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Dose and frequency of interferon treatment matter

INCOMIN and OPTIMS

Abstract Three different interferon beta (IFNβ) products are currently approved for the treatment of patients with relapsing-remitting multiple sclerosis (RRMS). However, the recommended method of administration, the dosage and the frequency of administration differ widely between each of the three products. Although controlled clinical trials have demonstrated the efficacy of both alternate-day IFNβ-1b (Betaferon®/Betaseron®) and once-weekly IFNβ-1a (Avonex™) compared with placebo, it is likely that patient compliance, efficacy and tolerability are affected by the dosage regimen used.

There are several issues to consider. Once-weekly administration may be associated with fewer adverse events and greater convenience, and it has been suggested that this may increase compliance. Conversely, frequent administration may be associated with increased overall efficacy. There is a convincing pharmacological rationale indicating that frequent dosing, with an interval of less than 72 h, is necessary to sustain the activity of intracellular molecular signalling pathways responsible for regulating IFNβ-induced gene expression. However, there was a need to explore the overall effectiveness of the two administration protocols in a comparative trial.

The INCOMIN (Independent Comparison of Interferon) study compared clinical and magnetic resonance imaging (MRI) efficacy of IFNβ-1b 250 µg (8 MIU) subcutaneously (s. c.) on alternate days and IFNβ-1a 30 µg (6 MIU) intramuscularly (i. m.) once weekly in patients with RRMS. INCOMIN demonstrated convincingly that clinical and MRI outcome measures were significantly better in the IFNβ-1b-treated group. Blinded MRI evaluation confirmed the clinical results. Despite some limitations of the study design, imposed by the ethical and practical challenges of conducting comparative trials of injectable therapies, the concordance of the clinical and MRI findings indicate that frequently administered IFNβ-1b reduced evidence of disease activity more effectively than once-weekly administered IFNβ-1a, with the clinical benefits for patients becoming more pronounced over time.

Given that the response to IFNβ appears to be dose dependent, the question that might be asked is whether greater efficacy can be obtained by increasing doses beyond those currently approved. OPTIMS (Optimization of Interferon dose for MS) is currently examining the safety and efficacy of a dose of IFNβ-1b that is higher than any currently marketed IFNβ. While OPTIMS is still underway, preliminary safety analyses indicate that higher doses are well tolerated.

Key words interferon beta-1b · interferon beta-1a · clinical trial · relapsing-remitting · multiple sclerosis · relapse

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Introduction

There are three interferon beta (IFNβ) products currently approved for the treatment of relapsing-remitting multiple sclerosis (RRMS). One product containing IFNβ-1b (Betaferon®/Betaseron®) is administered subcutaneously (s. c.) every other day at a dose of 250 µg (8 MIU). The other two are IFNβ-1a products, one administered intramuscularly (i. m.) once weekly (Avonex™) at a dose of 30 µg (6 MIU), the other s. c. three times a week (Rebif®) at a dose of 22 (6 MIU) or 44 µg (12 MIU).

The efficacy of all three IFNβ products has been demonstrated in patients with RRMS in randomised clinical trials [5–7, 10, 11, 14]. Beneficial effects have been observed on relapse-related measures of disease and on magnetic resonance imaging (MRI) outcomes, compared with placebo. However, questions regarding the optimal dose and administration frequency, and the duration of treatment remain unanswered.

Many patients are currently treated with once-weekly IFNβ – the perceived increase in convenience from fewer injections each week may be thought to increase the likelihood of compliance, although there is no published evidence to date to support this hypothesis. The requirement for prolonged treatment, particularly if disease stabilisation has occurred, could also push patients towards fewer weekly doses, again for reasons of convenience. However, any perceived increased convenience may be gained at the expense of efficacy.

Clinical and pharmacological evidence to date suggests that the efficacy of IFNβ is dosage dependent [5–9, 14, 16]. There is also evidence that simply increasing the dose is insufficient – more frequent administration is required [1, 13, 14]. Until recently, no data from direct comparisons of the different IFNβ formulations to support the superiority of high dose and frequent administration have been available. However, two studies comparing different IFNβ products, INCOMIN (Independent Comparison of Interferons) [2] and EVIDENCE (Evidence for Interferon Dose Effect: European-North American Comparative Efficacy) [9] have now been published. In addition, the findings from INCOMIN have been further extended to examine the possibility of reducing the IFNβ dose from every other day to once weekly in patients with RRMS and stable disease. These studies, together with other ongoing trials, will help to answer the question of the most appropriate IFNβ dose and frequency to use. This paper will provide an overview of the studies and the other evidence relating to these questions of dose and administration frequency.

The rationale for high-dose therapy

There is a body of evidence from a number of clinical and pharmacological studies indicating that clinical and biological responses are greater at higher IFNβ doses. A study comparing the biological effects of i. m. IFNβ-1a once weekly and s. c. IFNβ-1b every other day demonstrated a significant increase in the levels of several biological markers in favour of more frequent/higher dosing [17]. Levels of MxA, neopterin, β_2-microglobulin and interleukin (IL)-10 were maintained at a high level throughout the 1-week study period with IFNβ-1b, while after a single dose of i. m. IFNβ-1a, they typically returned to baseline within 5 days of administration. Rothuizen et al. [13] studied the immunological effects of IFNβ (the interferon-induced inhibition of pro-inflammatory cytokine production) by administering a weekly IFNβ dose of 66 μg to healthy volunteers, either as a single once-weekly dose, or as three separate 22 μg doses given during the week. The biological activity of IFNβ, as assessed by the inhibition of cytokine production, increased by as much as threefold when the IFNβ dose was administered three times weekly.

Clinical studies comparing different treatment regimens of IFNβ consistently demonstrate the greater efficacy of the higher dose [5, 6, 8, 11]. The original pivotal study of IFNβ-1b, which examined the efficacy of 50 and 250 μg every other day indicated significant benefits in relapse rate and MRI parameters for the 250 μg dose compared with both placebo and the 50 μg dose. In the case of the 50 μg dose, only the effect on relapse rate was significant relative to placebo [5, 6, 10]. Data from the PRISMS (Prevention of Relapses and Disability by Interferon beta-1a Subcutaneously in MS) trial examining the efficacy of s. c. IFNβ-1a indicated a significant benefit for the higher dose (44 μg) and a lower dose (22 μg) given three times weekly, compared with placebo [11]. Both doses had significant effects on relapse rate, time to first relapse, the proportion of patients remaining relapse free and time to disability progression. There were also significant reductions in MRI burden of disease and new lesion development. For each outcome measure, there were dose-related increases in effect, although only with the MRI parameters did these become significant [11].

When once-weekly s. c. IFNβ-1a (44 and 22 μg) was assessed in the OWIMS (Once-Weekly Interferon for MS) study, significantly greater effects on MRI measures were seen using the higher dose compared with either the lower dose or placebo. However, no significant clinical effects were observed relative to placebo [14].

The data from both PRISMS [9] and the original pivotal trial of IFNβ-1b [5], together with data from the Multiple Sclerosis Collaborative Research Group trial of once-weekly i. m. IFNβ-1a [7] were recently compared using evidence-based medicine measures and an intent-to-treat analysis [3]. Three evidence-based medicine measures were used for comparison – number needed to treat (NNT), relative risk (RR) and absolute risk reduction (ARR). Although all three studies demonstrated significant improvements in relapse-related and MRI measures of disease relative to placebo [5–7, 10, 11], only the analyses from the pivotal study of IFNβ-1b and PRISMS were based on the ITT population [5, 6, 10, 11]. Analyses based on the ITT population include data from all patients who begin therapy, regardless of whether they remain in the study, therefore providing a more accurate assessment of drug effects. The results of this comparison showed that significant reductions in relapse rates and MRI measures of disease were obtained only with frequently administered regimes, and that

once-weekly dosing failed to produce any significant effects [3].

When taken together, the results from these studies and analyses indicate that higher doses are more effective. This observation has been echoed by the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology, which, in a recent report on disease modifying therapies, suggested that there was evidence to support a clinically relevant dose-response relationship for IFNβ [4]. However, there is also evidence that simply increasing dose while maintaining once-weekly administration is insufficient to significantly increase efficacy [1] – more frequent administration may also be needed.

While there is obviously an emerging pattern in the clinical trials performed to date, the comparison of different studies performed at different times and on different cohorts is problematic at best. The only way to establish the most effective dose and administration regimen is to perform direct comparative studies on the different IFNβ preparations. Until recently, no such comparative clinical studies of different IFNβ doses and administration schedules had been performed. INCOMIN was designed to provide answers to the question of the most appropriate IFNβ dose and frequency of administration [2].

INCOMIN

INCOMIN was a prospective, randomised, 2-year study comparing IFNβ-1b (250 µg s. c.) administered every other day and IFNβ-1a (30 µg i. m.) administered once weekly in 188 patients with RRMS. The study was carried out independently of the pharmaceutical industry, with support from the Italian Ministry of Health and the Italian MS Society [2]. The primary clinical outcome measure was the proportion of patients remaining relapse free and the primary MRI outcome measure was the proportion of patients remaining free from new T2 lesions. The clinical evaluations were unblinded; however, MRI evaluations were performed in a blinded fashion. The INCOMIN study demonstrated that the higher dose frequently administered IFNβ-1b was superior to once weekly IFNβ-1a [2].

Significant benefits were seen in clinical outcomes, including the primary clinical outcome measure, the proportion of patients remaining relapse free (51 % versus 36 %, $P < 0.036$), and many of the secondary clinical outcome measures [2] (Fig. 1). The MRI results confirmed the clinical results. The proportion of patients remaining free of new T2 lesions was significantly increased relative to IFNβ-1a (55 % patients remaining free of new T2 lesions versus 26 %, respectively, $P < 0.0003$). Secondary MRI outcomes were also significantly improved in the IFNβ-1b-treated group [2]. The incidence of adverse events was similar between the two treatment groups with the exception of injection-site reactions, which were significantly higher in IFNβ-1b-treated patients, most likely associated with the 3.5-fold greater number of injections administered [2].

A second study, EVIDENCE, compared the efficacy of three-times-weekly s. c. IFNβ-1a (44 µg) with once-weekly i. m. IFNβ-1a (30 µg) over 48 weeks [9]. The results of this study demonstrated significantly greater clinical and MRI benefit for the more frequently administered treatment, both confirming the results seen in INCOMIN and providing further data in support of the rationale for higher dose, frequent administration of IFNβ [9].

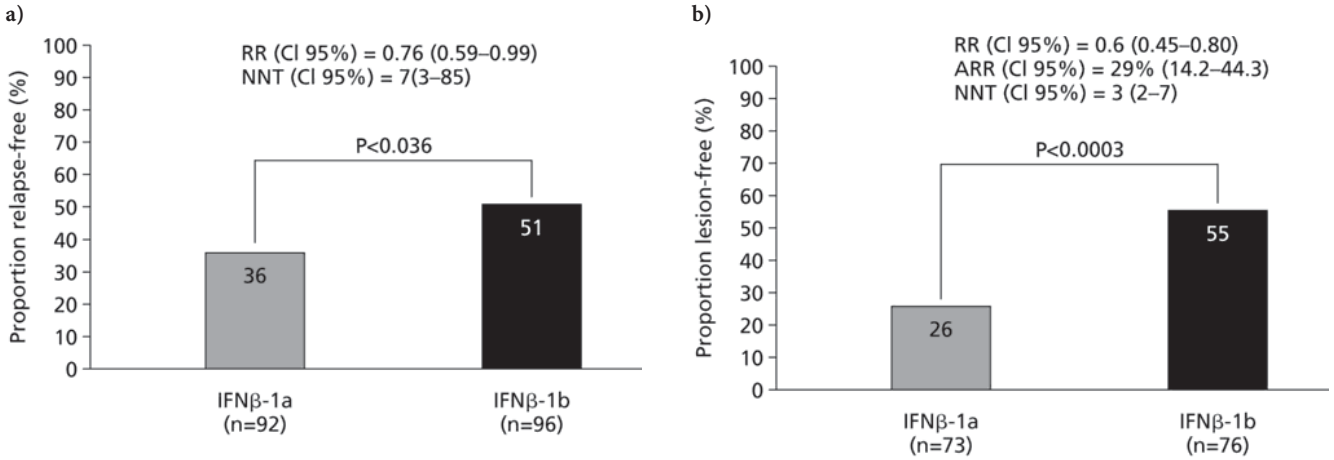


Fig. 1 INCOMIN primary outcome measures, **a** clinical, **b** MRI. Both are significantly improved with IFNβ-1b treatment compared to once-weekly IFNβ-1a

The consequences of reducing IFNβ dose – the Dose Reduction Study

Both INCOMIN and EVIDENCE support the notion that high-dose, frequently administered IFNβ is the more effective treatment for RRMS [2, 9]. However, MS is a chronic disease, requiring equally long-term treatment. Faced with the prospect of multiple injections each week for the foreseeable future, many patients might wish to reduce the dose and frequency of administration, in the hope of improved convenience, if they have achieved disease stability.

A further study was designed to test whether patients achieving disease stabilisation using IFNβ-1b (250 µg s. c. every other day) could maintain their clinical benefit if switched to once-weekly IFNβ-1a (30 µg i. m.) (Fig. 2).

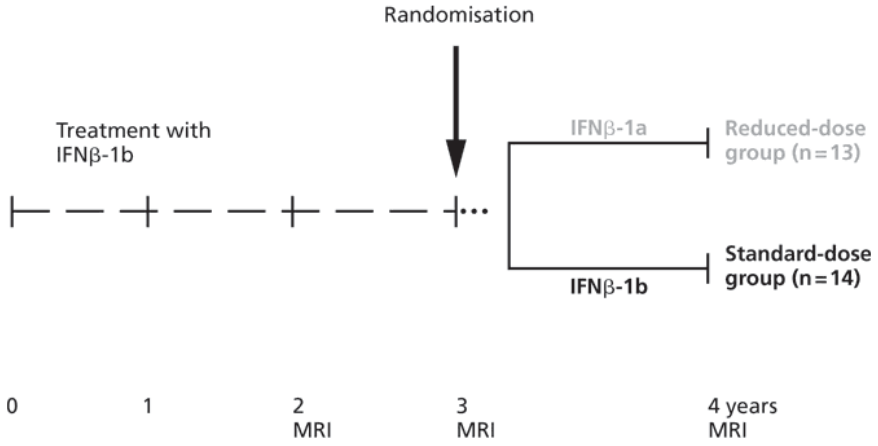
Some of the patients who participated in INCOMIN with definite RRMS and stable disease (defined as no relapses or progression of no more than 0.5 points in the previous 24 months, and no MRI activity in the last 12 months) who had been receiving IFNβ-1b for at least 36 months were included in the study. Patients were randomised either to continue receiving IFNβ-1b, or to gradually reduce the dose of IFNβ until they were receiving once-weekly i. m. IFNβ-1a (30 µg), then followed for 12 months.

Patients remaining on IFNβ-1b did significantly better than those receiving once-weekly IFNβ-1a. The number of patients remaining relapse free, the annual relapse rate and MRI outcome measures were all significantly better in those continuing to receive IFNβ-1b every other day (Fig. 3). The data from this study support the concept that not only are high dose and frequent administration important determinants of response, but also that, in order to maintain the clinical and MRI benefits, high-dose, high-frequency administration must be maintained.

The tolerability of higher doses – OPTIMS

As we have seen, the evidence obtained to date would appear to support the assertion that a regimen of high, multiple-weekly doses of IFNβ is more effective than once-weekly dosing [2, 9]. There is also evidence indicating that a dose-response relationship for IFNβ exists [5, 6, 8, 10, 11]. Not all patients respond optimally to the approved doses of IFNβ currently marketed and, given the above observations, it is reasonable to ask whether

Fig. 2 The Dose Reduction Study – trial design



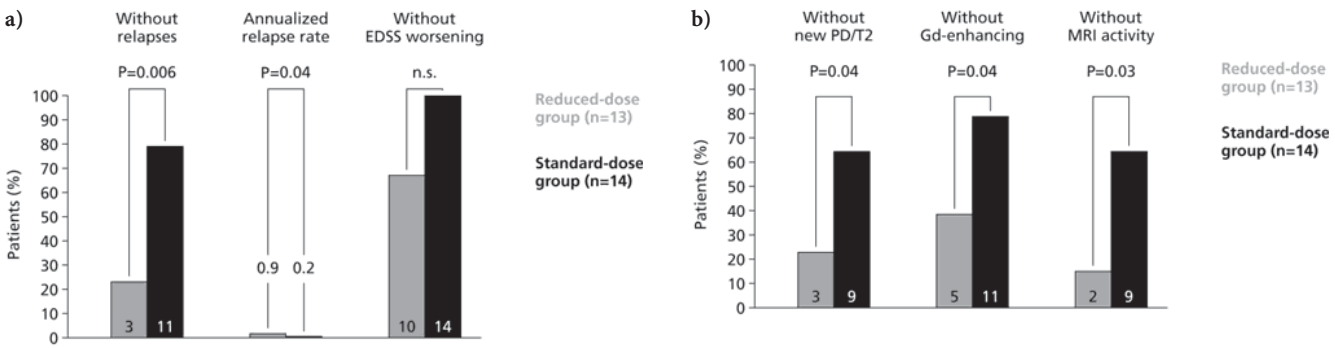


Fig. 3 High-frequency IFNβ-1b must be maintained in order to ensure continued treatment benefits for both **a** clinical and **b** MRI outcomes

using IFNβ doses higher than those currently approved could generate an improved response in these patients. There is some evidence from a pilot study that treatment responses to IFNβ-1b extend beyond the currently approved dose. In this study, IFNβ-1b was given to patients at doses of up to 500 µg. While none of the patients receiving this higher dose experienced relapses during the study period, adverse events – in the absence of any titration or forms of prophylaxis – meant that the majority had to be switched to a lower dose [8].

Since completion of this pilot study, much has been learned regarding the management of adverse events. While IFNβ is well tolerated, with a good safety profile, a number of adverse events are associated with therapy with these drugs. Typically, skin reactions (rash, erythema, pain) and flu-like symptoms (fever, chills, headache) predominate, and may be worse at the higher doses [15]. However, these adverse events can now be managed very effectively. Skin reactions can be reduced by measures that include injection-site rotation, and the use of automated injection systems [15]. Flu-like reactions become less frequent over time, and can also be managed with non-steroidal anti-inflammatory drugs (NSAIDs) or ibuprofen [12]. Gradually titrating the drug over a period of several weeks, to achieve the therapeutic dose, is also effective.

Given that adverse events can now be managed more effectively, there has been a greater focus on the use of doses above those currently approved, with the aim of increasing the number of patients benefiting from IFNβ-treatment. The first study designed to look at the question of higher dose therapy is the OPTIMS (OPTimization of Interferon for MS) study, which is investigating the use of 375 µg (12 MIU) IFNβ-1b administered s. c. every other day (Fig. 4). OPTIMS is a multicentre randomised 12-month study with a planned enrolment of 230 patients with RRMS. Patients will receive the standard IFNβ-1b dose for a 6-month run-in period, during which time they will undergo monthly MRI scans. Those patients assessed as responding optimally to the approved dose will continue with IFNβ-1b at the approved dose. Those patients with a sub-optimal response, as assessed by relapses, or the presence of new or enlarging T2 or Gd-enhancing lesions, will be randomised to receive either the standard treatment (250 µg), or 375 µg (12 MIU) IFNβ-1b s. c. every other day. All patients will then be followed for a further 6 months. It is hoped that a total of 100 sub-optimal responders and 100 normal responders will be recruited.

To date, some patients have completed the full year in the study, enabling comparison of adverse events in the two dose groups. Currently, the incidence of adverse events is no higher in the higher dose group, indicating that the higher dose is as well tolerated as the approved dose.

Conclusions

While IFNβ has been shown to be effective in the treatment of RRMS, the question of the optimal dose and frequency of administration remains a controversial one. Data from a number of different studies indicate that the response to IFNβ is dose dependent.

Data from INCOMIN and EVIDENCE suggest that frequent administration of IFNβ, several times per week, coupled with a high dose offers significantly better clinical and MRI benefits compared to once-weekly schedules. In addition, an extension of the INCOMIN study has shown that this treatment must be maintained, even after long periods of disease stability, in order to maintain these benefits. These data indicate that not only should patients receive frequent, high-dose IFNβ treatment in order to achieve the greatest clinical effect, but also that this therapy must be maintained in order to sustain this treatment benefit. Reducing dose to once-weekly IFNβ-1a may offer perceived benefits in terms of convenience, but this preference has a clinical cost.

Finally, it may also be possible to increase the IFNβ doses currently used in order to increase the number of patients benefiting from treatment. Several studies are

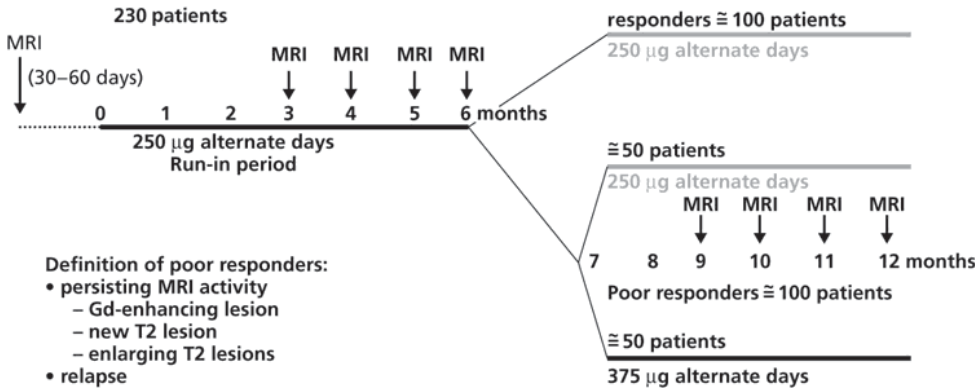


Fig. 4 The OPTIMS study – trial design

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