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EVALUATION OF FUNCTIONAL STATUS DURING BETA-INTERFERON THERAPY

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SUMMARY – Twenty patients (11 female and 9 male) with remitting relapsing multiple sclerosis were treated with beta interferon at University Department of Neurology, Sestre milosrdnice University Hospital. Thirteen patients were treated with interferon beta-1a (6 MIU 3 times weekly) and seven patients with interferon beta-1b (9.6 MIU every other day). The Expanded Disability Status Scale (EDSS) was recorded before interferon therapy and six months after initiation of interferon therapy. The mean EDSS score was slightly lower after six months of interferon therapy in both groups, but the difference was not statistically significant ($p=0.17$ in interferon beta-1a group and $p=0.36$ in interferon beta-1b group). Results in this small group of patients showed early improvement in the functional status of multiple sclerosis patients during interferon therapy. Further follow-up is required to get additional information on the course of functional improvement in multiple sclerosis patients after a prolonged period of interferon therapy.

Key words: *multiple sclerosis – drug therapy; interferon-beta – therapy use; adjuvants immunology therapeutic use*

Introduction

Multiple sclerosis (MS) is a dynamic disease, with almost constant lesion formation and a progressive clinical course leading to physical disability. MS affects females more than males, suggesting that hormonal component may play a role in the disease process. Males have a greater tendency to develop primary progressive MS, whereas females showa a predominance of remitting relapsing multiple sclerosis (RRMS)[1].

The Kurtzke Expanded Disability Status Scale (EDSS)[2] is still the most commonly used measure of disease progression, mainly due to the lack of alternatives. It comprises 20 grades from 0 (normal) to10 (death due to MS) progressing in a single-point step from 0-1 and 0.5 point steps upward. The functional system scores measure visual, pyramidal, cerebellar, brainstem, sensory, bowel, bladder and mental functions. Combining the functional system score and patient's degree of mobility or help required in daily activities produces EDSS score. Although the scale does not correspond linearly to common progression points for many patients, its widespread use and ease of implementation allow its utilization as a standardization measure for clinical trials[3]. The EDSS measures impairment rather than disability in patients who have lower scores on the scale from 0 to 3. Patients who have progressed beyond EDSS scores of 5.5-6 tend to respond poorly to the current treatment[4].

Preventing disease progression by use of available medications is essential in MS treatment, especially for patients who have been diagnosed early and will probably respond to treatment. Disease-modifying drugs may delay progression of disability and reduce the number of new MS lesions according to the magnetic resonance imaging (MRI) criteria[5].

Interferon acts through a common receptor that activates the pathway of signal transduction molecules leading to activation of interferon-responsive genes. Interferon beta may also decrease expression of a proinflammato-

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ry molecule on the surface of immune cells and increase the levels of anti-inflammatory mediators in the circulation of MS patients. Interferon beta-1a and -1b are indicated for RRMS and secondary progressive MS (SPMS)[6]. Interferon beta-1a is the most convenient drug to administer owing to a weekly schedule[7]. The frequency of development of neutralizing antibodies against interferon is higher with interferon beta-1b than with interferon beta-1a, but clinical significance is still unclear and controversial[6].

Patients and Methods

Twenty ambulatory patients with RRMS were treated with interferon beta at University Department of Neurology, Sestre milosrdnice University Hospital in Zagreb, Croatia.

Table 1. Patient population

	Interferon beta-1a	Interferon beta-1b
Mean age (yrs±SD)	34.92±9.55	37.29± 5.41
Female (yrs±SD)	35.73±8.70	36.00± 2.92
Male (yrs±SD)	34.43±7.85	40.50±10.61
Disease duration (yrs±SD)	4.62±2.81	6.71± 4.57

Eleven female and nine male patients, mean age 35.75±8.25 (±SD), age range 18-55 years, were included in the study (Table 1). Males were slightly older than females (35.78±8.21, range 25-50 *vs* 35.70±8.70, range 18-55 years). Thirteen patients were treated with interferon beta-1a (6 MIU subcutaneously, 3 times weekly), and seven patients were treated with interferon beta-1b (9.6 MIU subcutaneously, every other day). The interferon beta-1b group were slightly older than interferon beta-1a group (37.29±5.41, range 18-55 *vs* 34.92±9.55, range 33-48 years). In the interferon beta-1a group, female patients had a slightly higher mean age than male patients (35.73±8.70 *vs* 34.43±7.85 years). In the interferon beta-1b group, an inverse mean age relation was recorded (female 36.00 ±2.92 and male 40.50±10.61 years).

Interferon beta-1a patients had a mean disease duration of 4.62±2.81 (range 1-10) years, and interferon beta-1b patients of 6.71±4.57 (range 1-11) years.

Nonsteroidal anti-inflammatory drugs or paracetamol were recommended to reduce flu-like symptoms.

Functional status and EDSS score were recorded before and after six months of interferon therapy. EDSS score was employed as the most commonly used outcome measure in MS patients.

Statistical analysis was performed using Student's t-test. All conclusions were based on a significance level of $p<0.05$.

Results

The mean disease duration in the entire group of patients was 5.35±3.56 (range 1-11) years. Females suffered slightly longer from RRMS than males: 5.45±4.08 (range 1-11) *vs* 5.22±3.03 (range 1-10) years. Interferon beta-1b group had a longer disease duration than interferon beta-1a group: 6.71±4.57 *vs* 4.62±2.81 years.

The mean EDSS score of the whole patient group before interferon therapy was 3.03±0.50 (±SD), range 2-4. Pretreatment EDSS score was 3.00±0.63 (range 2-4) in female patients, and was slightly higher in male patients (3.06±0.30, range 2.5-3.5). After six months of interferon beta therapy, EDSS score in the whole group decreased to 2.92±0.67. At six months, EDSS score was 2.91±0.70 in female and 3.00±0.35 in male patients. In the interferon beta-1a group, pretreatment EDSS score was 3.00±0.61; 3.00±0.86 in female and slightly higher (3.07±0.35) in male patients. At six months, the female interferon beta-1a EDSS score was 2.83±0.93, whereas the male EDSS score was slightly higher (3.00±0.41). In the interferon beta-1b group, the mean pretreatment EDSS score was 3.07±0.19 and decreased to 3.00±0.28 at six months of therapy. Pretreatment EDSS was 3.10±0.22 in female and

Table 2. Expanded Disability Status Scale (EDSS) score before and after six months of beta interferon therapy

	Interferon beta-1a		Interferon beta-1b	
EDSS score	Pretreatment	At six months	Pretreatment	At six months
Female	3.00±0.86	2.83±0.93	3.10±0.22	3.00±0.35
Male	3.07±0.35	3.00±0.41	3.00±0.00	3.00±0.00

slightly lower (3.00±0.00) in male patients. After six months of interferon beta-1b therapy, EDSS score decreased to 3.00±0.35 in female patients and remained unchanged in male patients. The patients showed some improvement in balance and self-care activities irrespective of the type of interferon therapy. At six months of interferon therapy, the mean EDSS score of the patient group as a whole decreased slightly to 2.95±0.56, however, the difference was not statistically significant in either interferon beta-1a group (p=0.17) or interferon beta-1b group (p=0.36).

In the interferon beta-1a group, the mean EDSS score showed no statistically significant sex difference either before (p=0.67) or at six months of therapy (p=0.68). In the interferon beta-1b group, the mean EDSS score showed no statistically significant sex difference before (p=0.58) or at six months of therapy (p=1.00) either.

Adverse events associated with interferon beta treatment in the entire group of patients included injection-site reaction in three and flue-like symptoms in five patients.

Conclusion

Interferon beta tends to decrease the rate of new MRI lesions by approximately one third[5]. Interferon beta-1a was shown by the CHAMPS[9] trial to delay the onset of disease if administered to patients after an isolated demyelination event. Considerable controversy exists regarding whether the delay in the onset of new attacks by these drugs ultimately has a longterm impact on neurodegeneration and disability; these issues need to be addressed in future trials. Controversy has also existed regarding the eventual clinical impact of raising the dose of these medications to maximally tolerated levels. The INCOMIN trial study group[10] compared the effects of interferon beta-1a administered subcutaneously and interferon beta-1b administered intramuscularly[11], suggesting that higher and more frequent doses correlate with higher efficacy. Patients with secondary progressive forms and RRMS may be treated with interferon beta 1b, especially when the clinical course reflects an early phase of progression (EDSS score <6)[12].

Results in our small group of 20 RRMS patients showed a slight decrease in EDSS score after six months of beta interferon treatment in the whole patient group, although the difference did not reach statistical significance. Although the mean EDSS score was slightly lower at six months of therapy, there were no statistically significant differences in the mean EDSS score in either female or male patients.

Furthermore, there were no statistically significant differences between the pretreatment and six-month therapy scores in either interferon beta-1a or interferon beta-1b group.

As expected from previous studies, interferon beta was observed to slow down the progression of impairment. Supportive analyses of disease progression are required to get additional information on the functional status of MS patients after a prolonged period of interferon therapy.

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Sažetak

PROCJENA FUNKCIJSKOG STATUSA TIJEKOM LIJEČENJA BETA INTERFERONOM

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Dvadesetoro (11 ženskih i 9 muških) bolesnika s remitentnom rekurentnom mulitiplom sklerozom liječeno je beta interferonom na Klinici za neurologiju Kliničke bolnice "Sestre milosrdnice" u Zagrebu. Trinaestoro bolesnika liječeno je interferonom beta-1a (6 MIJ 3 puta na tjedan), a sedmoro bolesnika interferonom beta-1b (9,6 MIJ svakog drugog dana). Ljestvica EDSS (*Expanded Disability Status Scale*) bilježena je prije i šest mjeseci od početka liječenja interferonom. Prosječan zbir na ljestvici EDSS bio je u objema skupinama nešto manji nakon šest mjeseci liječenja interferonom, ali razlika nije bila statistički značajna (p=0,17 u skupini na interferonu beta-1a i p=0,36 u skupini na interferonu beta-1b). Rezultati dobiveni u ovoj maloj skupini bolesnika pokazali su rano poboljšanje funkcijskog statusa u bolesnika s multiplom sklerozom za vrijeme liječenja interferonom. Potrebno je daljnje praćenje kako bi se dobili dodatni podaci o tijeku funkcijskog poboljšanja u bolesnika s multiplom sklerozom uz dugotrajno liječenje interferonom.

Ključne riječi: