42) conclude from their results that “the data from the current study, combined with prior IFN [beta-1a] studies, confirm that benefit of IFN therapy is dependent on the total dose used and is more sustained with increased injection frequency...” Furthermore, they state: “The development of Nabs also showed a dose effect. Rising weekly doses of 22, 44, 66, and 132 µg resulted in Nab formation in 5%, 16%, 24%, and 12% of patients, respectively. There was no indication in either PRISMS or OWIMS that Nabs had a deleterious clinical impact...” but detailed analyses were not presented and, in particular, no longitudinal analysis is available. There is, indeed, for this type of interferon-beta some evidence for a dose-dependent increase both in efficacy (reduction of the relapse rate) and in the incidence of Nabs with the exception of a lower rate at the highest dose tested (see Table I). While this also holds true for the dose-dependency of efficacy when comparing the two doses of interferon beta-1b of 1.6 and 8 MIU every other day (e.o.d.) used in the pivotal trial in relapsing-remitting MS, there was no difference between the dose groups with regard to the incidence of Nab-positivity.

NEW RESULTS FROM THE STUDY OF INTERFERON BETA-1B IN SECONDARY PROGRESSIVE MS

As disability is a subject that continues to generate controversy, the results of the first large controlled study in secondary-progressive MS

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<th>Weekly dose (µg s.c.)</th>
<th>Relapse reduction</th>
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<tr>
<td>22 (OWIMS)</td>
<td>0</td>
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<tr>
<td>30 (MSCRG i.m.)</td>
<td>9.6%</td>
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<td>14%</td>
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<tr>
<td>44 (OWIMS)</td>
<td>19%</td>
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<td>16%</td>
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<td>66 (PRISMS)</td>
<td>33%</td>
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<td>132 (PRISMS)</td>
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Modified from Ref. 42.
(13) were awaited eagerly. The results of this interferon beta-1b study confirm those obtained in patients with the relapsing-remitting form of the disease. Seven hundred and eighteen (718) patients with secondary-progressive MS (EDSS 3.0-6.5) were treated either with placebo (358) or interferon beta-1b (8 MIU e.o.d. s.c.) for up to 36 months (mean duration of treatment about 800 days) in 32 European trial centres. There was a highly significant difference in “time to progression” (as well as in “time to wheelchair” as relevant and well-defined clinical outcome parameters) in favour of interferon beta-1b (with a range of 9-12 months difference between interferon beta-1b and placebo), and this effect was similar in patients with or without superimposed relapses. As in relapsing-remitting MS, there was also a significant reduction in the frequency and severity of relapses (if present) and the number of MS-related hospitalizations. The known safety profile of the product was confirmed and no increased evidence of depression or suicide attempts was found. Twenty-eight per cent (28%) of the patients developed Nabs at some point in the study whilst being treated with the active drug and again about 47% and 37% were found to become Nab-negative and persistently negative again, respectively. As for the study in patients with relapsing-remitting MS a negative influence of Nabs was found only for the relapse rate, while MRI- and EDSS-related efficacy parameters were again found to be either unaffected or even influenced in a positive way by the Nab-positive status.

In order better to put into perspective the importance of these statistical findings with respect to therapeutic decisions in individual patients, the following examples from the study in secondary-progressive MS are meant to show the variability and unpredictability of the disease course and its relation to the Nab status. There are patients who, despite having high Nab titers, remain clinically stable or, as assessed by MRI, stabilize again while high Nab titers are maintained.

In other patients there is some coincidence between Nab-positivity and a relapse and an increase in EDSS; however, while the titers can remain very high, the clinical situation normalizes again. There are a few patients who have initially high antibody levels which subsequently disappear whilst the EDSS increases steadily and relapses occur. Others show very low antibody titers, again accompanied by an increase in EDSS: whilst this score further increases and relapses occur, the antibodies return within the normal range. These are just a few random examples selected from Nab-positive patients in order to underline the importance, when it comes to making therapeutic decisions, of the individual clinical course rather than the Nab status.

These observations confirm the long-term observations of Henry McFarland’s group who were also unable, in patients with very frequent gadolinium-positive lesions who had shown a dramatic response to interferon beta-1b treatment, to detect any straightforward pattern once Nabs could be found (37 and personal communication).

CONCLUDING REMARKS

There has been much debate over the potential clinical significance of Nabs for beta-interferon therapy of MS, and part of this debate has already been summarized (14,15,39,40,43, 44). The state of the art still appears to be best summarized by the conclusions of the 1997 New York meeting of experts, which were echoed in other review articles and which are supported by our experience:

• All endogenous and exogenous class 1 interferons are capable of eliciting an antibody response.
• All interferon-beta modifications in clinical use share the same antigenic epitopes and Nabs do cross-react.
• As a rule, about one quarter of patients treated for more than 1 year will become antibody-
positive, with most of them returning negative again over the years. Even at high titers, antibody levels may sporadically fall and/or disappear.

- No clinically validated “low titer” and “high titer” cut-off points for anti-interferon antibodies have been established.
- Although interferon-beta Nabs may have some statistical association with reduced efficacy in a few parameters in some patients, there are no clear or consistent correlations between the appearance of these antibodies and the clinical course of MS in individual patients.
- Compared with patients with low titers of anti-interferon antibodies, those with high titers may be more likely to become temporary non-responders to treatment; however, some antibody-positive patients with high titers continue to respond to treatment, and some antibody-negative patients become treatment-non-responders as well.
- There is no proven association between anti-interferon-beta antibodies, various biological response markers of interferon-beta activity and ultimate clinical efficacy.

In summary, Nabs might have some clinical significance but at this moment, it is very hard to draw conclusions: they might be more important at lower beta-interferon dosages (as suggested by the interferon beta-1b pivotal trial as well as the PRISMS study) and if so, their effects could be overcome by higher doses (as in insulin therapy of diabetes). Clearly, it is not possible simply to say that “presence of antibodies = absence of efficacy”. As the immune reaction is rather weak, corticosteroids might suppress it rather easily and possibly with lasting efficacy, and results of a recently presented study show that monthly glucocorticosteroid courses led to a prevention of Nab development (45) reducing the incidence of Nab-positivity from 24.6% to 12.5% (after 12 months of treatment, with a definition of one positive titer only).

Given the lack of information, it is not reasonable to speculate whether different brands, modifications or subtle chemical or structural differences have an influence on the incidence of Nabs. There is no reason to switch from one product to another but continuation of treatment based upon clinical evaluation is probably a good option as the antibodies, if present, are quite likely to disappear after several months or years of therapy. Furthermore, there is also no evidence for any correlation between the occurrence or the titers of Nabs and systemic or local adverse effects. As stated at the New York meeting (14), however, the clinical significance of anti-interferon antibodies, at least in MS, is probably less than assumed previously (12), and low titer antibody activity is best ignored (46).

From all these conclusions it appears obvious that, until further information is available, it is the clinical course of the disease in the individual patient that must be the basis for decision-making in the treatment of MS in the best interests of the patients suffering from this severe and unpredictable disease.

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