SHORT REPORT

Interferon β treatment for multiple sclerosis has a graduated effect on MRI enhancing lesions according to their size and pathology

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Abstract

***Objective*—The ability of recombinant human interferon β-1a (rh-IFN β-1a) to suppress multiple sclerosis activity, evaluated from MRI, was assessed across a range of lesions enhancing at different gadolinium-DTPA (Gd) doses and with different sizes.**

***Methods*—Every 4 weeks, standard dose (Sd; 0.1 mmol/kg Gd) and triple dose (Td; 0.3 mmol/kgGd) MRI were obtained from 18 patients with relapsing-remitting multiple sclerosis for 3 months before and 4 months after starting treatment with 44 μg rh-IFN β-1a subcutaneously, once a week.**

***Results*—The total numbers of enhancing lesions were 145 and 126 on Sd scans and 278 and 192 on the Td scans obtained before and after treatment. The introduction of treatment decreased, on average, the rate of appearance of new enhancing lesions seen on Sd and Td scans by 37% ($p<0.001$). Treatment effects on new enhancing lesions seen on Td scans was, on average, 28% higher than on those seen on Sd scans. The distribution of lesion sizes on Td scans changed significantly during the treatment period ($p=0.05$), due to a marked decrease in the number of small lesions.**

***Conclusions*— The effect of 44 μg rh-IFN β-1a in reducing multiple sclerosis disease activity, as monitored by Gd enhanced MRI, is not homogeneous, but graduated according to the pathological characteristics and size of the lesions.**

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In patients with relapsing-remitting multiple sclerosis, treatment with interferon (IFN) β-1b[1–3] or IFN β-1a[4–7] results in a significant reduction in the number of active multiple sclerosis lesions, as measured by the frequency of enhancement on serial T1 weighted MRI with a standard dose (Sd) of gadolinium-DTPA (Gd) contrast agent. However, recent studies have shown that the yield of active multiple sclerosis lesions can be increased using several strategies.[8–10] Of these, the use of a triple dose (Td) of contrast agent is by far the most effective.[9 10]

Lesions which are only seen to enhance after injecting a Td of Gd form a large subgroup of the population of active multiple sclerosis lesions, and are thought to represent those with a low grade inflammation.[11] These lesions have indeed a less damaged blood-brain barrier and a less severe tissue disorganisation, as measured by magnetisation transfer ratio (MT ratio) changes, at the time of their formation and during a 3 month follow up compared with those enhancing on Sd scans.[11]

The high sensitivity of Td enhanced MRI to multiple sclerosis activity may result in earlier detection of a treatment effect and a reduction in the number of scans needed to show it.[10] On the other hand, the magnitude of the effect of IFN β on lesions enhancing at different Gd doses may give further information about the mode of action of the drug in multiple sclerosis. In the present study, we evaluated the ability of 44 μg recombinant human IFN β-1a (rh-IFN β-1a) administered once a week to suppress multiple sclerosis activity, measured across a range of enhancing lesion types.

Patients and methods

PATIENTS

Eighteen patients (nine women and nine men) with clinically definite multiple sclerosis[12] and a relapsing-remitting course[13] entered the study. Their mean age was 30.8 years (range 23–43 years), mean duration of disease was 5.3 years (range 2-12 years), and median expanded disability status scale (EDSS)[14] at entry was 1.5 (range 1.0–3.5). None of the patients had taken immunosuppressive or immunomodulating treatments for at least 12 months before entry to the study. In addition, they had had neither relapses nor steroid treatment during the preceding 3 months. Local ethics committee approval at each centre and written informed consent from all the patients were obtained before study initiation. Twelve relapses (five before and seven after treatment initiation) were recorded during the follow up period in eight patients; 10 relapses (four before and six

after treatment initiation) were treated with intravenous methylprednisolone (1g/day for 3 days).

STUDY DESIGN

A baseline versus treatment trial design was used. Brain MRI was performed every 28 (± 5) days on eight separate occasions, and treatment with rh-IFN β-1a was initiated the day after the fourth MRI session. In cases of steroid treatment, MRI was always scheduled either before the start of the treatment or 10 days after the end. No other immunosuppressive or immunomodulating treatment was allowed during the study.

TREATMENT

Treatment consisted of administration of 44 μg rh-IFN β-1a (Rebif ®, Ares-Serono, Geneva, Switzerland) subcutaneously, once a week.

MAGNETIC RESONANCE IMAGING

Scanners operating at 1.5 Tesla were used at all three centres. On each scanning occasion, the MRI examination was split into two sessions, separated by an interval of between 12 and 24 hours. During the first session, the following scans were performed: (*a*) dual echo conventional spin echo (CSE) (TR=2000–2400, first echo TE=30–50, second echo TE=80–100, number of acquisitions=1); (*b*) precontrast T1 weighted CSE (TR=560–768, TE=14–15, number of acquisitions=2); (*c*) postcontrast T1 weighted scans, with the same acquisition parameters as before Gd injection, 5 minutes after the injection of Gd. During the second session, the following were performed with the same parameters as above: (*a*) precontrast T1 weighted scan; (*b*) postcontrast T1 weighted scans 5 minutes after the Gd injection. The dose of Gd was randomised so that in the first session the patient received either an Sd (0.1 mmol/kg) or Td (0.3 mmol/kg) of Gd, with the opposite dose given during the second session.

For all the scans, 24 contiguous interleaved axial slices were acquired with 5 mm slice thickness, 192–256×256 raw data matrix, and 220–250 mm square field of view. For follow up scans, the scan planes were carefully repositioned according to published guidelines.[15]

IMAGE REVIEW

The enhanced T1 weighted scans were assessed to determine the total number of enhancing lesions and the number of new enhancing lesions, in a manner described in previously published studies.[10 16] A single technician, unaware of the Gd dose used, the patient to whom the scans belonged and the time point of the acquisition, measured the volumes of enhancing lesions using a semiautomated local thresholding technique.[17] After observing the volume distribution of the pooled Sd and Td enhancing lesions, the enhancing lesions were classified according to their size into three groups containing equal numbers of lesions: small (in which the volume was smaller than 0.06 ml), intermediate (volume greater than 0.06 ml but less than or equal to 0.13 ml), or large (volume greater than 0.13 ml).

STATISTICAL ANALYSIS

The effect of Gd dose and treatment on the number of new enhancing lesions was evaluated by a Poisson regression model with patients considered as blocks. The distribution of the mean lesion rates on monthly scans for small, intermediate, and large lesions during the baseline and the treatment periods (seen on both Sd and Td scans) were compared by analysis of variance (ANOVA).

Results

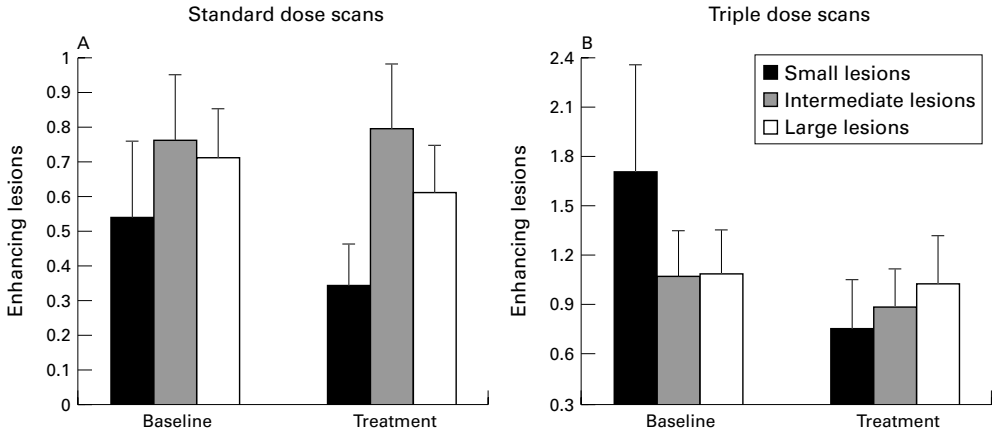
The total numbers of enhancing lesions were 145 (39 small, 55 intermediate, and 51 large) on 47/72 Sd scans obtained during the baseline period, 126 (25 small, 57 intermediate, and 44 large) on 46/72 Sd scans obtained during the treatment, 278 (123 small, 77 intermediate, and 78 large) on 54/72 Td scans obtained during the baseline period, and 192 (54 small, 64 intermediate, and 74 large) on 48/72 Td scans obtained during treatment. One patient had no enhancing lesions on Sd or Td scans during the baseline period, whereas this was the case for three patients during the treatment period.

On Sd scans, 78 new enhancing lesions were detected over the 3 month baseline period and 79 over the 4 month treatment period. On Td scans, 132 new enhancing lesions were detected over the 3 month baseline period and 96 over the 4 month treatment period. In the table, the estimated frequencies of appearance of new enhancing lesions in each of the four experimental conditions are presented. The final model of the Poisson regression analysis showed that, during the baseline period, the average number of new enhancing lesions seen on Td scans was 69% (95% confidence interval (95% CI) 28–124%) higher (p=0.002) than that estimated for Sd scans. The introduction of the treatment decreased, on average, the rate of appearance of new enhancing lesions seen on Sd and Td scans by 37% (95% CI 24–49%) (p<0.001). However, the model also showed that the dose of Gd used changed the apparent treatment effect: on average a more pronounced effect (mean+28%; 95% CI 52 to +8%) was seen on Td scans compared with Sd scans. This was confirmed by the evaluation of the treatment effects on the new enhancing lesions rates seen on Sd (average reduction−24% (range−45% to +3%), p=0.09) and Td (average reduction −45% (range−58% to −29%), p<0.001) scans.

Mean (95% CI) for the new enhancing lesion rate on standard dose and triple dose scans during the baseline and the treatment periods estimated using a Poisson regression model

	Mean number (95% CI) of new enhancing lesions/patient/month	
	Sd scans	*Td scans*
Baseline period	1.44 (1.15–1.80)	2.44 (2.06–2.90)
Treatment period	1.09 (0.88–1.37)	1.33 (1.09–1.63)

Sd=Standard dose; Td=triple dose.



Distribution of enhancing lesion volumes on standard and triple dose scans during the baseline and the treatment periods. The charts show the mean number of enhancing lesions/patient/month with the error bars representing the standard errors.

On Sd scans, the distribution of lesions sizes did not change significantly after treatment (p=0.70), whereas it did on the Td scans (p=0.05, figure). In detail, on Td scans, the number of small lesions decreased by 56%, intermediate by 17%, and large by only 5% during the treatment period. Furthermore, when comparing lesion sizes for Sd and Td, we found that treatment reduced the differences between the two distributions of lesion size. During the baseline period, small lesions were 27% of the total on Sd and 44% of the total on Td scans, whereas, during the treatment period, small lesions were 20% of the total on Sd and 27% of the total on Td scans.

Discussion

This study indicates that the effect on enhancing multiple sclerosis lesions of 44 μg of rh-IFN β-1a administered once a week is much weaker than with higher doses and more frequent administration[5 7]; the effect also varies according to the nature and size of the lesions. However, other factors may also contribute to the discrepancy between the results of the present study and those of previous trials using the same or other forms of IFN β-1a[4–7] or IFN β-1b.[1–3] Our patient sample was relatively small, and they were followed up for only a short period. Nevertheless, other studies,[1–3 5] which were conducted with even smaller sample sizes[2 3] or had comparable durations of follow up periods,[1–3 5] found a 60%-90% reduction in the number of enhancing lesions. The disparity may have arisen because we selected patients with a lower MRI baseline activity than some of the previous studies,[1–3] in which there was an inclusion criterion of a mean of at least 0.5 lesions/month over the 6 month baseline period.[1–3] Pozzilli *et al*[5] and Paty *et al*,[7] although they did not use baseline enhancement as an inclusion criterion, had a mean number of enhancing lesions on the baseline scans which was higher than we had on Sd scans (1.8 *v* 1.2). A higher enhancing lesion frequency on the baseline scans would lead to a more pronounced regression to the mean.

The main finding of interest from the present study is that the effect of rh-IFN β-1a on enhancing multiple sclerosis lesions is not homogeneous, and is greater for small lesions and those seen to enhance after Td Gd. This confirms previous statistical simulations,[10] which suggested that the higher sensitivity of Td scanning, compared with Sd, for detecting enhancing multiple sclerosis lesions would increase the likelihood of showing a treatment effect, when using the same number of scans. However, a corollary of such an approach is that there may be a risk of picking up an effect that has no clinical relevance. There are indeed several pieces of evidence suggesting that the degree of blood-brain barrier disruption and the severity of the associated damage in the brain parenchyma are mild in Td lesions.[18] Small enhancing lesions may also represent areas in which a less severe pathological process is occurring. Thus the present study would suggest that the effect of the drug is inversely related to the degree of blood-brain barrier disruption, in agreement with previous results[4 7 19 20] which showed that the effect of the interferons on the frequency of appearance of new enhancing lesions is two to three times greater than on the clinical relapse rate.

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