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Efficacy of interferon beta-1a in Iranian multiple sclerosis

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Abstract

Objective: To evaluate the clinical efficacy of once- weekly intramuscular interferon beta-1a (IFN B-1a, Avonex Biogen) in Iranian multiple sclerosis (MS) patients. *Methods:* A 12 months, single blind clinical trial conducted from January 2001 to September 2003. Eighty patients with definite MS age 20 to 50 years were allocated to two groups. The first group received 30 microgram (6MIU) IFN B-1a weekly. Patients with nearly similar clinical disease but did not receive any active treatment were followed up as the control group. The relapse rates and disability at 2, 4, 6, 12 months after commencement of study were compared between the two groups. *Results:* The female : male ratio was 3 : 1. Mean Extended Disability Scale Score (EDSS) showed no significant increase in the treatment group (2.97 to 3.01, $p>0.05$), but a significant increase in the control group (2.71 to 3.06, $p<0.001$). The frequency of yearly relapses decreased in both groups with greater changes in the treatment than the control group (1.5 to 0.6 vs 1.1 to 0.9, $p<0.005$). Within the treatment group, the EDSS increased more in the patients with EDSS of 4 and above as compared to patients with score of lower than 4 (0.53 vs 0.07, $p<0.001$). There was no significant differences in change of EDSS between the treatment and control groups in patients with secondary progressive MS (0.45 vs 0.67, $p>0.05$)
Conclusion: IFN B-1a was effective in the reduction of relapse rate and worsening of disability in Iranian MS patients.

INTRODUCTION

Multiple sclerosis (MS) is a chronic, inflammatory, demyelinative disease of the central nervous system (CNS) that most commonly affects women, with an onset typically between 20 and 40 years of age.[1,2] It represents the second most common cause of neurological disability in young adult.[3] The disease is unpredictable and clinically variable from patient to patient. Its most characteristic clinical course is the occurrence of relapses with acute or subacute onset of clinical dysfunction that usually reaches its peak from several days to several weeks, followed by a remission during which the symptoms and signs resolves to a variable extent. Eventually progressive clinical course intervenes leading to permanent disability.[4,5] Although the aetiology of MS is not established, the bulk of evidence suggests that it is an immune-mediated disease characterized by localization of several types of inflammatory cells in the MS lesions with altered levels of inflammatory cytokines in the serum, cerebrospinal fluid and CNS.[5]

In the second half of the twentieth century the treatment of MS has advanced from relief of symptoms to the use of disease-modifying agents.[6] The beta interferons are a family of cytokines with anti-viral, anti-proliferative and immunomodulating properties.[7,8] The multiple actions of the beta interferon suggest that they may be beneficial in controlling the MS disability.[9] Interferon beta-1a (IFN B-1a, Avonex) is a natural sequence glycosylated recombinant Chinese hamster ovary product with a structure basically identical to that of natural human interferon. It has been shown to be beneficial in the treatment of patients with established MS. The benefits include slowing of the progression of physical disability, reducing the rate of clinical relapse and reducing the brain lesions as assessed by magnetic resonance imaging (MRI).[7,8] The efficacy was at the range of 30-40%.[10] The present study was performed to assess the effectiveness of IFN B-1a in Iranian MS patients.

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METHODS

This single blind clinical trial was performed from January 2001 to September 2003 in 80 Iranian MS patients. Consecutive patients who were referred with a diagnosis of MS to the neurology clinic in Al-Zahra Hospital (affiliated to Isfahan University of Medical Sciences), Iran, were evaluated for recruitment. The inclusion criteria were definite relapsing-remitting (RR) or secondary progressive (SP) MS according to the Poser's criteria[11]; at least two documented exacerbations in the last two years; age 18 years and above, and baseline EDSS score between 0 and 6. The exclusion criteria were**:** pregnancy or planning to become pregnant[12]; presence of any disease other than MS that compromised the organ function or assessment of disability; depression and epilepsy.[13]

The study was approved by the Ethical Review Committee of Isfahan University of Medical Sciences. The nature of the trial was explained to the patients and written consent obtained. Eighty-four patients were selected by simple random sampling from the patients referred to the neurology clinic and were divided into two groups according to their economic ability to purchase Avonex. Patients who did not opt for interferon treatment (or immunosuppressive drugs) were followed as controls. IFN B-1a was administered as a once weekly intramuscular injection of 30µg (6 million unit) in the treatment group.

The demography of the patients, their relapse rate during previous years, clinical course of disease and their Extended Disability Scale Score (EDSS) at baseline of study were recorded. Follow up visits were scheduled at 2, 4, 6 and 12 months after the first visit. The clinical assessment of patients was performed by the same neurologist who was blinded. Patients with relapse were treated with intravenous methylprednisolone and reexamined after at least one month. Steroid administration was limited to acute exacerbation.

Two patients discontinued interferon due to severe low back pain and changes of menstruation, and two others due to severe myalgia. Ultimately 80 patients completed the study. The changes in the frequency of relapse during the study period were compared with that during the previous year and the EDSS changes were also compared in the two groups.

An Increase of one point on the EDSS which persisted for at least two scheduled visits indicated progression of disability. If a relapse occurred during a scheduled visit, the EDSS assessment was performed at least one month later.

All data were analyzed using the SPSS software. Baseline characteristic, exacerbation rates and changes in disabilities were compared using Students t-test. A p-value of less than 0.05 was considered significant.

RESULTS

A total of 80 patients were recruited during the accrual period, with 40 patients in each group. There were no significant differences between the two groups concerning sex ratio, age and annual relapse rate (Table 1). Overall, the number of women was three times more than men. The age of onset in 40% of treatment group and 55% of control were in the 20-30 years range. 73% of treated patients (29 patients) and 65% of control (26 patients) had relapsing-remitting course.

There was significant progression in the EDSS in the control group (2.71 to 3.06) compared with the treatment group (2.97 to 3.01, $p<0.001$). The score increased in 23 % of treatment group and in 45% of controls. Within the treatment group, EDSS increased more in the patients with initial score of 4 and above compared with the patients with an initial score of lower than 4 (0.53 vs 0.07, $p <0.001$) (Table 2).

The frequency of yearly relapses decreased in both groups with greater changes in the treatment group (1.5 to 0.6) than the control group (1.1 to 0.9, $p<0.005$).

In patients with SPMS, there was no significant difference in the change of EDSS between the treatment and control groups (0.45 vs 0.67, $p>0.05$). However, there was significant decrease in the annual relapse rate in the treatment group (0.7) as compared to the control group (0.3, $p<0.05$)

DISCUSSION

Although the indication for using IFN B-1a in RRMS is based on large placebo controlled clinical trials[10,14], the fact that treatment is only partially effective, the difficulty in distinguishing "responders" from "non-responders", the unknown long term efficacy and side effects, and the high cost of the therapy warrant further evaluation in our local setting. It is also known that there are racial modifications of clinical manifestations of MS.[15,16]

Evaluation of the disability scores indicated statistically significant increase of EDSS in control group (p-value<0.001), but not in the treatment group (p-value =0.69). This suggests that IFN B-1a is beneficial in prevention of disease

Table1: Characteristic of treatment and control groups of patients

Characteristic	Treatment group	Control group
Number of patients	40	40
Mean age in years	27	26
Female : Male	27 : 13	33 : 7
RRMS : SPMS	29 : 11	26 : 14
Mean duration of symptom in years	4.6 ± 2.8	5.4 ± 3.6
Mean baseline EDSS	2.97 ± 1.7	2.71 ± 1.6
Mean EDSS after one year	3.01 ± 2.1	3.06 ± 1.8
Mean relapses in previous one year	1.5 ± 0.6	1.1 ± 0.5
Mean relapses during the study period	0.6 ± 0.7	0.9 ± 0.6

RRMS: Relapsing remitting multiple sclerosis; SPMS: Secondary progressive multiple sclerosis; EDSS: Mean Extended Disability Scale Score

Table 2: Increased of disability in treatment group from baseline EDSS

	No. of patients	Mean increase in EDSS
EDSS < 4	29 (73%)	0.07
EDSS = 4	11 (28%)	0.63
p value		0.001

EDSS: Mean Extended Disability Scale Score

progression. EDSS increased in 23% of treated patients but in 45% of control suggesting that treatment is effective in halting disease progression in 22% of patients, a finding similar to that reported by Rudick *et al* in 1997.[17]

There is also a 41% reduction in relapse rate in the treatment group, a finding similar to those previously reported. In the EVIDENCE study, those who received Avonex had 48.2% decrease in the rate of developing second attack.[18] The reduction in relapse rate was 28.5% in a study from Mexico.[19]

In subgroup analysis, treatment with IFN B-1a was found to be more effective in patients with EDSS of 4 or less, contrary to the study of Vermersh *et al.*[6] IFN B-1a treatment was also found to reduce the relapse rate, but not the progression of disability of SPMS.

In summary, IFN B-1a is effective in the treatment of MS among Iranians, especially RRMS with early disease.

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