Interferon beta-1b is effective and has a favourable safety profile in Chinese patients with relapsing forms of multiple sclerosis

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Abstract

Background & Objective: No clinical study of any interferon beta therapy has yet been successfully conducted in Chinese multiple sclerosis patients, probably due to the low incidence of this disease in China. The primary objective of this study was to demonstrate that treating multiple sclerosis patients of Chinese origin with interferon beta-1b has a beneficial effect on disease course, as measured by the decrease of newly active lesions on magnetic resonance imaging. *Methods:* Chinese patients diagnosed with relapsing-remitting or secondary-progressive multiple sclerosis were enrolled in this multicenter, open label, single-arm study. Following a 3-month pre-treatment phase, patients were treated with 250 μg interferon beta-1b subcutaneously every other day for 6 months. Patients had regular assessments for treatment safety and efficacy of the treatment. *Results:* Thirty seven patients completed the trial. Significant decreases in the number of newly active lesions were observed in the 6-month treatment period compared with the pre-treatment period (median decrease 1.5 lesions, p<0.001). Most adverse events were mild and transient and no serious ones were observed.
Conclusions: Treatment with interferon beta-1b significantly reduced the occurrence of new lesions and was well tolerated in this Chinese population. These findings support the use of interferon beta-1b for treating Chinese MS patients.

INTRODUCTION

Multiple sclerosis (MS) is the most common, non-traumatic cause of neurologic dysfunction in young adults in Western countries, with MS rates as high as 200/100,000 inhabitants in some northern European countries.[1,2] The prevalence in Asia is significantly lower, with estimations of approximately 5/100,000 inhabitants in the Western Pacific region and 2.8/100,000 inhabitants in South East Asia.[3] In a recently published survey conducted in Shanghai the prevalence of MS in the Chinese population was estimated to be 1.39/100,000, comparable to the prevalence noted in other MS studies from South-East Asia.[4]

Interferon beta-1b (IFNB-1b, trade name Betaferon/Betaseron in the United States) was the first recombinant IFNB preparation approved for the treatment of relapsing-remitting MS (RR-MS) and later also for relapsing forms of secondary-progressive MS (SP-MS) in the United States and Europe. Efficacy was demonstrated in terms of reducing the frequency and severity of relapses and/or lesion number and load as per MRI and in delaying disease progression in SP-MS.[5-8] The efficacy of the treatment was also studied and proven in patients with a first clinical event suggestive of MS (CIS).[9] These pivotal studies included patients of various ethnic origins (North

American RR-MS study, European SP-MS study, North American SP-MS study, European and Canadian CIS study).[5-10] In a study of Japanese patients with RR-MS, the efficacy of IFNB-1b was also demonstrated for that patient population.[11] Based on this study and results from pivotal trials, IFNB-1b was approved in Japan and selected other Asian countries.

The reports available to date seem to indicate that clinical and epidemiologic aspects of MS in China might be, in general, similar to those seen, for example, in Japanese and Korean MS patients.[4,12,13] However, the low prevalence of MS, relative paucity of specialized centers and long distance travel for individual patients to reach those centers seem to have thus far been challenging when conducting large scale epidemiologic studies[4] and controlled clinical trials evaluating disease modifying therapy in Chinese patients. Thus, many first-line disease-modifying therapies used in Western countries are not yet available for MS therapy in China. In their population-based survey of MS from Shanghai, China, Cheng *et al*. report that corticosteroids are the most frequently prescribed therapy, with 96% of their cohort being treated with this drug, while only three patients (of 123) had additional therapy with subcutaneous IFNB-1a, the first disease-modifying therapy approved for MS treatment in China.[4]

The primary objective of this study was to demonstrate that IFNB-1b treatment in MS patients of Chinese origin positively impacts on the course of their disease as evidenced primarily by the decrease of newly active lesions on MRI. Clinical disease parameters such as relapses and disease progression were also assessed in an exploratory fashion. In addition, safety and tolerability of IFNB-1b treatment in this patient population were assessed and compared with the well-established safety profile known from clinical studies and long-term worldwide market experience in predominantly Caucasian patients. A longitudinal design comparing MRI lesion rates before and during treatment was chosen for this study in Chinese patients, as it significantly reduced the number of patients and the observation periods without immunomodulatory treatment in a very significant way.

METHODS

Patients

Patients of Chinese origin aged 16–55 years with a diagnosis of RR-MS (according to McDonald criteria 2001) or SP-MS were eligible for enrollment into the study (NCT00370071). Other inclusion criteria were no relapse during 30 days before screening, at least three T2 lesions in the screening (visit 1) MRI, at least 1Gd-enhancing lesion in the screening (visit 1) MRI, and Expanded Disability Status Scale (EDSS) score between 0 and 5.0 inclusive. Women of child-bearing potential had to provide agreement to practice adequate contraception methods and had to have negative urine pregnancy test results (beta-HCG).

Exclusion criteria included any disease other than MS that could better explain the patient's signs and symptoms, serology indicating HIV infection or active hepatitis A infection or syphilis, history or signs of immunodeficiency, epilepsy not adequately controlled by treatment, other serious conditions or complications, psychiatric disease, pregnancy or lactation, any condition that could interfere with the MRI or any other evaluation in the study, previous use of a number of substances within specified time frames, and previous enrollment into this study.

The conduct of this clinical study was in compliance with the protocol, in accordance with the ethical principles defined in the Declaration of Helsinki, and in agreement with International Conference on Harmonisation–Good Clinical Practice guidelines as well as the local regulatory requirements of the People's Republic of China. Patients provided written informed consent prior to study entry.

Study design

This was a multicenter, open-label single-arm study. Patients of Chinese origin with RR-MS and SP-MS were enrolled into a 3-month pretreatment phase with no MS-specific treatment, followed by a 6-month treatment period. Treatment consisted of 250 μg IFNB-1b (8 MIU) as subcutaneous injections every other day. The 250 μg IFNB-1b formulation and dose regimen used in this study is approved and marketed in many countries worldwide.

Study medication was started with a dose titration period: days 1, 3 and 5: 0.25 mL; days 7, 9 and 11: 0.5 mL; days 13, 15 and 17: 0.75 mL; from day 19 onward: 1 mL (full dose).

The study was conducted at four centers in the People's Republic of China (Huashan Hospital, Shanghai; PUMC, Beijing; Beijing Hospital, Beijing; Beijing Tiantan Hospital, Beijing). Patients underwent regular assessments at the study centers. In addition there were one EDSS

reference center and one MRI analysis center. Repeated MRI evaluations of MS-associated lesions were performed for a comparison of lesion number and lesion volume before treatment, during the treatment period and at the end of the study. T1-weighted (after Gd injection) and dual-echo MRI scans of the brain were performed on scanners with at least 1.0 Tesla magnetic field strength imaging 44 contiguous slices of 3 mm thickness.

Patients had two visits, at the start and at the end of the 3-month pretreatment period: the screening and baseline visits (visits 1 and 2). Therapy was started at the earliest time point after the baseline visit (day 1, visit 3). During the treatment period patients had monthly visits for the first 3 months (visits 4, 5, 6) and then the last visit after 6 months on therapy (visit 7).

MRIs were performed every 3 months, ie, at visits 1, 2, 6 and 7 (Figure 1). EDSS was assessed at visits 1, 3 and 7. Relapse assessment was done at all scheduled site visits.

Primary efficacy variable

The primary efficacy variable was the cumulative number of newly active lesions during the 6-month treatment period (from visit 3 to visit 6, plus from visit 6 to visit 7) divided by 2 (number of newly active lesions per 3 months) as compared with the number of newly active lesions during the 3-month pretreatment period (from visit 1 to visit 2). The number of newly active lesions was defined as the sum of new Gd-enhancing lesions on T1-weighted scans as compared with previous scan and non-enhancing lesions on T1-weighted scans but appearing new (or enlarged) on T2-weighted scans as compared with the previous scan. A sensitivity analysis was performed to adjust the observed number of newly active lesions for unequal time intervals between MRI scans, ie, not exactly meeting the 3-month (12 weeks) time interval.

Secondary efficacy variables

The secondary MRI variables included the two components of the primary endpoint, ie, the cumulative number of new Gd-enhancing lesions and the new or enlarged T2 lesions non-enhancing on T1, during the 6-month treatment divided by 2 (number of new lesions per 3 months) as compared with the number of new lesions during the 3-month pretreatment period, the change in volume of Gd+ lesions as well as the total number of Gd+ and T2 lesions.

Exploratory analysis of clinical efficacy variables

For exploratory purposes, descriptive analyses of clinical disease activity (relapses) and progression (by EDSS measurements) were performed in the pretreatment and the treatment period.

The following relapse-based variables were evaluated: relapse rate, number of relapses, proportion of relapse-free patients and proportion of patients who were free from major relapses. The relapse rate was calculated on an annualized basis.

Disease progression was assessed using the EDSS score by time and the proportion of patients free from EDSS progression. EDSS progression was defined as increase in EDSS ≥ 1.0 point (in the treatment period compared with baseline), without requirement of confirmation at a subsequent visit.
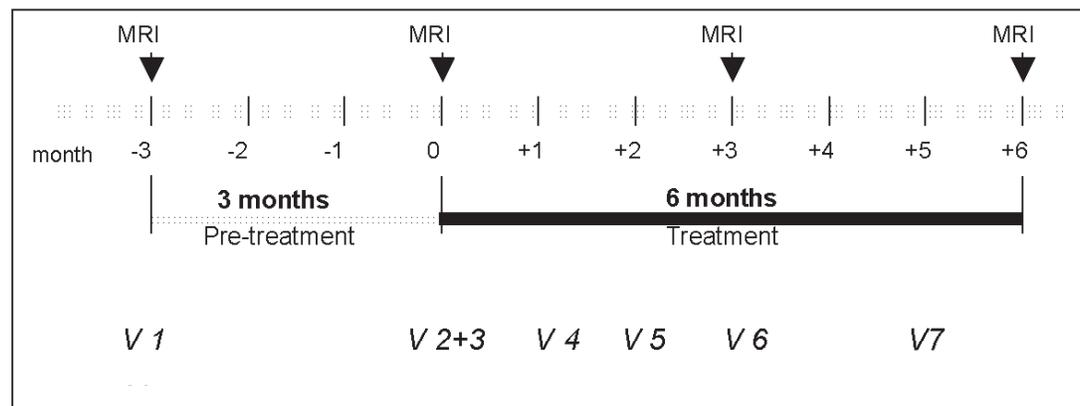

Figure 1. Schedule of visits (V) and MRI evaluations.

Safety

Safety was assessed throughout the study; detailed analyses were performed for all patients who received any amount of the study drug. Safety evaluations included assessment of adverse events (AEs), laboratory data, 12-lead ECG, vital signs and physical examination.

Pharmacodynamic evaluation

Neopterin was chosen as biological response marker for this study and assessed at screening and at the end of study visit.

Statistical methods

Patients who discontinued study participation before receipt of the first dose of study medication were excluded from any statistical analysis of efficacy. All other patients were assigned to at least one of the analysis sets defined as follows:

- The full analysis set (FAS) included all patients who received at least one dose of study medication and had at least one postbaseline visit;
- The MRI set (MRS) included all FAS patients with at least one evaluable postbaseline MRI scan;
- The primary MRI set (pMRS) included all MRS patients with at least one newly active lesion during pretreatment;
- The per-protocol set (PPS) included all MRS patients with no premature withdrawal from the study and no major protocol deviations.

The safety analysis set (SAF) included all subjects who received any amount of the study medication.

Primary and secondary efficacy variables were evaluated for the MRS, the pMRS and the PPS; clinical efficacy variables were explored for the FAS. Analysis set assignment to PPS, FAS and SAF was done before database release. Assignment to MRS and pMRS was done via statistical programming.

Statistical comparisons for the primary efficacy variable (including sensitivity analyses) were performed using the Wilcoxon signed-rank test at a one-sided test level of 2.5% (corresponding to a two-sided test at level 5%). For exploratory purposes, the Wilcoxon signed-rank test was also applied for comparisons with respect to the secondary efficacy variables. Clinical variables were analyzed by means of descriptive statistics. Statistical analyses were performed using the

SAS® System (Release 9.1 [SAS Institute, Cary, North Carolina, USA]).

RESULTS

Study population

A total of 84 subjects were screened at the four centers. Forty-five patients discontinued the study during pretreatment: three withdrew their consent, 40 did not meet the inclusion/exclusion criteria and two died. Thirty-nine patients entered the treatment period. Of these, 37 completed the trial.

The FAS and the MRS (ie, all patients with ≥1 evaluable postbaseline MRI scan) comprised all 39 patients. Twenty-nine patients, who had at least one newly active lesion diagnosed during the pretreatment phase, were assigned to the pMRS. The PPS comprised 27 patients; two patients (5.1%) discontinued treatment prematurely due to withdrawal of consent.

All patients were of Chinese origin. The mean age at study entry was 31.6 years, 66.7% of the patients were females. Thirty-six patients (92.3%) presented with RR-MS, three patients (7.7%) had SP-MS.

The mean (SD) time since onset of MS was 3.5 years (4.6 years); the mean (SD) EDSS score at screening was 2.26 (1.39) and the mean (SD) number of previous MS relapses was 2.8 (1.7).

Efficacy

Primary efficacy variable

In the 6-month treatment period, significant decreases were observed in all analysis sets with respect to the number of newly active lesions per 3 months (cumulative number of newly active lesions divided by 2) as compared with the number of newly active lesions during the 3-month pretreatment period (MRS: median decrease of 1.5 lesions, $p < 0.0001$; pMRS: median decrease of 2.5 lesions, $p < 0.0001$; PPS: median decrease of 1.5 lesions, $p = 0.0001$ [Table 1, Figure 2]). In the MRS, the median/mean (SD) number of newly active lesions per 3 months was 2.0/4.8 (7.1) during pretreatment and 0.5/1.6 (2.7) during treatment (for details to pMRS see Table 2). Sensitivity analyses adjusting the primary endpoint for the actual time between MRI evaluations confirmed these positive findings (Table 3).

Table 1: Number of newly active lesions per 3 months in the MRI set of patients (MRS)

MRS (n = 39)	Pretreatment (3 months)	Month 1–3 Visit 6	Treatment Month 4–6 Visit 7	Month 1–6[a]
Number of newly active lesions				
Mean (SD)	4.8 (7.1)	1.9 (3.4)	1.1 (2.6)	1.6 (2.7)
Median	2	1	0	0.5
Min–Max	0–39	0–14	0–11	0–12.5
Change from pretreatment				
Mean (SD)	–	–3.0 (6.1)	–3.7 (7.2)	**–3.3 (6.5)**
Median	–	–1	–1.5	**–1.5**
Min–Max	–	–31 to 8	–39 to 5	**–35– to 6.5**
p Value[b]	–	0.0001	< 0.0001	**< 0.0001**

[a]Cumulative number of newly active lesions during 6-month treatment divided by 2.
[b]One-sided p value from Wilcoxon signed rank test (one-sided test level 2.5%).

Secondary efficacy variables

For both components of the primary endpoint, decreases were observed under treatment compared with pretreatment. For the number of new Gd-enhancing lesions (T1 lesions) per 3 months, changes were as follows: MRS: median decrease of 0.5 lesions, $p < 0.0001$; pMRS: median decrease of 1.5 lesions, $p < 0.0001$; PPS: median decrease of 0.5 lesions, $p < 0.0001$ (Figure 3). In the MRS, the median/mean (SD) number of new Gd-enhancing lesions per 3 months was 1.0/2.6 (4.1) during pretreatment and 0/0.6 (1.1) during treatment. In the pMRS, the median/mean (SD) number of new Gd-enhancing lesions per 3 months was 2.0/3.5 (4.5) during pretreatment and 0/0.7 (1.3) during treatment.
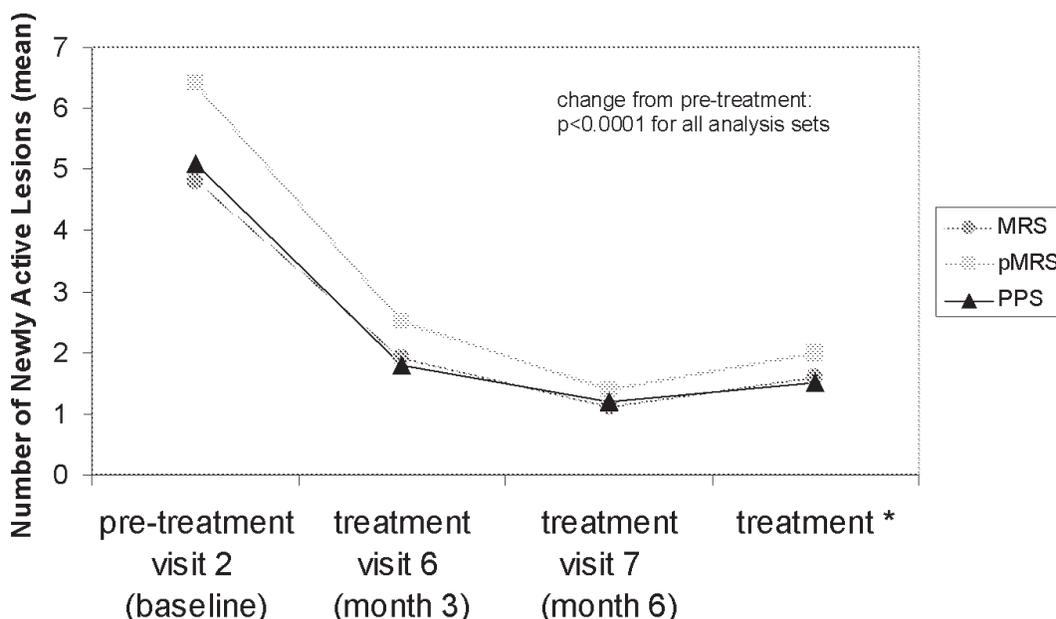

Figure 2. Mean number of newly active lesions by visits as compared to previous MRI scan (*number of lesions at month 6 is the cumulative number of newly active lesions during 6-month treatment divided by 2). MRS, MRI set of patients – all patients from the full analysis set with at least one evaluable postbaseline MRI scan; pMRS, primary MRI set – all MRS patients with at least one newly active lesion during pretreatment; PPS, per-protocol set of patients – all MRS patients with no premature withdrawal and no major protocol deviations.

Table 2: Number of newly active lesions per 3 months in the primary MRI set of patients (pMRS)

pMRS (*n* = 29)	Pretreatment (3 months)	Month 1–3 Visit 6	Treatment Month 4–6 Visit 7	Month 1–6[a]
Number of newly active lesions				
Mean (SD)	6.4 (7.6)	2.5 (3.7)	1.4 (3.0)	2.0 (3.0)
Median	4	1	0	1
Min–Max	1–39	0–14	0–11	0–12.5
Change from pretreatment				
Mean (SD)	–	–3.9 (6.8)	–4.9 (8.0)	**–4.4 (7.2)**
Median	–	–2	–3	**–2.5**
Min–Max	–	–31 to 8	–39 to 5	**–35 to 6.5**
p Value[2]	–	0.0001	< 0.0001	**< 0.0001**

[a]Cumulative number of newly active lesions during 6-month treatment divided by 2.
[b]One-sided *p* value from Wilcoxon signed rank test (one-sided test level 2.5%).

For the number of new T2 lesions per 3 months, changes were as follows: MRS: median change of ±0 (mean change –1.24 lesions), *p* = 0.0017; pMRS: median decrease of two lesions, *p* = 0.0017; PPS: median decrease of one lesion, *p* < 0.0076 (Figure 4).

In the MRS, the median/mean (SD) number of new or enlarging T2 lesions per 3 months was 2.0/2.2 (3.2) during pretreatment and 0.3/1.0 (1.9) during treatment. In the pMRS, the median/mean (SD) number of new or enlarging T2 lesions per 3 months was 2.0/2.9 (3.4) during pretreatment and 0.5/1.3 (2.1) during treatment.

Gd-enhancing lesion volumes decreased in all analysis sets. In the MRS analyses, Gd-enhancing lesion volumes at baseline (median volume of 132 mm³) were reduced at month 3 (median volume of 0 mm³, *p* < 0.0001) and at month 6 (median volume of 0 mm³, *p* = 0.0019).

Results from pMRS and PPS analyses are in line with the MRS findings (decrease from median volume of 235 mm³ at baseline to median volume of 0 mm³ at month 3, *p* < 0.0001 and median volume of 0 mm³ at month 6, *p* = 0.0020 in the pMRS and decrease from median volume of 151 mm³ at baseline to median volume of 0 mm³ at

Table 3: Number of newly active lesions per 3 months time adjusted (sensitivity analysis) in the MRI set of patients (MRS)

MRS (*n* = 39)	Pretreatment (3 months)	Month 1–3 Visit 6	Treatment Month 4–6 Visit 7	Month 1–6[a]
Number of newly active lesions				
Mean (SD)	4.2 (6.6)	1.6 (2.8)	1.5 (4.3)	1.6 (3.1)
Median	1.9	0.8	0	0.5
Min–Max	0–37.3	0–11.9	0–23.0	0–16.0
Change from pretreatment				
Mean (SD)	–	–2.7 (5.8)	–2.6 (7.6)	**–2.7 (6.5)**
Median	–	–1.0	–1.3	**–1.3**
Min–Max	–	–30 to 4.8	–37.3– to 18.8	**–33.7 to 11.8**
p Value[b]	–	0.0002	0.0004	**< 0.0001**

[a]Cumulative number of newly active lesions during 6-month treatment divided by 2.
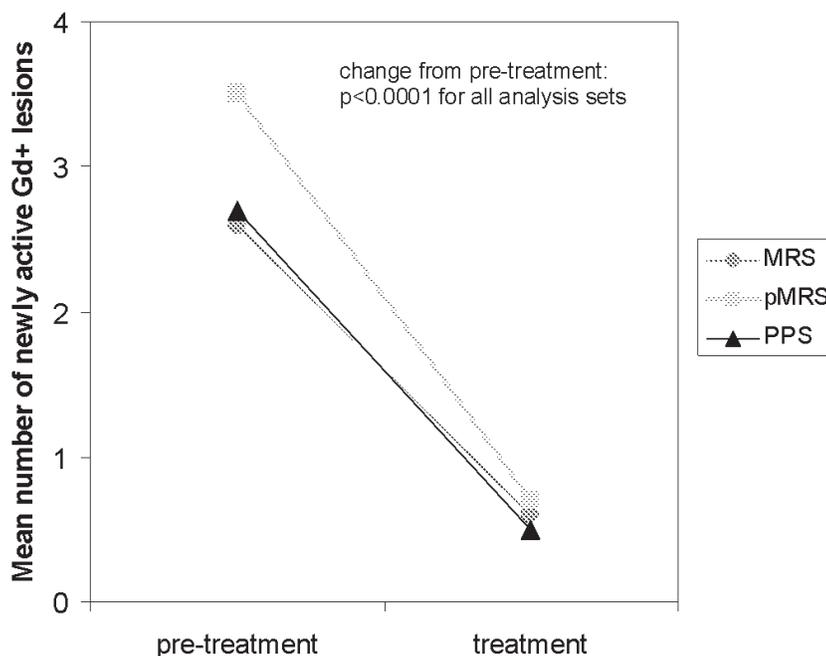[b]One-sided *p* value from Wilcoxon signed rank test (one-sided test level 2.5%).

Figure 3. Mean number of new T1 Gd-enhancing lesions per 3 months. MRS, MRI set of patients – all patients from the full analysis set with at least one evaluable postbaseline MRI scan; pMRS, primary MRI set – all MRS patients with at least one newly active lesion during pretreatment; PPS, per-protocol set of patients – all MRS patients with no premature withdrawal and no major protocol deviations.

month 3, $p < 0.0001$ and median volume of 0 mm³ at month 6, $p = 0.0090$ in the PPS).

Exploratory analysis of clinical efficacy variables

Clinical efficacy variables were evaluated for the FAS ($n = 39$).

Relapse assessments

Thirteen relapses in 10 patients were recorded. During the pretreatment period, six relapses were reported in six patients, and during the treatment period seven relapses occurred in six patients. Thirty-three patients (84.6%) were relapse free during treatment. One relapse, occurring under treatment, was assessed as major relapse. The annualized relapse rate decreased from 0.45 during the pretreatment period to 0.38 during the treatment period.

EDSS assessments

The mean EDSS was 2.26 at screening, 2.06 before start of treatment (visit 3) and 1.81 at end of study. This calculation disregards two patients who had no EDSS assessment at the end of the study. Their initial scores were 5 and 5.5, respectively. EDSS progression of ⩾1 point from baseline to month 6 was observed in three patients.

Safety results

Safety was assessed throughout the study; detailed analyses were performed for all patients who received any amount of the study drug. Thirty-nine patients were valid for the SAF. During the 6-month-treatment period, 100 AEs were recorded in 34 (87.2%) patients. To avoid redundancy, symptoms of MS captured in the EDSS were not documented as AEs. 'Flu-like symptoms' were the most commonly reported events, occurring 28 times in 22 patients (56.4%). This symptom complex combines the reported AEs 'influenza-like illness' (17 events in 16 [41.0%] patients), hyperhydrosis (one event in one patient [2.6%]), myalgia (seven events in five patients [12.8%]) and pyrexia (three events in three patients [7.7%]). Other frequently recorded AEs were injection site conditions, occurring 10 times in nine patients (23.1%), hepatic function abnormality (seven events in seven [17.9%] patients), headache (eight events in six [15.4%] patients) and arthralgia (four events in four [10.3%] patients).

Most AEs were mild and transient: 56.4% of the patients experienced mild AEs only. In 11 patients (28.2%) moderate AEs were recorded. One AE (nephrolithiasis) was severe. Ninety-eight percent of the events were resolved or resolving at the end of the study period. No patient discontinued
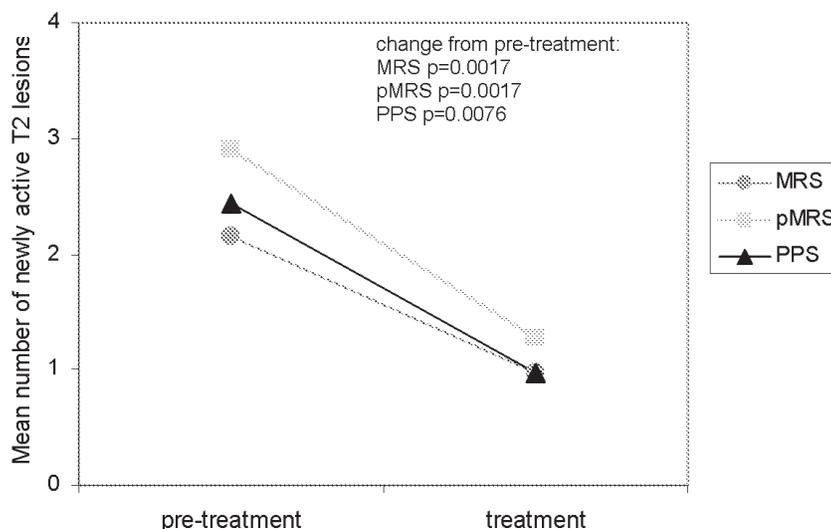
Figure 4. Mean number of new or enlarging T2 lesions (non-enhancing on T1) per 3 months. MRS, MRI set of patients – all patients from the full analysis set with at least one evaluable postbaseline MRI scan; pMRS, primary MRI set – all MRS patients with at least one newly active lesion during pretreatment; PPS, per-protocol set of patients – all MRS patients with no premature withdrawal and no major protocol deviations.

treatment prematurely due to AEs. Permanent dose reduction was performed for one patient with injection site pain.

No deaths or serious AEs were recorded for the 39 patients included in the SAF.

Alterations of hepatic enzymes and hematological parameters (mainly leukocyte and lymphocyte count) occurred during the study. Most of the observed hepatic and hematological laboratory toxicities were transient and of mild to moderate intensity. No clinically relevant changes over time were detected for vital signs, ECG or physical examination. No pregnancies were reported.

Pharmacodynamic evaluation

Neopterin was assessed in 37 of 39 patients. Neopterin levels increased from 7.08 ± 2.87 nmol /l at screening to 15.08 ± 8.20 nmol/l at the end of study.

DISCUSSION

This is the first study that has been successfully completed in Chinese MS patients. The study evaluated the effects of IFNB-1b in patients of Chinese origin using the number of newly active MRI lesions as the primary outcome variable. During our 6-month treatment period, highly significant decreases in lesion counts were observed for all analysis sets compared with the pretreatment period. Nearly all patients (36 of 39) showed a decrease in the number of newly enhancing lesions. Sensitivity analyses adjusting the primary endpoint for the actual time between MRI evaluations confirmed these robust and compelling findings. Results were also supported by the favorable outcomes on the secondary endpoints, eg, the number of new Gd-enhancing lesions and number of new T2 lesions.

The study was not powered to show significant differences on relapses and disability progression endpoints. However, descriptive statistics suggest a beneficial effect of IFNB-1b on some relapse- and EDSS-based outcomes.

Safety assessments confirmed the favorable profile of IFNB-1b also in Chinese patients, as they gave results very much in line with prior findings in the pivotal studies mainly conducted in Caucasian patients. There were no new or unexpected AEs and, even more importantly, no serious AEs. The frequency and intensity of well-known AEs associated with the drug, eg, flu-like symptoms or injection site reaction as well as hematologic or hepatic laboratory abnormalities, were also similar to findings from larger and longer studies conducted in Caucasian patients. Considering the short duration of this study, it is likely that prevalence rates might even decrease over time, since it is well known that many of these AEs occur more frequently at the beginning of therapy.

The change in the neopterin levels evaluated in the Chinese patients before treatment and on treatment (7.92 ± 8.10 nmol/l) was similar with that seen in a previous study of healthy Caucasian subjects (8.96 ± 2.86 nmol/l) treated with 8 MIU IFNB-1b s.c.[14] suggesting that also the biological response to IFNB-1b exposure is comparable between Chinese and Caucasian subjects.

The usefulness of serial MRIs for the monitoring of the effects of IFNB-1b has been described previously.[15,16] Stone et al., in a study performed in 14 RRMS patients followed for 7 months pretreatment and 6 months on therapy, noted a significant reduction in the total and new enhancing lesion frequency when the patient collective was analyzed as a whole.[16] Moreover, they found that 13 of their 14 patients demonstrated a reduction in new enhancing lesion frequency over the 6 months on therapy. Even when the authors extended the baseline pretreatment period to include natural history MRI data obtained in the participating patients as far back as, in the case of one patient, 58 months, the before versus on-therapy differences of new and total lesion frequency were still significantly in favor of the period on therapy.

The value and validity of MRI findings has moreover been shown and recognized in many clinical trials for MS treatment, starting with the very first pivotal trial in RR-MS conducted with IFNB-1b.[5,7] Since then MRI has been widely used and has also become an integral part of algorithms for timely and adequate MS diagnosis, the most established being the McDonald criteria—both the initial (2001) and revised (2005) versions.[17,18] These previous results and the compelling and robust reduction in new MRI lesions seen in our longitudinal study[19] indicate that Chinese patients also have significant therapeutic benefits from treatment with IFNB-1b given subcutaneously every other day .

MRI measures are usually employed as secondary endpoints in large international registration phase III studies, or as primary outcomes in smaller scale proof-of-concept phase II studies.

As a non-invasive and increasingly available approach, MRI offers several advantages over accepted clinical outcome measures for MS, including an increased sensitivity to disease activity, ie, the capability to detect earlier and smaller changes[20,21], the potential to increase objectivity (compared with more subjective clinical measures like EDSS) and a better association with histopathology findings than that with clinical manifestations.[22] MRI also provides highly reproducible measures on ordinal scales thus allowing a more powerful statistical approach.[23] It is now generally accepted that if the aim of a new therapy is to prevent relapses, new Gd-enhancing and T2 lesions as evaluated in the Betaferon China study can be considered an appropriate surrogate outcome measure of relapses.[24-26]

The open-label crossover design (baseline versus treatment) counts among the frequently used designs for MS studies using primary MRI outcomes.[20] This design was originally proposed by McFarland[27] and was used in a modified version in our study: It involves repeated MRIs performed over a pretreatment period to obtain information on each patient's natural history followed by serial MRI and clinical examinations at the same scanning interval while patients are on therapy (treatment phase). The main advantage is that because the patient serves as his/her own control only a small sample size is required.[20]

Given the low prevalence of MS in Chinese patients only a small number of MS patients could reasonably be expected to be recruited. In addition, the inclusion of a control arm using placebo for an extended period was considered inappropriate also from an ethical viewpoint, especially in the case of Betaferon where there are a wealth of data not only in Caucasian but also some in Asian patients, for whom a significant treatment effect and a good safety profile have already been demonstrated. Thus, by choosing the (intra-individual) pretreatment comparison design using MRI endpoints for this study in Chinese patients, we could reduce the number of patients and the extent of observation periods without immunomodulatory treatment in a very significant way, and yet we obtained very meaningful and clinically relevant results.

Indeed, the results of the study proved the design to be adequate; in the 6-month treatment period, highly significant decreases in lesion counts were observed for all analysis sets compared with the pretreatment period. Sensitivity analyses adjusting the primary endpoint for the actual time between MRI evaluations confirmed these robust and compelling findings. Results were also supported by the favorable outcomes on the secondary endpoints.

To summarize, IFNB-1b therapy significantly reduced the occurrence of new MS-associated lesions and of lesion volume on MRI. IFNB-1b treatment also demonstrated activity to reduce the frequency and severity of clinical symptom

relapse and the overall EDSS score. IFNB-1b was well tolerated and the safety evaluation did not highlight any concern that would be specific to the Chinese population. These findings support the usage of Betaferon for immunomodulatory treatment of Chinese MS patients in the same manner as in Caucasian patient populations.

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DISCLOSURE

The study was sponsored by Bayer Healthcare.

Conflict of Interest:

Huashan Hospital (investigator Zhen-xin Li) has received research support from Bayer Pharma AG for serving as lead center in this multiple sclerosis clinical trial sponsored by Bayer Pharma AG. Dr. Li has received research grants and lecture fees from Bayer Pharma AG. Huashan Hospital (investigator Chuan-Zhen Lu) has received research support from Bayer Pharma AG for serving as lead center in this multiple sclerosis clinical trial sponsored by Bayer Pharma AG. Xing-hu Zhang and Beijing Tiantan Hospital have received research support from Bayer Pharma AG in this multiple sclerosis clinical trial, and also received grant and lecture fee from Bayer Pharma AG. Li-Ying Cui and PUMC have received research support and research grant from Bayer Pharma AG in this multiple sclerosis trial. Xian-hao Xu has received speaking and consulting fees, and/or clinical research support from Bayer Pharma AG, Merck Serono, Sanofi Aventis, Novartis, Elsail. Ernst-Wilhelm Radue: The author declares that there is no conflict of interest. Liangrong Wang is a salaried employee of Bayer Pharma AG, Shanghai, China. Shu-guang Chu received grant support and related travel expenses from Bayer Pharma AG for performance of MRI analyses in the clinical trial. Karola Beckmann is a salaried employee of Bayer Pharma AG, Berlin. Johannes Lampe was a salaried employee of Bayer Pharma AG, Berlin at the time of study conduct. Christoph Pohl is a salaried employee of Bayer Pharma AG, Berlin. Brigitte Stemper is a salaried employee of Bayer Pharma AG, Berlin. Rupert Sandbrink is a salaried employee of Bayer Pharma AG, Berlin.

REFERENCES

1. McDonnell GV, Hawkins SA. High incidence and prevalence of multiple sclerosis in south east Scotland: evidence of a genetic predisposition. *J Neurol Neurosurg Psychiatry* 1999; 66:411.
2. Rothwell PM, Charlton D. High incidence and prevalence of multiple sclerosis in south east Scotland: evidence of a genetic predisposition. *J Neurol Neurosurg Psychiatry* 1998; 64:730-5.
3. WHO Atlas MS Resources in the World 2008, P14. http://www.who.int/mental_health/neurology/Atlas_ms_WEB.
4. Cheng Q, Miao L, Zhang J, *et al.* A population-based survey of multiple sclerosis in Shanghai, China. *Neurology* 2007; 68:1495-500.
5. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. The IFNB Multiple Sclerosis Study Group. *Neurology* 1993; 43:655-61.
6. Kappos L, Polman C, Pozzilli C, Thompson A, Beckmann K, Dahlke F; European Study Group in Interferon beta-1b in Secondary-Progressive MS. Final analysis of the European multicenter trial on IFNbeta-1b in secondary-progressive MS. *Neurology* 2001; 57:1969-75.
7. Paty DW, Li DK. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. II. MRI analysis results of a multicenter, randomized, double-blind, placebo-controlled trial. UBC MS/MRI Study Group and the IFNB Multiple Sclerosis Study Group. *Neurology* 1993; 43:662-7.
8. Interferon beta-1b in the treatment of multiple sclerosis: final outcome of the randomized controlled trial. The IFNB Multiple Sclerosis Study Group and The University of British Columbia MS/MRI Analysis Group. *Neurology* 1995; 45:1277-85.
9. Kappos L, Polman CH, Freedman MS, *et al.* Treatment with interferon beta-1b delays conversion to clinically definite and McDonald MS in patients with clinically isolated syndromes. *Neurology* 2006; 67:1242-9.
10. Kappos L, Weinshenker B, Pozzilli C, *et al*; European (EU-SPMS) Interferon beta-1b in Secondary Progressive Multiple Sclerosis Trial Steering Committee and Independent Advisory Board; North American (NA-SPMS) Interferon beta-1b in Secondary Progressive Multiple Sclerosis Trial Steering Committee and Independent Advisory Board. Interferon beta-1b in secondary progressive MS: a combined analysis of the two trials. *Neurology* 2004: 63:1779-87.
11. Saida T, Tashiro K, Itoyama Y, Sato T, Ohashi Y, Zhao Z; Interferon Beta-1b Multiple Sclerosis Study Group of Japan. Interferon beta-1b is effective in Japanese RRMS patients: a randomized, multicenter study. *Neurology* 2005; 64:621-30.
12. Cheng Q, Cheng XJ, Jiang GX. Multiple sclerosis in China--history and future. *Mult Scler* 2009; 15:655-60.
13. Cheng Q, Miao L, Zhang J, *et al.* Clinical features of patients with multiple sclerosis from a survey in Shanghai, China. *Mult Scler* 2008; 14:671-8.

14. Stuerzebecher A, Maibauer R, Henuer A, Beckmann K, Aufdembrinke B. Pharmacodynamic comparison of single doses of IFN-beta 1a and IFN-beta 1 b in healthy volunteers. *J Interferon Cytokine Res* 1999; 19:1257-64.

15. Frank JA, Stone LA, Smith ME, Albert PS, Maloni H, McFarland HF. Serial contrast-enhanced magnetic resonance imaging in patients with early relapsing-remitting multiple sclerosis: implications for treatment trials. *Ann Neurol* 1994; 36 Suppl:S86-90.

16. Stone LA, Frank JA, Albert PS, *et al*. The effect of interferon-beta on blood-brain barrier disruptions demonstrated by contrast-enhanced magnetic resonance imaging in relapsing-remitting multiple sclerosis. *Ann Neurol* 1995; 37:611-9.

17. McDonald WI, Compston A, Edan G, *et al*. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. *Ann Neurol* 2001; 50:121-7.

18. Polman CH, Reingold SC, Edan G, *et al*. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria". *Ann Neurol* 2005; 58:840-6.

19. Zhao Y, Traboulsee A, Petkau AJ, Li D. Regression of new gadolinium enhancing lesion activity in relapsing-remitting multiple sclerosis. *Neurology* 2008; 70(13 Pt 2):1092-7.

20. Li DK, Li MJ, Traboulsee A, Zhao G, Riddehough A, Paty D. The use of MRI as an outcome measure in clinical trials. *Adv Neurol* 2006; 98:203-26.

21. Miller DH, Barkhof F, Nauta JJ. Gadolinium enhancement increases the sensitivity of MRI in detecting disease activity in multiple sclerosis. *Brain* 1993; 116(Pt 5):1077-94.

22. Traboulsee A. MRI relapses have significant pathologic and clinical implications in multiple sclerosis. *J Neurol Sci* 2007; 256(Suppl 1):S19-22.

23. Barkhof F, Filippi M, van Waesberghe JH, *et al*. Improving interobserver variation in reporting gadolinium-enhanced MRI lesions in multiple sclerosis. *Neurology* 1997; 49:1682-8.

24. Miller DH, Albert PS, Barkhof F, *et al*. Guidelines for the use of magnetic resonance techniques in monitoring the treatment of multiple sclerosis. US National MS Society Task Force. *Ann Neurol* 1996; 39:6-16.

25. Arnold DL, Goodin DS. Magnetic resonance imaging as a surrogate for treatment effect on multiple sclerosis relapses. *Ann Neurol* 2009; 65:237-8.

26. Sormani MP, Bonzano L, Roccatagliata L, Cutter GR, Mancardi GL, Bruzzi P. Magnetic resonance imaging as a potential surrogate for relapses in multiple sclerosis: a meta-analytic approach. *Ann Neurol* 2009; 65:268-75.

27. McFarland HF, Frank JA, Albert PS, *et al*. Using gadolinium-enhanced magnetic resonance imaging lesions to monitor disease activity in multiple sclerosis. *Ann Neurol* 1992; 32:758-66.