

The Therapeutic Effect of Avonex, Rebif and Betaferon on EDSS and Relapse in Multiple Sclerosis: A Comparative Study

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Abstract- We aimed to compare the therapeutic effect of Avonex (Av), Betaferon (Be) & Rebif (Re) on the Expanded Disability Status Scale (EDSS) in Multiple Sclerosis (MS). Ninety patients referring to Farshchian Hospital were entered in this study. The patients were divided into three equal groups: group 1 received Av, group 2 received Re and group 3 received Be, and after 24 months, comparison was done by calculating primary and final EDSS and the relapse rate. For comparison of the primary and final EDSS in each group, the relapse rate between the groups and side effects between the drugs, the paired samples t.test, the One-Way ANOVA test and the Pearson- chi-square were used. Average age was 31.11 ± 8.62 years, 80% being female. Comparison of the average primary and final EDSS using the paired samples t.test showed a significant statistical difference ($P < 0.05$). Motor and visual disturbances (respectively 68.3% and 60.3%) were the most common signs and relapsing- remitting form was the most common form (42.1%). The average EDSS change of groups Av, Be and Re was respectively, 1.28 (29.76%), 1.30(24.30%) and 1.26 (26.63%), showing no significant statistical difference in reducing EDSS. Groups Av and Be, showed no significant statistical difference in the average relapse rate before and after treatment, but in group Re there was a significant difference ($P < 0.05$). Treatment with these drugs reduces motor disability, with no significant difference between them. Also in comparison, Re has a greater effect in reducing the relapse rate, but again with no significant statistical difference among them.

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Introduction

MS is the most common autoimmune inflammatory chronic disease of the CNS that is characterized by demyelination and loss of axons (1,2) and as for clinical manifestations is characterized by episodes of focal and multifocal disturbances of the brain, spinal cord and the optic nerve (3). It seems that a group of factors including: defect of the immune system, genetic predisposition, infectious diseases, emotional stresses, biochemical factors, diet, vitamin deficiency and allergic reactions are causative in this disease (4).

The most important influential factor in the course of the disease is the number of relapses. These are described as acute or subacute clinical disturbances that usually occur days or weeks after a period of improvement and last for at least 24 hours.

The number of relapses, its acute or subacute nature, duration, severity and the nature of improvement after the relapse, has a close correlation with the site of CNS

involvement. Generally the number of relapses are more in the first years of the disease and as time passes by, this declines. Approximately 15% of the patients never experience a relapse (1).

The disease has been divided into four groups: 1) Relapsing Remitting Multiple Sclerosis (RRMS), 2) Primary Progressive Multiple Sclerosis (PPMS), 3) Secondary Progressive Multiple Sclerosis (SPMS), 4) Progressive Relapsing Multiple Sclerosis (PRMS) (1).

Nowadays the scale most frequently used for evaluation of disability of patients afflicted with MS is the EDSS (1).

Most patients have an EDSS of 1- 6. The time interval for development of disability varies with every

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patient. For patients with EDSS of 4 or 5, median time of remaining at these levels was 1.2 years, whereas for those at EDSS 1 and EDSS 6 median time of remaining at those levels were respectively, four years and three years.

There is no cure for MS and treatment of the patients aims mainly at modifying the course of the disease and reducing the complications.

One of the drugs used for modifying the course of the disease is the β - interferon. Three types of β -interferons are used in treating MS: β - interferon 1a (Av), β - interferon 1a (Re), β - interferon 1b (Be), which differ in method of production, chemical structure, method of injection and dosage. Treatment with all forms of β - interferons is accompanied with mild, moderate and severe side effects (5).

Each of these drugs have a significant effect in reducing the relapse rate, progression of disease and MRI findings though none of them has a positive effect on PPMS (6).

The criteria for no response to treatment include two attacks in an interval of a year or a numerical increase of +1 in EDSS (1).

In placebo control studies, all of these β - interferons showed similar results in the form of a 30% reduction in MS attacks in patients with RRMS (7-9).

Results of a study by Etemadifar et al showed that these drugs have a significant effect in reducing relapse and EDSS (10).

In another study in 1999 a 20.5% reduction in progression of disability under the effect of these drugs has been reported, but no comparison has been carried out (11).

Due to the fact that in previous studies the effect of these drugs on the progression of the disability of the patients has been variably reported and in most of the studies the therapeutic effect of these drugs has been compared with placebo group and on the other hand there has been no study to compare the average relapse rate in these three drug groups, the present study was carried out with the aim of comparing the therapeutic effect of these drugs on EDSS and relapse rate.

Patients and Methods

The study was a randomized clinical trial and included all the patients with MS referring to the Farshchian Hospital, Hamadan (West Iran) during the year 2005-2006, who had the following criteria:

Age between 14 – 50 yrs, definite diagnosis of MS based on clinical manifestations and performing MRI

according to McDonald's criteria, acceptance of the 24 month protocol by the patients, not being pregnant or lactating, history of having received a kind of β -interferon under the supervision of a neurologist in a period of no more than 30 days prior to the study. At the onset of treatment all of the patients had an EDSS of less than 6.

Exclusion criteria were as follows: 1) history of malignancy within the past five years 2) history of HIV infection, positive serology for hepatitis B and C 3) history of infectious disease within six weeks prior to the study and need for hospitalization from an infectious cause within two months prior to the study 4) any kind of hematological abnormality such as lymphocyte count $\leq 1 \times 10^9/L$, platelet count $\leq 100 \times 10^9/L$, neutrophil count $\leq 1.5 \times 10^9/L$, and hemoglobin level ≤ 8.5 g/dl 5) any kind of definite functional abnormality in body organs that disables the patient for treatment with β -interferons (criteria for functional abnormality in such cases included: creatinin ≥ 1.6 mg/dl, AST or ALT $\geq 2.5 \times$ maximum normal values, alkaline phosphatase $\geq 2.5 \times$ maximum normal values, and history of heart failure, myocardial infarction or arrhythmia within six months prior to the study) 6) vaccination using live virus vaccines within four weeks prior to the study 7) use of antimetabolites or cytotoxic drugs within six months prior to the study 8) patients with PPMS 9) any kind of elective surgery during the study 10) rise in hepatic enzymes or severe drug reactions during the follow up period.

The total sample volume was 90 patients divided into three equal groups.

According to the inclusion criteria the patients were treated as follows: 30 patients received Av (30 mcg IM on a weekly basis), 30 patients received Re (44 mcg SC three times a week) and 30 patients received Be (250 mcg SC on an alternate day basis).

The patients' EDSS was calculated and the necessary lab tests for possible drug reactions were performed. The patients in all three groups were evaluated at the end of months 6, 12, 18, 24 and in case of development of reactions were excluded from the study. At the end of 24 months the patients were again evaluated for EDSS, and the number of relapses for each patient was calculated (cases of pseudoexacerbation were not considered as relapse).

Statistical analysis

The obtained information were entered in a questionnaire so that the amount of increase or decrease of the patients' disability after the end of treatment in

the three groups could be evaluated and compared. For comparison of the primary and final EDSS in each group the paired samples t.test, for comparison of the changes in the primary and final EDSS between the groups, the One-Way ANOVA test and for comparison of side effects between the three drugs, the Pearson- chi-square were used.

Finally analysis was performed using SPSS v13.

Results

Ninety patients were included in this study with an average age of 31.11 ± 8.62 with a minimum of 14 and maximum age of 50.72(80%) were female and 18(20%) were male. At presentation, the most common signs were motor (68.3%) and visual (60.3%) disturbances, and the least common was cognitive disorder (3.2%). In evaluating the various type of the disease RRMS was the most common form (42.1%) and Clinically Isolated Syndrome (CIS) was the least common form (4.8%).

Findings with regards to relapse before and after treatment and pulses of steroid received showed that :in general ,prior to treatment ,27% of the patients had received no pulses and most of them (42.1%) had received one pulse, while by the end of treatment the proportion of patients receiving no pulse and one pulse was respectively 57.1% and 19.8%.

In the Av group 33.7% had received no pulse prior to treatment but 66.3% had received steroid (36.7% one pulse, 10% two pulses,3.3% three pulses,5% four pulses,1.7% five pulses,3.3% ten pulses).Up to the end of treatment 58.3% received no pulse and overall 41.6% (13.3% one pulse, 15% two pulses, 3.3% three pulses, 3.3% four pulses, 5% five pulses, 1.7% seven pulses) had received steroid(relapse). In the Be group 16.7% had received no pulse prior to treatment but 83.3% had received steroid (53.3% one pulse, 13.3% two pulses, 10% three pulses,3.3% four pulses,3.3% five pulses).Up to the end of treatment 53.3% received no pulse and overall 46.7% (26.7% one pulse, 6.7% two pulses, 13.3% three pulses) had received steroid(relapse).

In the Re group 19.4% had received no pulse prior to treatment but 80.6% had received steroid (41.7% one pulse, 11.1% two pulses, 8.3% three pulses, 2.8% four pulses, 11.1% five pulses, 2.8% six pulses, 2.8% ten pulses).Up to the end of treatment 58.3% received no pulse and overall 41.6% (25% one pulse, 8.3% two pulses, 8.3% four pulses) had received steroid (relapse).

Results of comparative study of the average interval of relapse before and after treatment is shown in tables 1 and 2.

Table 1. Comparison of average relapse interval before and after treatment

Group	Relapse		P value
	Before treatment (mean± SD)	After treatment (mean± SD)	
Avonex	1.5 ± 2.86	1.1 ± 1.80	P = 0.495
Betaferon	1.40 ± 1.19	0.80 ± 1.06	P = 0.109
Rebif	2 ± 2.24	0.8 ± 1.24	P = 0.022

Comparative study of the average First and Final EDSS, using the paired sample t.test, showed a significant statistical difference in all three groups (Table 3).

Comparison of the average change in EDSS by using the One-Way ANOVA test showed no significant difference in the reduction of EDSS (Table 4).

Study of adverse effects, in Av group showed that 1.7% of the patients had no side effects and 98.3% experienced minor side effects including dermal reactions at the site of injection, numbness of this area, flu-like syndrome and irregular menses. In the Be group, two female patients developed severe necrotizing vasculitis that were excluded from the study and the rest had minor side effects and finally in the Re group all the patients showed evidence of minor side effects.

The Pearson Chi-Square statistical test showed no significant difference in this regards.

2.4% of the patients had positive family history .In these patients, the following values were obtained: average First EDSS 4 ± 1 with a minimum of 3 and a maximum of 5 , and an average Final EDSS 1.67 ± 0.82 with a minimum of 0 and a maximum of 4.

Table 2. Comparison of average decrease in relapse

Group	Decrease in relapse		P value
	Decrease rate	Decrease percent	
Avonex	0.40	61%	0.447
Betaferon	0.60	45%	
Rebif	1.20	48%	

Table 3. Comparison of average First & Final EDSS

Group	EDSS Scales		P value
	First (mean± SD)	Final (mean± SD)	
Avonex	4.3 ± 1.61	3.01 ± 2.05	0.004
Betaferon	5.35 ± 1.82	4.05 ± 1.73	0.000
Rebif	4.73 ± 1.61	3.46 ± 1.95	0.000

Table 4. Comparison of average EDSS change

Group	EDSS change		P value
	Average change	Change percentage	
Avonex	1.28	29.76%	0.998
Betaferon	1.30	24.30%	
Rebif	1.26	26.63%	

In the patients that had no familial history, an average First EDSS of 4.75 ± 1.73 with a minimum of 1 and a maximum of 9.5, and an average Final EDSS 3.39 ± 2.14 with a minimum of 0 and a maximum of 8 was obtained.

Study of the analgesic used before injection revealed that in most of the patients (89.7%) Naproxen was used.

Study of the time interval between the diagnosis and treatment revealed the following data: Av 2.75 ± 3.95 years is 2.35 ± 3.63 years and Re 2.86 ± 3.19 years.

Discussion

In the present study that was carried out with the aim of comparing the therapeutic effect of Av, Re and Be on EDSS and relapse rate of patients afflicted with MS, an average age of 31.11 ± 8.62 years (14-50) was encountered. In the study by Cotrell *et al.* (12) the average age of the patients was reported to be about 39 years and in another study (13) the average age of the patients was reported to be about 38 years, therefore our patients had a lower age of onset.

In our study, the rate of affliction of females was four times of that of males- a rate higher than other studies (12,13) which yielded a rate of about 1.5 to 1. According to the statistics stated in references, the sex ratio of female to male has been reported to be about 1.77 to 1 and some references have stated this ratio to be 2 to 1 or even 3 to 1 (1). In this regards, one might consider the role of certain factors such as race and genetic, which warrants further studies.

At presentation, the most common signs were motor and visual disturbances, and the least common was cognitive disorder. In evaluating the various type of the disease RRMS was the most common form and Clinically Isolated Syndrome (CIS) was the least common form, which is comparable to similar studies (1).

Studies with regards to the number of attacks before and after treatment(steroid pulses),showed that generally, before treatment 27% of the patients had received no pulses and most of them(42.1%) had

received one pulse, while up to the end of treatment, the number of these patients was respectively 57.1% and 19.8%.With regards to the average relapse rate ,our study showed no significant statistical difference in groups Av and Be, before and after treatment, while the results of other studies performed in Italy (14) and in Spain (15), showed a significant decrease in relapse using Av.

According to the performed studies (6), Av caused an 18% decrease in relapse rate and using it with a dose of 44 mcg reduced the number of relapses by 33% within three years.

Also, in the study in Iran by Kalani (16), Av caused a significant decrease of 32% in attacks. Contrary to the other studies, in our study Av did not cause a significant decrease in the number of relapses, but caused a significant decrease in relapse rate, which was higher than the Kalani study (16), yet lower than the other studies (14,15).

On the other hand, Re caused a significant statistical difference in the average relapse rate before and after treatment ($P < 0.05$), and compared to the other two drugs, it had a greater effect on decrease in relapse (62.5%). In another study, all these drugs caused a similar 30% decrease in relapse (17). Various studies in numerous centers, have reported that using betaferon with a dose of 250 mcg for two years, has led to a significant decrease in MRI findings and also caused a 32% drop in relapse and yearly attacks (18).

According to statistics stated in references ¹, the EDSS of most patients is in the range of 1 to 6, while in this study, the First EDSS was in the range of 1 to 9.5, and the Final EDSS was in the range of 0 to 8.Using Paired samples t.test comparison of the average First and Final EDSS in all three groups showed a significant statistical difference ($P < 0.05$).

With regards to the reduction of EDSS, and by comparing the average EDSS change of the three groups, we noticed no significant statistical difference.

In a review of twenty-one studies between 1993 and 2001 on the effect of beta-interferons on progression of disability, it was reported that beta-interferon 1a (Av & Re) caused a significant decrease, while beta-interferon 1b (Be) had no effect (19).

In another study, discontinuation of Re in patients with SPMS, caused an increase in EDSS after 12 months which was in favor of increased severity of the disease (20). Also in separate studies on the effect of beta-interferons 1a and 1b on the progression of disability, relative improvement in EDSS was noted in both drug groups (21,22).

According to various studies, incidence of familial MS varies from 3% to 23% and in our study 2.4% of the patients had a positive familial history. In these patients, the average First EDSS was calculated to be 4 ± 1 with a minimum of 3 and a maximum of 5 and the average Final EDSS was calculated to be 1.67 ± 0.82 with a minimum of 0 and a maximum of 4. In conclusion, results of this study are in accordance with prior studies regarding the relative improvement in EDSS using each of these drugs, yet there is no significant difference between them in reducing disability. On the other hand, Re caused a significant reduction in the number of relapses, but again comparing the three groups; there was no significant decrease in reduction of relapse.

Since all these drugs have a similar effect on motor disability and cause similar side effects, and due to the fact that Av is more easily administered (weekly dose) and better accepted by the patients, we suggest that using this drug as the first therapeutic option might be better. Also, when in need of reducing relapse, one can benefit from the positive effect of Re in this regards.

Finally, similar studies in other centers, and studies with larger sample volumes and longer periods, and comparing their results with our results could be beneficial.

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