Acta Clin Croat 2009; 48:183-186 Review

EFFECTS OF RELAPSING-REMITTING MULTIPLE SCLEROSIS TREATMENT WITH INTERFERON BETA-1B RESULTS OF A THREE-YEAR FOLLOW-UP STUDY

Aleksandar Ješić, Dragana Stefanović, Nenad Delibašić, Marija Semnic, Lorand Sakallasz, Dragica Dobrenov, Željko Živanović, Tamara Rabi-Žikić and Milorad Žikić

Clinic of Neurology, Clinical Center of Voivodina, Novi Sad, Serbia

SUMMARY – The aim of this prospective study was to evaluate therapeutic effects in a cohort of 32 patients with relapsing-remitting multiple sclerosis (RRMS) that were continuously treated with interferon beta-1b during a three-year period and to compare the results obtained with literature data available. Additionally, dropouts and side effects were assessed. The annual relapse rate at three years of treatment as the primary study end-point decreased by 60.5% compared with the relapse rate throughout the pretherapeutic course of disease (0.39±0.55 *vs.* 0.97±0.46; P<0.001) and by 71.3% compared with the relapse rate one year prior to treatment (0.39±0.55 *vs.* 1.34±0.65; P<0.001). The mean Extended Disability Status Scale (EDSS) increased significantly from 2.46±0.86 at baseline to 2.90±1.30 (P<0.01) at three years of treatment, whereas the mean progression index (EDSS/disease duration) decreased significantly from 0.76±0.50 prior to treatment to 0.43±0.24 (P<0.001), yielding a 56.6% improvement and proving the disease modifying effect of interferon beta-1b. Seventeen (53.12%) patients remained relapse-free during the course of therapy. Among patients that experienced disease relapse, the mean time to first exacerbation was 11.5±8.34 months. Our study results were consistent with similar studies performed worldwide, clearly indicating that Interferon beta-1b therapy decreased the disease activity and had a beneficial effect on the progression of RRMS, with low incidence and severity of serious side effects. This study has paved way for further long-term follow up studies at our institution.

Key words: *Multiple sclerosis – drug therapy; Interferon-beta – therapeutic use; Adjuvants – immunologic therapeutic use; Follow up studies*

Introduction

Interferon beta-1b is the first medicine with proven efficacy in the treatment of patients with relapsing-remitting multiple sclerosis (RRMS)[1,4]. In Serbia, it was approved in 1997. The National Health Insurance Fund and the drug manufacturer have been financing the interferon beta-1b therapy for 150 patients since 2004. In 2005, at Clinic of Neurology in Novi Sad as the referral institution for the region of Voivodina, we started treating 44 RRMS outpatients that were selected according to the criteria proposed by the National Committee. The inclusion criteria were: 1) relapsing- remitting form of the disease according to Poser criteria[2]; 2) clinically and laboratory definitive MS supported by McDonald criteria[3]; 3) the Expanded Disability Status Scale (EDSS) 0-3.5; 4) age 18-50; and 5) disease duration of at least two years, with at least two exacerbations in the two-year period prior to treatment. Relapses were treated with methylprednisolone 1 g i.v. ed for five days.

Correspondence to: *Aleksandar Ješić, MD*, Clinic of Neurology, Clinical Center of Voivodina, Hajduk Veljkova 1-7, 21000 Novi Sad, Serbia
E-mail: jesic@nscable.net
Received April 4, 2009, accepted May 20, 2009

Material and Methods

This prospective study included 32 patients continuously treated with interferon beta-1b 250 mcg (8 MIU) s.c. eod during a three-year period. The aim of the study was to evaluate the effects of interferon beta-1b and to compare the results obtained with literature data available. The primary end-point was the annual relapse rate

after three-year treatment with interferon beta-1b compared with the annual relapse rate throughout the course of disease prior to treatment and the relapse rate over one-year prior to treatment. Secondary end-points were: 1) EDSS alterations after three-year treatment; 2) assessment of the disease progression using the progression index (EDSS/disease duration); 3) number of relapse-free patients; 4) time to first exacerbation; and 5) clinical and hematologic side effects of interferon beta-1b.

Statistical analyses were performed using two-tail T-test.

Each patient underwent neurologic examination prior to therapy introduction and subsequently every six months, or earlier in case of suspected exacerbation. Laboratory tests (leukocytes, erythrocytes, platelets, AST, ALT and GGT) were performed monthly and thyroid hormone tests (T3, T4 and TSH) every three months.

Results

During the course of treatment 11 dropouts were recorded. Three patients were excluded for noncompliance to the treatment regimen. In two patients, therapy was discontinued due to worsening of their depression that had existed before the initiation of interferon beta-1b treatment in both cases. Two patients were excluded because of rapid progression and failure of therapeutic response. One patient had AST, ALT and GGT levels more than 5 times over the upper limits of normal, which was found to have been related with the drug and was therefore excluded from the study. One patient conceived during the course of therapy, which was resumed after delivery and breastfeeding period. One patient was excluded because the diagnosis was revised. One patient moved to another country. Overall, demographic data did not differ between the study group and dropouts (Table 1). The baseline EDSS was significantly higher in dropouts (2.95±0.69) as compared to study patients (2.46±0.86; P<0.001).

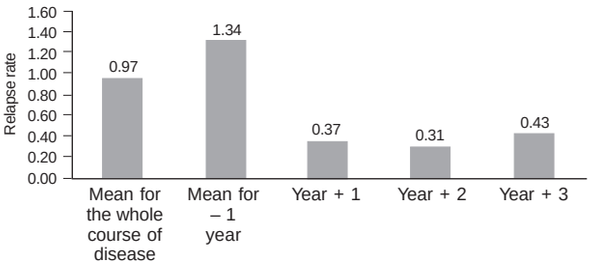

Fig. 1. Relapse rate during the course of therapy

The mean annual relapse rate was 0.97±0.46 throughout the course of disease prior to treatment and 1.34±0.65 one year prior to treatment with interferon beta-1b. The difference between the two rates was on the verge of statistical significance (P=0.0013). The annual relapse rate at three years of treatment was 0.39±0.55, yielding a 60.5% decrease as compared with the relapse rate throughout the course of disease prior to treatment and 71.3% decrease from the relapse rate one year prior to treatment, both clinically significant (p<0.001). The results clearly showed a marked decrease in the disease activity as the result of interferon beta-1b therapy (Fig. 1).

The EDSS score increased significantly but with less statistical power during the course of therapy, from the mean of 2.46±0.86 at baseline to the mean of 2.90±1.30 (P<0.01) at three years of treatment (Fig. 2). The mean increase in EDSS was 0.43±0.76. The mean progression index (EDSS/disease duration) prior to treatment with interferon beta-1b was 0.76±0.50 and decreased significantly to 0.43±0.24, making an improvement of 56.6% (P<0.001) and clearly proving the favorable effect of this medicine on the disease progression. Five patients experienced EDSS improvements, minimal 0.5 points in three patients and maximal 1 point in two patients.

Table 1. Demographic data

	All patients	Continuously treated	Dropouts
Number of patients	43	32	11
Male/female	8/35	7/25	1/10
Age, years (mean±SD)	29.97±8.10	32.91±7.42	30±7.95
Duration of disease, years (mean±SD)	4.88±4.21	4.93±4.21	4.59±2.92
EDSS baseline (mean±SD)	2.46±0.84	2.46±0,86	2.95±0.69

EDSS = Expanded Disability Status Scale

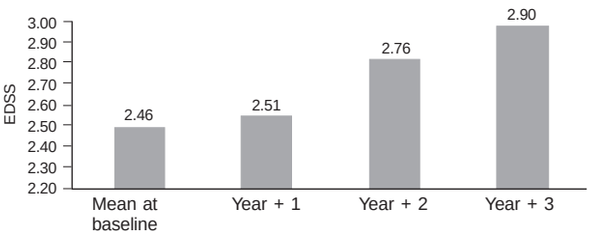

Fig. 2. EDSS changes during the course of therapy

At three years of treatment with interferon beta-1b, 17 (53.12%) patients remained relapse-free. In patients that experienced relapse, the time to first exacerbation was 11.5±8.34 months. Three patients progressed to the secondary progressive (SPMS) form of the disease, showing a sustained one-point increase on two consecutive examinations exceeding EDDS 4.5 and without clinical presentations of relapses.

During the first months of therapy, typical clinical side effects described in the literature, such as flu-like symptoms and local injection site reactions, occurred but were transitory. In one patient subclinical hyperthyroidism was diagnosed during the course of therapy, which was successfully treated and therapy was resumed. No other patient except for the one mentioned above had significant laboratory side effects that would have led to treatment interruption.

Discussion

The 60.5% decrease in the annual relapse rate observed at three years of treatment compared with the relapse rate recorded throughout the course of disease prior to treatment and the 71.3% decrease compared with the relapse rate one year prior to treatment were in agreement with similar open studies lasting one to three years that report 50%-86% decrease in the relapse rate[5-8].

The significant increase in the EDSS observed in our study was consistent with the results reported elsewhere. The 56.6% improvement in the progression index was in line with similar open studies reporting index reductions in the range of 50%-70%[5,8].

Our proportion of 53.12% of relapse-free patients was also consistent with previous open and double-blind studies, in which the percentage of relapse-free patients varied between 22% and 55%[5,6,8,9]. The same holds for the time to first exacerbation[8,9].

Since we had only one patient with clinically overt liver damage related to the drug, we could not draw any definite conclusions on the severity and frequency of side effects in our follow-up study. However, considering that no other patient had any side effects that would have urged dose reduction or treatment cessation, we conclude that interferon beta-1b is relatively safe for medium- or long-term use[5-9].

The significance of this study lies in the fact that it was the first observational study of interferon therapy conducted at our clinic. The results obtained help us evaluate the effects of the therapy that has recently been made available to our patients and gain valuable experience in the field. It also opens the possibility of further long-term follow-up of our patients. The drawbacks of the study were the lack of blinding, the small number of patients, and unavailability of MRI and neutralizing antibody evaluations. However, our study clearly indicated that interferon beta-1b therapy decreased the activity and progression of RRMS.

Acknowledgments. The authors are thankful to the following persons for their major contributions to the study: Prof. C. Nadj, D. Radojičić, S. Božić, S. Banić-Horvat, A. Kopitović, M. Ilin, M. Krklješ, V. Suknjaja and B. Pavkov. Special thanks to Lj. Stanković, N. Radovanov and S. Pavlović for their unselfish dedication and immense patience in the care of patients.

References

1. IFNB Multiple Sclerosis Study Group, University of British Columbia MS/MRI Analysis Group. Interferon beta-1b in the treatment of multiple sclerosis: final outcome of the randomized controlled trial. Neurology 1995;45:1277-85.
2. CARACCIO N, DARDANO A, MANFREDONIA F, MANCA L, PASQUALI L, IUDICE A, *et al*. Long-term follow-up of 106 multiple sclerosis patients undergoing interferon-beta 1a or 1b therapy: predictive factors of thyroid disease development and duration. J Clin Endocrinol Metab 2005;90(7):4133-7.
3. POSER CM, PATY DW, SCHEINBERG L, *et al*. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. Ann Neurol 1983;13:227-31.
4. POLMAN CH, REINGOLD SC, EDAN G, FILIPPI M, HARTUNG HP, KAPPOS L, *et al*. Diagnostic criteria for multiple sclerosis: 2005 revisions to the McDonald Criteria. Ann Neurol 2005;58(6):840-6.
5. BENCSIK K, RAJDA C, FÜVESI J, JÁRDÁNHÁZY T, TÖRÖK M, VÉCSEI L. Experiences with interferon-beta-1b treatment in MS after three year follow-up. Swiss Med Wkly 2002;132(17-18):237.
6. BENCSIK K, FÜVESI J, FRICSKA-NAGY Z, RAJDA C, LOSONCZI E, TÖRÖK M, *et al*. Short communication:

treatment of relapsing-remitting multiple sclerosis patients with IFN-beta1b: results of a 6-year follow-up. J Interferon Cytokine Res 2006;26(2):96-100.

7. FILIPPINI G, MUNARI L, INCORVAIA B, EBERS G, POLMAN C, D'AMICO R, *et al*. Interferons in relapsing remitting multiple sclerosis: a systematic review. Lancet 2003;361 (9357):545-52.
8. PATTI F, PAPPALARDO A, FLORIO C, POLITI G, FIORILLA T, REGGIO E, *et al*. Effects of interferon beta-1a and -1b over time: 6-year results of an observational head-to-head study. Acta Neurol Scand 2006;113(4):241-7.
9. KOCH-HENRIKSEN N, SØRENSEN PS, CHRISTENSEN T, FREDERIKSEN J, RAVNBORG M, JENSEN K, *et al*; Danish Multiple Sclerosis Group. A randomized study of two interferon-beta treatments in relapsing-remitting multiple sclerosis. Neurology 2006;66:1056-60.

Sažetak

UČINAK LIJEČENJA RELAPSNO-REMITENTNE MULTIPLE SKLEROZE INTERFERONOM BETA-1b: REZULTATI TROGODIŠNJE STUDIJE PRAĆENJA

A. Ješić, D. Stefanović, N. Delibašić, M. Semnic, L. Sakallasz, D. Dobrenov, Ž. Živanović, T. Rabi-Žikić i *M. Žikić*

Cilj ove prospektivne studije bio je procijeniti učinkovitost terapije interferonom beta-1b u grupi od 32 bolesnika oboljela od relapsno-remitentne forme multiple skleroze liječenih tokom trogodišnjeg perioda, te dobivene rezultate usporediti sa rezultatima dostupnim u literaturi. Pacijenti kod kojih je iz različitih razloga obustavljena terapija također su detaljno obrađeni. Primarni pokazatelj, godišnja stopa egzacerbacije nakon tri godine terapije, pokazala je statistički značajan pad za 60,5% u odnosu na stopu egzacerbacije tokom cijelog trajanja bolesti (sa 0,97±0,46 na 0,39±0,55), odnosno za 71,3% u odnosu na godinu prije započinjanja terapije (sa 1,34±0.65 na 0,39±0,55; P<0.001). Prosječna vrijednost EDSS se značajno povećala od 2,46±0,86 prije započinjanja terapije do prosječnih 2,90±1,30 (P<0,01), ali je srednji indeks progresije bolesti (EDSS/ duljina trajanja bolesti) bio značajno niži nakon tri godine terapije (0,43±0,24) u odnosu na indeks progresije tokom cjelokupnog trajanja bolesti (0,76±0,50; P<0.001), što čini poboljšanje od 56,6% i ukazuje na pozitivan učinak interferona beta-1b u smislu modificiranja toka bolesti. Tokom provođenja terapije 53,17% (17 pacijenata) nije imalo egzacerbaciju bolesti. Prosječno vrijeme do prve egzacerbacije među pacijentima koji su imali egzacerbaciju bilo je 11,5±8,34 mjeseci. Rezultati ove studije su u suglasnosti sa rezultatima sličnih objavljenih prospektivnih studija i pokazuju da interferon beta-1b ima pozitivan efekt na aktivnost i progresiju multiple skleroze, kao i da se ozbiljna neželjena djelovanja lijeka rijetko javljaju. Ova studija otvara mogućnost za izvođenje dugoročnih studija praćenja.

Ključne riječi: *Multipla skleroza – terapija lijekovima; Interferon-beta – terapijska primjena; Pomoćni lijekovi – imunološka terapijska primjena; Studije praćenja*