Interferon-beta in Pediatric Multiple Sclerosis Patients: Safety in Short-Term Prescription

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Abstract- None of the approved immunomodulatory drugs in adults Multiple Sclerosis (MS) patients have been officially approved for the pediatric patients and are currently used off-label in this population. In this study, we evaluated the effectiveness and tolerability of intramuscular interferon beta1-a (Avonex®) and subcutaneously injected interferon beta1-b (Betaferon®) in children with definite relapsing-remitting MS (RRMS). Thirteen patients aged younger than 16, who were recently diagnosed with definite RRMS according to the McDonald's criteria, were enrolled in this study. Six patients were treated with Avonex® 30 µg, intramuscularly every week, and seven patients were treated with Betaferon® 250 µg, subcutaneously every other day. All patients were treated with adult doses; initially interferon-beta was prescribed with half dose, and it was increased to full adult dose steadily. Eleven girls and two boys, mean (SD) age of 14.7 (1.9) years, were studied. Following nine months of using interferon-beta, nine patients (69.2%) had no relapses and the remaining four, experienced only one relapse. The mean EDSS score was decreased significantly after the study period. The present study provides reasonable data for the use of interferon-beta in Pediatric MS due to lack of short-term complications and safety. Studies with larger sample size and longer follow up duration are required to shed light on the long term impact of the interferon-beta therapy in children.

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Introduction

Occurrence of multiple sclerosis (MS) before 16 years of age is less common, varying from 1.2–7% in different studies and is about 6.6% in our region (1). The course of early onset multiple sclerosis (EOMS) is mostly relapsing-remitting (RR), and 40-60% of patients will suffer a relapse during the first year after the onset, reflecting more susceptibility to relapses in children than in adults (2,3). Onset of MS during the childhood has the potential profoundly affect educational performance and cognitive outcomes (4). Moreover, patients with EOMS reach mild disability [Expanded Disability Status Scale (EDSS) score=3–4] and severe disability (EDSS≥6) at younger ages; therefore, at a given age, patients with EOMS are more disabled than the corresponding patients with the adult onset MS (AOMS) (5,6). Consequently, recent evidences have led clinicians to consider the commencement of early immunomodulatory therapy for reducing relapse rates, disease progression, and shifting rate to the irreversible damage phases (6-8).

Interferon beta (IFNB) is an immunomodulatory drug, which is proved to decrease the relapse rate and MRI activity in adult patients with relapsing-remitting MS (Class I evidence) (8,9). Two kinds of IFNB-1a and one kind of IFNB-1b are approved by Food and Drug Administration (FDA) for RR form of MS in adults. None of these therapies have been officially approved for the pediatric age group, and they are currently used off-label in this population (9). The literature is sparse on the effectiveness, safety and tolerability of interferon-

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beta in pediatric MS patients. In this study, we evaluated the safety and tolerability of intramuscular IFNB-1a (Avonex®) and subcutaneously INFB-1b (Betaferon®) in patients with definite RR EOMS.

Materials and Methods

Thirteen patients younger than 16 years who were recently diagnosed (less than 6 months) with definite RRMS according to the revised McDonald's criteria (10), were recruited from Isfahan Multiple Sclerosis Society. Informed consent was obtained from the parents of children. All patients were of expected weight and height for their age. Interferon-beta was initially prescribed with half dose and increased to full adult dose steadily. Six patients were treated with Avonex®, 30 µg intramuscularly every week, and 7 patients were treated with Betaferon®, 250 µg subcutaneously every other day. We performed prospective follow-ups with scheduled visits for 9 months and clinical status, common adverse effects, EDSS scores, and relapses were monitored. No patient was drawn out of the study because of adverse effects.

Data analysis was performed using SPSS 13 statistical package (SPSS Inc. Chicago, IL, USA). The Wilcoxon test was used to identify significant differences between dependent samples *i.e.* EDSS, and relapsing time. Kaplan-Meier survival test was used to determine free time disease survival during 9-month follow up. Forward conditional Stepwise binary COX regression model was applied for the prediction of outcome during the follow up. The level of significance was set at 0.05.

Results

Eleven girls and two boys with mean±SD age of 14.7±1.9 years and definite RRMS, were treated with interferon-beta. The patients' initial presentations and demographic status are demonstrated in the table 1.

Brain MRI demonstrated supratentorial lesions in 10 patients (76.9%), and in remaining 3 (23.1%), periventricular and infratentorial lesions (brainstem, cerebellum and spinal cord) were seen. Totally, twelve patients had optic neuritis; in addition, cerebellar, corticospinal, motor, and sensory signs were observed in 7 patients.

Following 9 months of treatment with interferon-beta, nine patients (69.2%) had no relapses and the remaining four experienced only one relapse (Figure 1). Age, sex, type of treatment, and the number of involved neurological sites had no effect in the relapse-free time of patients as shown by Cox regression. The mean EDSS score was decreased significantly after nine months (P=0.015) (Figure 2).

Before the initiation of treatment, six patients (46.2%) had two relapses; six (46.2%) had one relapse and one (7.7%) had three; however, after the initiation of therapy, only 4 patients (30.8%) had just one relapse (P=0.001).

In this study, the mean EDSS score decreased significantly after 9 months and the mild clinical side effects (flu like syndrome, mild leucopenia) were transient in the cases.

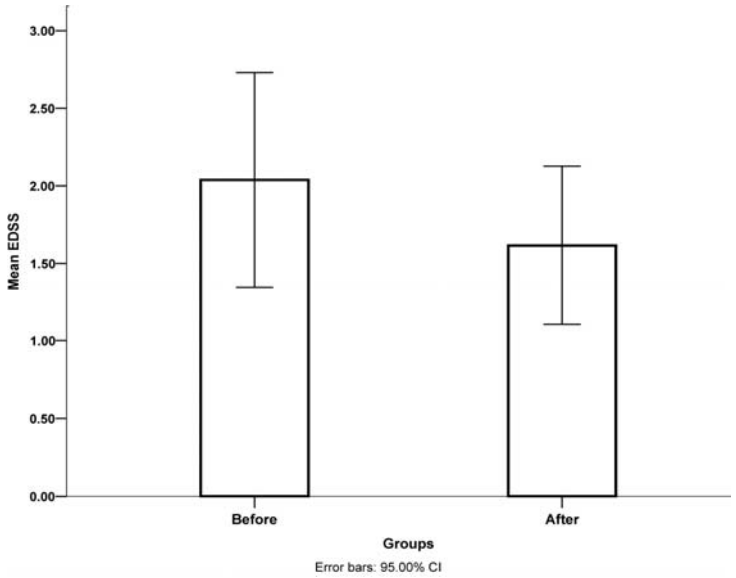

Figure 1. Expanded disability status scale (EDSS) score in patients before and after receiving interferon-beta.

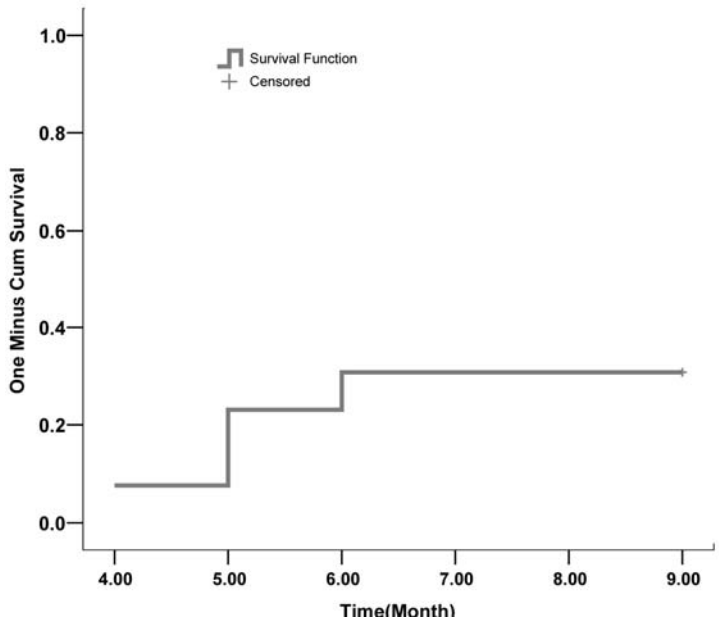

Figure 2. Relapse-free time of patients after treated with interferon-beta

Table 1. Demographic data of patients.

Parameter	N
Sex (F/M)*	11 / 2
Age (SD)**	14.7 (1.9)
Symptom	N (%)
Headache	2 (15.4)
Blurred vision	8 (61.5)
Paresthesia	2 (15.4)
Double vision	4 (30.8)
Vertigo	2 (15.4)
Type of treatment	N (%)
Avonex®	6 (46.2)
Betaferon®	7 (53.8)
Organ Involvement	N (%)
Only optic nerve involvement	6 (46.2)
More than one organ involvement	7 (53.8)

* M: male, F: female ** SD: standard deviation

Discussion

INFB is currently used in the treatment of adult MS patients, but its effect has not been adequately tested in children with MS. Evidences about high relapse rate in some patients with relapsing remitting pediatric MS (11), shifting to severe disability in a short time (12), and the fact that the treatment is more effective in the early phases of the disease (6,13), encourage physicians to apply immunomodulators for the pediatric MS patients. Some small cohorts studied the safety and tolerability of using interferon-beta in PMS (5-7). Ghezzi *et al.,* reported a mean 36 month follow-up of patients with PMS treated with immunomodulators; in their study, the mean EDSS was unchanged at the end of the follow-up and there were some patients who discontinued the treatment because of ineffectiveness, lack of compliance, and side effects (6). Pakdaman *et al.,* (7) conducted a prospective randomized trial in patients with multiple sclerosis under the age of 16, and they divided the patients into two groups of eight. The first group was treated with intramuscular interferon beta-1a 15 micrograms once a week and the second group received no disease-modifying therapy. The patients were followed for four years, and the interferon group favored the control group regarding relapse rates, disability progression, and new T2 lesions.

The favorable results observed in our series are similar to those observed by Mikaeloff *et al.,* in a study of 13 PMS subjects treated with INFB-1a IM (14).

Important issues such as the effect of immunomodulators on growth and puberty, or their long term adverse effects on the immature immune system have not been answered yet. Moreover, all immunomodulatory drugs have not been prescribed for more than 16 years in adults, so unexpected long term adverse effects - with particular importance in younger patients - remain possible.

A limitation factor in this survey was the small number of patients entered into the study due to infrequent occurrence of MS in the children age group; on the other hand, short-term follow-up was another

limitation; as a result, in this study, the short-term safety of IFNB could be highlighted and for the long-term effectiveness, further follow-up in the future is required. In conclusion, our results might extend the current knowledge on safety and tolerability of INFB in children and support a reasonable profile for its usage; however, the long term impact of treatment could be addressed only by long term follow-ups.

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