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Research Article

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Clinical, Radiological and Electrophysiological Comparison of Immunomodulatory Therapies in Multiple Sclerosis

Multipl Sklerozda İmmunmodulatuvar Tedavilerin Klinik, Radyolojik ve Elektrofizyolojik Olarak Karşılaştırılması

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ABSTRACT

Introduction: Although it's been shown that immunomodulatory therapies (IMTs) in multiple sclerosis (MS) can modify the course of the disease by reducing the relapse rate, and relatively delaying the progress of disability, no study comparing IMTs head-to-head in terms of clinical, radiological, and electrophysiological changes is available. We aimed to investigate the effects of interferon-beta (IFN-B) 1b, IFN-B-1a subcutaneous (sc), IFN-B-1a intramuscular (im) and glatiramer acetate (GA) therapies on clinical, electrophysiological and radiological findings.

Methods: A cohort of 85 MS patients were evaluated who followed up at least 2 years and had complete charting including pre-treatment and post-treatment clinical, radiological, and electrophysiological findings. We compared IMTs' effects on these findings retrospectively.

Results: Annual relapse rates were 0.1 for IFN-B-1a sc; 0.2 for IFN-B-1b; 0.3 for GA, 0.5 for IFN-B-1a. (p=0.01). The percentage of relapse-free patients after one year ranged 54.5% for IFN-B-1a im and GA, 82.9% IFN-B-1a sc, to 86.4% for IFN-B-1b, and after two years varied from 27.3% for IFN-B-1a im, 54.5% for GA, 72.7% for I FN-B-1b, to 78% for IFN-B-1a (p<0.05). Disability scores after 2 years increased in IFN-B-1a im, 0.1 point increased prior to 1st year of the therapy as well as continued decline prior to pre-therapy in IFN-B-1a sc, whereas no changes have been observed in IFN-B-1b and GA. Within 2-year treatment period no significant increase in the number of magnetic resonance (MR) T2 lesions was determined. No significant difference was found during therapy in terms of evoked potentials.

Conclusion: Our results revealed that high-dose, more-frequent regimens are more effective in terms of reducing the relapse rate whereas there's no difference in terms of efficacy on radiological and electrophysiological findings between groups. Additional prospective studies comparing the efficacy of IMTs on MS are needed.

Keywords: Multiple sclerosis, interferon beta, glatiramer acetate, relapse rate

ÖZET

Amaç: İmmunmodulatuvar tedavilerin (İMT) multipl sklerozda (MS) atak oranını azaltarak ve özürlülüğün ilerlemesini göreceli olarak geciktirerek hastalığın seyrini değiştirebileceği gösterilmekle birlikte; klinik, radyolojik ve elektrofizyolojik değişiklikler açısından başabaş karşılaştıran bir çalışma bulunmamaktadır. Çalışmamızda interferon-beta (IFN-B) 1b, IFN-B-1a subkutan (sc), IFN-B-1a intramuskuler (im) ve glatiramer asetat (GA) tedavilerinin klinik, elektrofizyolojik ve radyolojik bulgular üzerine etkilerini araştırmayı amaçladık.

Yöntem: İMT başlangıcından sonra en az 2 yıl takibi olan, tedavi öncesi ve sonrası klinik, elektrofizyolojik ve radyolojik bulguları dosyalarında mevcut olan 85 MS hastası retrospektif olarak değerlendirilmiştir. İMT'lerin bu bulgular üzerine etkileri karşılaştırılmıştır.

Bulgular: Yıllık atak oranı IFN-B-1a sc'de 0,1; IFN-B-1b'de 0,2; GA'da 0,3, IFN-B-1a im'de 0,5 olarak gözlenmiştir (p=0,01). Tedavinin 1. yılında ataksız hasta oranı IFN-B-1b'de %86,4, IFN-B-1a sc'de %82,9, IFN-B-1a im ve GA'da %54,5; ikinci yılda ise IFN-B-1a sc'de %78, IFN-B-1b'de %72,7, GA'da %54,5 ve IFN-B-1a im'de %27,3 olarak tespit edilmistir (p<0,05). Özürlülük skorları 2. yılda IFN-B-1a im'de artış göstermiş, IFN-B-1a sc'de tedavi öncesine göre azalma devam etmiş olmakla birlikte ilk yıla göre 0,1 puanlık artış gözlenmiştir. IFN-B-1b ve GA'da bir değişiklik gözlenmemiştir. İki yıllık tedavi süresinde manyetik rezonans (MR) T2 lezyon sayılarında anlamlı bir artış tespit edilmemiştir. Tedavi öncesine göre tedavinin 1. ve 2. yılında tüm ilaç gruplarında uyarılmış yanıtlarda bozukluk açısından farklılık bulunmamıştır.

Sonuç: Çalışmamızın sonuçları yüksek doz ve sık uygulamanın atak sıklığını azaltmada daha etkili olduğunu ortaya koymakla birlikte, radyolojik ve elektrofizyolojik etkinlikleri arasında belirgin bir fark bulunmamaktadır. İmmunmodulatuvar tedavilerin MS'teki etkinliğini karşılaştıran ek prospektif çalışmalara ihtiyaç vardır.

Anahtar kelimeler: Multipl skleroz, interferon beta, glatiramer asetat, atak oranı

INTRODUCTION

Multiple sclerosis (MS) is an autoimmune inflammatory demyelinating disease of central nervous system (CNS) usually presenting with episodes of relapses and remissions, and sometimes progression of the disease which may be triggered by environmental factors on the genetic background (1). Magnetic resonance imaging (MRI) provides significant data in MS regarding diagnosis, demonstration of the clinic-lesions relationship, activation and treatment follow-up (2). Examinations of evoked potentials (EPs) are simple and non-invasive methods that are important in confirming clinical signs and symptoms as well as revealing silent lesions and the multisystem involvement. Particularly, visual evoked potentials (VEPs), brainstem auditory evoked potentials (BAEPs) and somatosensory evoked potentials (SEPs) are used to define

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lesions in CNS afferent pathways electrophysiologically, and they reveal the multifocal involvement characteristics of the disease.

Since episodes may recover on their own and progression varies among patients or even in the same patient over time, it is difficult to decide whether treatment in MS is effective in the short run. Treatment interventions vary depending on the disease type and clinical period. In all randomized, placebo-controlled studies, Interferon Beta (IFN-B) and Glatiramer acetate (GA) have been shown to reduce the frequency of episodes and MRI activity in relapsing-remitting multiple sclerosis (RRMS). These treatments should be given to patients diagnosed with RRMS with Expanded Disability Status Scale (EDSS) <5.5, who had two or more episodes lasting longer than 24 hours, with new symptoms/deterioration of previous symptoms with no fever. Debates as to which agent should be selected for which patient, time to start treatment, duration of treatment, and roles of side effects in efficacy, are ongoing. We aimed to compare these agents in clinical, radiological, electrophysiological, and to determine whether these agents showed any differences in efficacy, and side effects.

METHODS

Study Population

We chose a cohort of 85 patients older than 18 years of age who applied to MS outpatient clinic of Gülhane Military Medical Academy between April 2006 and April 2009, and were being followed up with "Clinically Definite MS" diagnosis according to Poser and McDonald criteria. These patients had relapsing-remitting type, and were receiving immunomodulatory therapy (IMT) for at least 2 years, and they were followed up regularly for at least 2 years by clinical, radiological, and electrophysiological evaluation.

Study Design

In the present retrospective study, effects of 4 IMT agents (namely IFN-B-1a intramuscular (im), IFN-B-1a subcutaneous (sc) 44 mcg, IFN-B-1b, and GA) used in RRMS were investigated in terms of annual relapse rates, mean relapse numbers before, after one and two years of the therapy, the percentage of relapse-free patients after therapy, MRI activity, electrophysiological tests, and disability. Additionally side effects and patient compliance to treatment were also investigated. Clinical signs and disease activity with patient compliance were considered in drug selection.

Clinical follow up was performed monthly within the first 3 months of drug initiation, and then it was performed once in every 6 months. Neurological examination, routine biochemistry tests were also performed. EDSS scores and side effects of these drugs were also recorded. The relapse was defined as emergence of a non-existent finding or deterioration of a previous finding lasting longer than 24 hours, and absence of a disorder such as infection, fever, and metabolic disorder that might be the cause. For relapses developed during treatment periods, the relapses with examination findings determined at our center and the relapses which had been filed at other centers' records, were taken into consideration.

Electrophysiologically, VEP, median nerve SEP (MSEP), tibial nerve SEP (TSEP), and BAEP values before treatment, at the first and second years of treatment were evaluated, and normal values of our neurophysiology laboratory were used. In examination of EPs, pathological values were accepted as elongations of P100 latency more than 120 msec for VEP or intraocular latency difference more than 10 msec; N20 latency longer than 21 msec for MSEP; P40 latency longer than 42 msec for TSEP; and I-III and III-IV wave interpeak latencies longer than 2 msec for BAEP.

Radiologically, the number of T2 sequence lesions in MRI were evaluated when treatment was started, in the first and second years of treatment.

Local ethics committee approval was obtained for the present study.

Statistical Analysis

Non-parametric tests were used for comparisons. Dual comparisons were performed for multiple group comparisons. Chi square test was used for percentage comparisons of groups.

Table 1. Mean total relapse numbers before treatment

Drug	N	Mean	Std. Deviation	Median	Minimum	Maximum	p*
Before treatment							
IFN-B-1a im	11	2.7	0.6	3	2	4	0.282
IFN-B-1a sc	41	3.1	1.0	3	2	6	
IFN-B-1b	22	2.9	1.4	2	2	7	
GA	11	2.7	1.0	2	2	5	
All groups	85	3.0	1.1	3	2	7	

*Kruskal-Wallis test

Table 2. Dual comparison of the number of relapses in the first and second years of treatment

Dual comparison	p*	Dual comparison	p*
First year of treatment			
IFN-B-1a im vs. IFN-B-1a sc	0.049	IFN-B-1a sc vs. IFN-B-1b	0.724
IFN-B-1a im vs. IFN-B-1b	0.048	IFN-B-1a sc vs. GA	0.039
IFN-B-1a im vs. GA	0.852	IFN-B-1b vs. GA	0.041
Second year of treatment			
IFN-B-1a im vs. IFN-B-1a sc	0.002	IFN-B-1a sc vs. IFN-B-1b	0.600
IFN-B-1a im vs. IFN-B-1b	0.027	IFN-B-1a sc vs. GA	0.100
IFN-B-1a im vs. GA	0.390	IFN-B-1b vs. GA	0.291

*Mann-Whitney U test (Level of significance=0.0083)

RESULTS

Of 85 participants included in the study, 60 were females, and 25 were males with an age range between 21 and 58 years of age (mean=36.1±8.3 years). Of the patients, 12.9% were receiving IFN-B-1a im, 48.2% were receiving IFN-B-1a sc, 25.9% were receiving IFN-B-1b, and 12.9% were receiving GA. No difference was identified between groups (IFN-B-1a im, IFN-B-1a sc 44 mcg, IFN-B-1b, GA) in terms of age at recruiting to the study, age at onset of the disease, and gender. The disease duration was determined as 8-10 years, which was not also different between groups.

Efficacy on Relapses

There was no significant difference in mean total relapse numbers before treatment between groups, but it was determined that total relapse numbers in IFN-B-1a sc and IFN-B-1b groups before treatment were higher when compared with those in IFN-B-1a im and GA groups (Table 1).

The mean number of relapses in the first year for IFN-B-1a im was 0.5; 0.2 for IFN-B-1a sc; 0.1 for IFN-B-1b; and 0.5 for GA. Therefore, it was determined that relapse numbers were the least in the first year in IFN-B-1b group. In the second year of treatment, the mean relapse numbers were 0.9 for IFN-B-1a im; 0.3 for IFN-B-1a sc; 0.4 for IFN-B-1b; and 0.6 for GA (p=0.01). It was observed in dual comparisons that the difference in the second year was due to the difference between IFN-B-1a sc and IFN-B-1a im (Table 2, Figure1).

When annual relapse rates during 2 years were evaluated, it was found that annual relapse rates were 0.1 in IFN-B-1a sc group, 0.2 in IFN-B-1b group, 0.3 in GA group, and 0.5 in IFN-B-1a im group (p=0.017) (Table 3, Figure 2). It was observed that this difference was due to comparison of IFN-B-1a sc and IFN-B-1a im (p=0.002); but no difference was identified among the others.

In the first year, the percentage of relapse-free patients was 86.4% in IFN-B-1b group, 82.9% in IFN-B-1a sc group, 54.5% in both IFN-B-1a im and GA groups (p=0.044). When the percentage of relapse-free patients in the second year was examined, the rates were determined as 78% in IFN-B-1a sc group, 72.7% in IFN-B-1b group, 54.5% in GA group, and 27.3% in IFN-B-1a im group (p=0.011) (Figure 3). When the percentage of relapse-free patients between groups were compared according to years, 3 out of 6 patients who had no relapse in the first year were remained without any relapses in the second year in IFN-B-1a im group. In GA group, 6 patients who had no relapse in the first year, remained without any relapses in the second year. While 16 out of 19 patients had no relapse in the second year in IFN-B-1b group, 32 out of 34 patients remained without any relapses in IFN-B-1a sc group. No significant difference was determined in these comparisons (Mc Nemar test).

Efficacy on Disability, Side effects and Drug Compliance

The mean EDSS scores before treatment were determined as 0.5 in IFN-B-1a im group, 0.9 in IFN-B-1a sc group, 0.8 in IFN-B-1b group, and 0.7 in GA group; so mean EDSS scores in all groups were determined <1. The mean EDSS scores in the first year were determined as 0.6 in IFN-B-1a im group, 0.8 in IFN-B-1b group, and 0.7 in both IFN-B-1a sc and GA groups. According to this, while there was a 0.1 increase in IFN-B-1a im group in the first year of treatment, no change was observed in both IFN-B-1b and GA groups, but mean EDSS decrease of 0.2 was determined in IFN-B-1a sc group. In the second year of treatment, disability scores continued to increase in IFN-B-1a im group, and the mean EDSS scores were determined as 0.9 at the end of the second year. Although a decrease was determined in IFN-B-1a sc group when compared with the time before treatment, an increase of 0.1 point was determined when compared with the first year. No changes were observed in the mean EDSS scores in IFN-B-1b and GA groups. Disability scores were unchanged in the first two years in IFN-B-1b and GA groups, a decrease of 0.1 point when compared with the time before the treatment was determined in IFN-B-1a sc group at the end of the second year, whereas 0.4-point increase was determined in IFN-B-1a im group. While there was no significant difference was determined in the mean EDSS scores in IFN-B-1a sc, IFN-B-1b and GA groups, significant increase was determined in IFN-B-1a im group (p=0.022) (Table 4, Figure 4).

When drug groups were evaluated in means of EDSS score deterioration 1 point, improvement or remaining unchanged in the second treatment year when compared with before treatment, EDSS values remained unchanged in 6 patients (54.5%) in IFN-B-1a im group; in 23 patients (56.1%) in IFN-B-1a sc group; in 19 patients (86.4%) in IFN-B-1b group; and in 9 patients (81.8%) in GA group, and it was observed that there was no

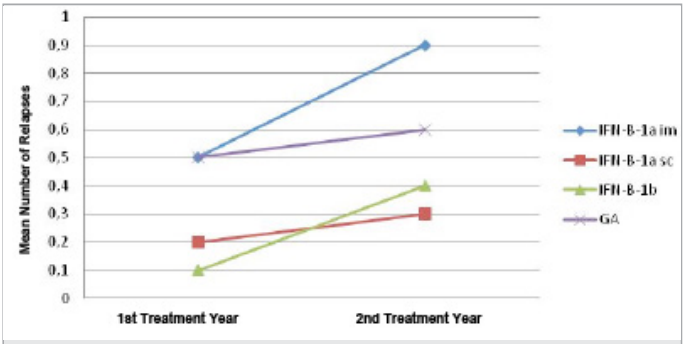

Figure 1. Mean number of relapses in the first and second year in immunomodulatory drug groups

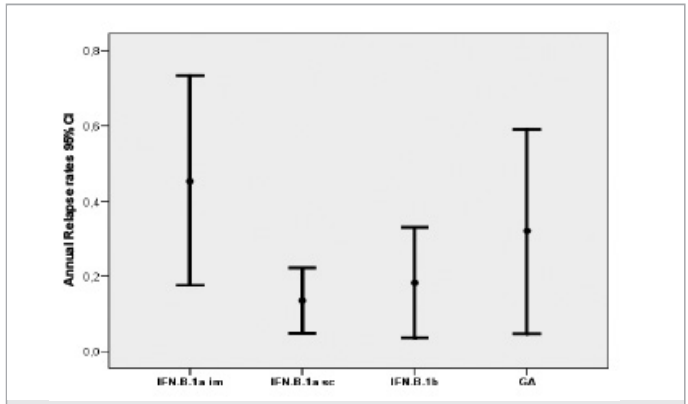

Figure 2. Annual relapse rates in the immunomodulatory treatment groups

Table 3. Dual Comparison of the mean annual relapses rates

Dual comparison	p*	Dual comparison	p*
IFN-B-1a im vs. IFN-B-1a sc	0.002	IFN-B-1a sc vs. IFN-B-1b	0.600
IFN-B-1a im vs. IFN-B-1b	0.027	IFN-B-1a sc vs. GA	0.100
IFN-B-1a im vs. GA	0.390	IFN-B-1b vs. GA	0.291
*Mann-Whitney U test (Level of significance=0.0083)			

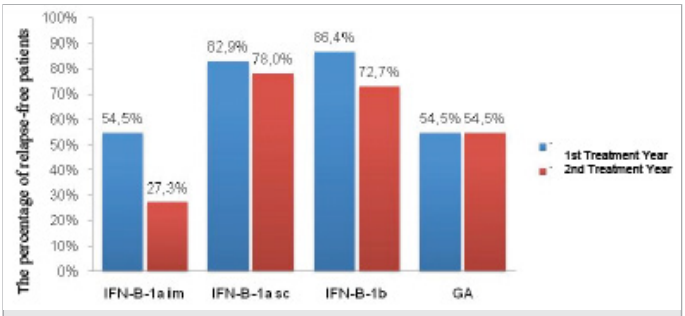

Figure 3. The percentage of relapse-free patients in the immunomodulatory treatment groups

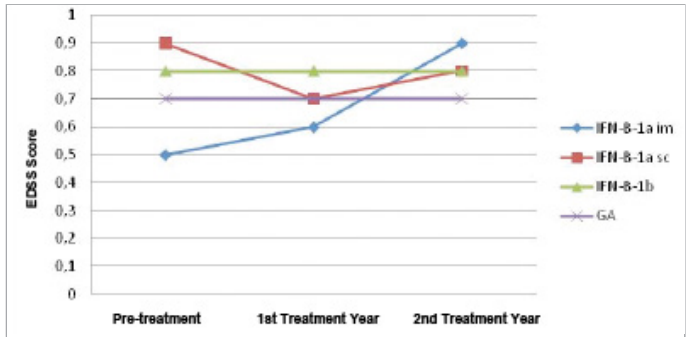

Figure 4. Mean EDSS Scores of Immunomodulatory Treatment Groups

Table 4. Mean EDSS scores before treatment, years 1 and 2 of treatment

Drug	N	Mean	Std. Deviation	Median	Minimum	Maximum	p*
Before treatment							
IIFN-B-1a im	11	0.5	0.7	0	0	2	0.384
IFN-B-1a sc	41	0.9	0.7	1	0	3	
IFN-B-1b	22	0.8	1.1	0.5	0	4	
GA	11	0.7	0.8	1	0	2	
All Groups	85	0.8	0.8	1	0	4	
Year 1 of treatment							
IFN-B-1a im	11	0.6	0.9	0	0	3	0.971
IFN-B-1a sc	41	0.7	0.8	1	0	3	
IFN-B-1b	22	0.8	1.1	0.5	0	4	
GA	11	0.7	0.9	0	0	2.5	
All Groups	85	0.7	0.9	0	0	4	
Year 2 of treatment							
IFN-B-1a im	11	0.9	0.9	1	0	3	0.935
IFN-B-1a sc	41	0.8	0.9	0	0	3	
IFN-B-1b	22	0.8	1.1	0.5	0	4	
GA	11	0.7	0.9	0	0	2.5	
All Groups	85	0.8	0.9	1	0	4	

*Kruskal-Wallis test

Table 5. Changes in EDSS

Before treatment – year 2 of treatment							
			Deterioration (+)	**No change**	**Improvement (+)**		
Drug	IFN-B-1a im	Number	5	6	0	11	0.021
		Percentage	45.5	54.5	0,0	100.0	
	IFN-B-1a sc	Number	7	23	11	41	
		Percentage	17.1	56.1	26.8	100.0	
	IFN-B-1b	Number	1	19	2	22	
		Percentage	4.5	86.4	9.1	100.0	
	GA	Number	1	9	1	11	
		Percentage	9.1	81.8	9.1	100.0	
Entire Group		Number	14	57	14	85	
		Percentage	16.5	67.1	16.5	100.0	

Chi square test (Monte-Carlo method was utilized)

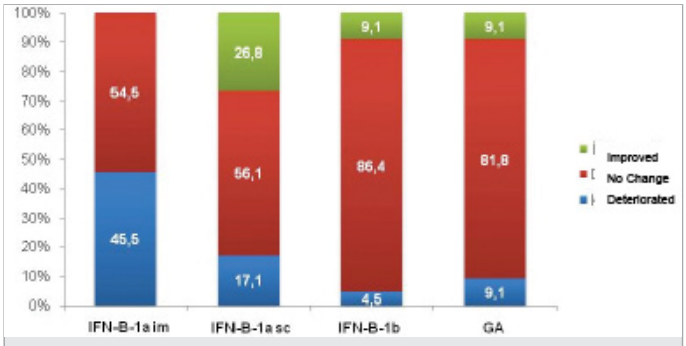

Figure 5. Comparisons of EDSS scores for 1 point of deterioration, improvement or no change in Year 2 of Treatment against before treatment

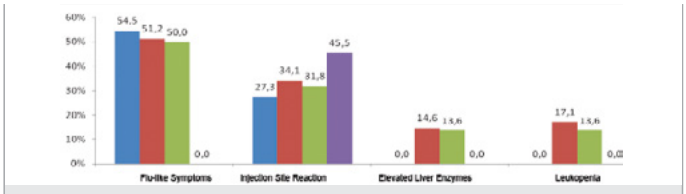

Figure 6. Side Effects of Immunomodulatory Treatments

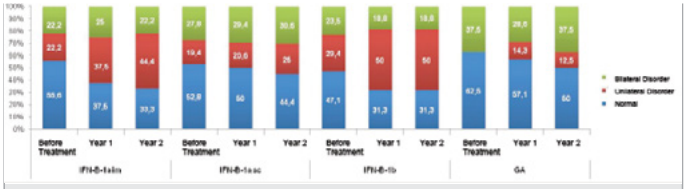

Figure 7. Effects of Immunomodulatory Treatments on VEP

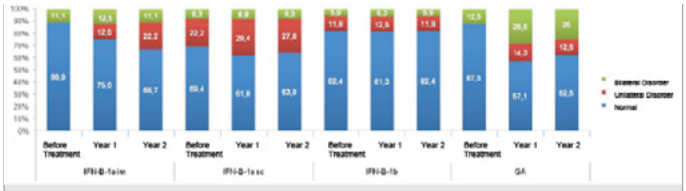

Figure 8. Effects of Immunomodulatory Treatments on MSEP

change in disability in the majority of cases in IFN-B-1b and GA groups. At the end of the second year, 1 point of deterioration in disability scores were determined in 5 patients (45.5%) in IFN-B-1a im group, in 7 patients (17.1%) in IFN-B-1a sc group, 1 patient (4.5% and 9.1%, respectively) in each group of IFN-B-1b and GA. According to this, ratio of patients whose disability scores were deteriorated was lower in IFN-B-1b and GA groups, whereas ratio of patients without any change was determined higher. Mild decrease in disability scores were identified in 11 patients in IFN-B-1a sc group at the end of the second year (Table 5, Figure 5).

When side effects were evaluated, flu-like symptoms were observed approximately in half of all patients receiving interferon, but in none of patients in GA group (p=0.009). There were no difference among the groups in injection site reaction, elevation of hepatic enzymes, and leucopenia (Figure 6). No patient discontinued the drug due to side effects so tolerability was high in general.

Effects on Evoked Potentials

No significant difference was determined between four drugs between pre-treatment and second-year VEP abnormalities (Figure 7). VEP abnormality was determined more frequently when compared to other evoked response abnormalities, and it was observed that visual pathways were similarly affected during treatment in each group, and deterioration continued.

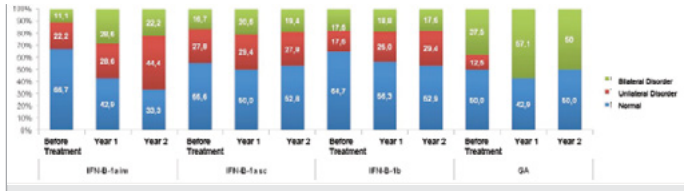

Figure 9. Effects of Immunomodulatory Treatments on TSEP

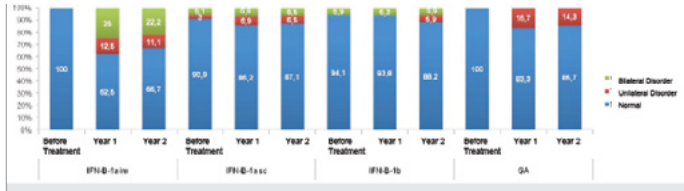

Figure 10. Effects of Immunomodulatory Treatments on BAEP

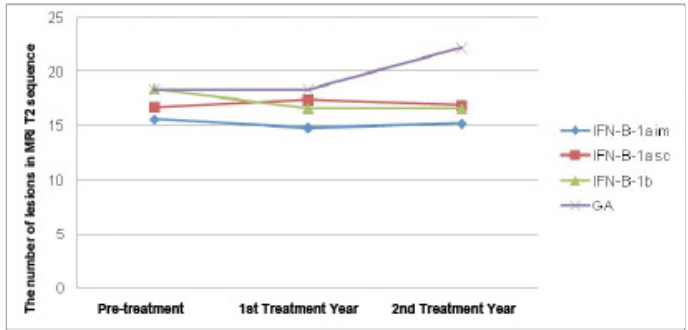

Figure 11. Effects of Immunomodulatory Treatments on MRI Findings

When four groups were compared for MSEP abnormality, no significant difference was determined during two-year follow up (Figure 8).

When immunomodulatory drugs were evaluated for TSEP abnormality, no significant difference was determined during two-year follow up (Figure 9). Depending on these findings, sensorial pathways during treatment period were similarly and progressively affected.

When immunomodulatory drugs were evaluated for BAEP abnormality, no significant difference was determined (Figure 10). Although BAEP abnormality was determined in fewer patients than the other evoked responses, it was observed that hearing pathways at the brainstem were similarly affected during treatment, and the disorder continued to progress. When patient records were reviewed, it was observed that the cases followed up for BAEP were majorly patients with brain stem involvements.

Effects on MRI Findings

The number of T2 lesions before, in the first and second year of treatment were 15.6, 14.8 and 15.2 in IFN-B-1a im group; 16.7, 17.4 and 16.9 in IFN-B-1a sc group; 18.4, 16.6 and 16.6 in IFN-B-1b group; and 18.3, 18.3 and 22.2 in GA group respectively. There was no difference between groups before treatment and in the first year of treatment. At the end of the second year, it was observed that the number of T2 lesions was similar in IFN-B-1a im and IFN-B-1a sc groups, whereas it was decreased in IFN-B-1b group and increased in GA group. However none were statistically significant. Effects of each drug were similar on the number of T2 lesions, and no significant difference was observed within two years (Figure 11).

DISCUSSION

The aim of the treatment in multiple sclerosis is to suppress disease activity, to decrease the number of relapses to the minimum, and prevent or delay the progression which is the disease's natural course. It is known that

widely used immunomodulatory drugs provide their clinical and radiological efficacies with the effects on immune system, but the differences between their efficacies cause controversy (3). In the literature, there is no prospective head-to-head study comparing these four immunomodulatory drugs in terms of relapse frequency, the percentage of relapse-free patients, MRI lesion load, and electrophysiological changes.

In the present study, there was no statistically significant differences in total relapse numbers, electrophysiological and radiological findings before treatment between the groups. Since treatment durations were different in each group, data in the first and second years of treatment, which were recorded objectively, were taken into consideration instead of long-term effects of drugs. As it was known that inefficacy due to neutralizing antibodies were developed after the second year of treatment, we assumed that there was no neutralizing antibody effects of drugs in our study.

As to the number of relapses after treatment, it was identified that IFN-B-1a sc, IFN-B-1b and GA groups had lower numbers than IFN-B-1a im group. The results indicated that this efficacy was more prominent in the second year of treatment and it continued. As no difference between numbers of relapses in the first and second years of treatment for all drugs, we interpreted this as all drugs continued their first year efficacies in the second year.

In randomized, placebo controlled studies in which immunomodulatory drugs were approved, the decrease in the number of relapses were determined as 18% for IFN-B-1a im, 34% for IFN-B-1b, 32% for IFN-B-1a sc, and 29% for GA groups (4,5,6,7). It was observed that high dose and frequently administered interferons had similar effects with GA, and they were relatively more effective than IFN-B-1a im. In studies of IFN-B-1b and IFN-B-1a sc approval for RRMS, drugs were compared with high and low doses in addition to placebo which was different from IFN-B-1a im studies, and more favorable results were revealed for high doses in numbers of relapses (5,6).

In EVIDENCE trial, relapse rates in 24th week were determined as 0.29 for IFN-B-1a sc group; 0.40 for IFN-B-1a im group, and the difference of 27% which was in favor of IFN-B-1a sc group was determined significant (p=0.022). In Week 48, a difference of 16% was determined in favor of IFN-B-1a sc (p=0.093) (8).

Khan et al. (9) reported that IFN-B-1b and GA were superior in terms of efficacy on the number of relapses than IFN-B-1a im. In our study, we determined the efficacy of GA relatively low. Indeed, there are publications in the literature showing that GA efficacy has been observed later than the others (7,10). On the other hand, Khan et al. (9) showed that efficacy of IFN-B-1b appeared immediately and it continued. Opposite to this hypothesis, Haas and Firzlaff (11) proposed that GA effects on decreasing relapse rates started at the sixth month, and its clinical efficacy was not delayed. The difference between our study and this study regarding the effects of GA on relapse rates may result from our cohort, absence of criteria for patient and drug selection, and absence of randomization between the groups in our study. However, as Haas and Firzlaff (11) did not include 44-mcg dose of IFN-B-1a sc in the comparisons, it is not possible to directly compare these two studies.

Consequently, our results regarding the number of relapses were similar to the pivotal studies of immunomodulatory drugs. We determined that the mean number of relapses in the first and second years of treatment was lessby high dose, frequent dose administration. This result was supporting data indicating that high dose and frequent administration of drug were more effective for decreasing the number of relapses (8,12). As we did not have a placebo group, we could not determine decrease rate in relapse number. However, when we consider pre-treatment total relapse numbers, it is clearly observed that the number of relapses was decreased. Furthermore, our study affirms the fact that immunomodulatory agents are beneficial in decreasing the number of relapses in RRMS patients. However, as we did not include the data from patients who did not receive this treatment, we are not able to the state the amount of this benefit exactly.

In the present study, annual relapse rates in two-year treatment period were 0.1 in IFN-B-1a sc group; 0.2 in IFN-B-1b group; 0.3 in GA group; and 0.5 in IFN-B-1a im group. Annual relapse rates of IFN-B-1a sc group were found significantly lower than the IFN-B-1a im group. This result indicated that high dose and frequent administration were more favorable for decreasing the annual relapse rate in the first and second years of the treatment. In the approval study of IFN-B-1b for RRMS, significant difference for the efficacy was identified in favor of high dose group (5). In the five-year data of the same study, it was also indicated that high dose administration was more effective (13). In the 4-year data of the approval study of IFN-B-1a sc for RRMS, it was shown that 44 mcg group was superior to 22 mcg group (p=0.046) (14). In INCOMIN trial comparing IFN-B-1b and IFN-B-1a im, favorable outcomes were obtained in annual relapse rates for high dose administration (12).

In a double-blind, placebo-controlled randomized clinical trial of IFN-B-1a in RRMS patients who received intramuscular injections once a week, annual relapse rate in treatment group was significantly lower than the placebo group (4). Annual relapse rates of GA in RRMS were determined lower when compared with the plasebo group (7,10).

There are few studies in the literature comparing the effects of immunomodulatory drugs on annual relapse rates. Carra's et al. (15) study has the similarities with our study in terms of significant decreases in annual relapse rates in all four drug groups, and absence of this effect in IFN-B-1a im group. As for QUASIMS study, no significant difference was determined in annual relapse numbers between the groups (16).

Consequently, annual relapse rates were found lower in high dose and frequent administration groups in our study which are similar to the results of approval studies of IFN-B-1b and IFN-B-1a sc in RRMS, and results of INCOMIN study. However, annual relapse rates in all drug groups in our study were lower than those in the pivotal studies. This might be related with the absence of randomization in our study, and inclusion of the patients who were relatively at early stages of the disease.

When we evaluated the effects of treatments on the percentage of relapse-free patients, it was determined that the percentage of relapse-free patients was higher in the first year, and this was decreased slightly in the second year, but the efficacies of all drugs still continued. When the percentage of relapse-free patients were examined according to first and second year of the treatment, it is noticeable that 3 out of 6 patients who had no relapse in the first year under IFN-B-1a im treatment experienced relapses in the second year whereas 6 patients who had no relapse in the first year under GA treatment, experienced no relapses in the second year. This condition suggests the different action mechanism of GA, and its probable neuroprotective effect.

On the other hand, it was observed that the percentage of relapse-free patients was similarly high in IFN-B-1b and IFN-B-1a sc groups. After 2-year treatment, approximately ¾ of patients receiving IFN-B-1b and IFN-B-1a sc and ¼ of IFN-B-1a im receivers remained without any relapses. The results are consistent with the pivotal study of IFN-B-1a sc for RRMS, EVIDENCE, and INCOMIN studies. (6,8,12). In terms of the percentage of relapse-free patients, our results were not similar to the retrospective results reported by Haas and Firzlaff (11), Carra et al. (15), and Khan et al. (9) This might be related to the selected patient population and study design.

A meta-analysis which reviewed randomized controlled studies reported highly evidences that IFN-B-1a sc was superior than other treatments when compared to placebo in preventing clinical relapses within 24 month period. This meta-analysis presents moderate level of evidence for IFN-B-1b. It was concluded that IFN-B-1a im had unfavorable benefit/risk ratio for RRMS. Results of this meta-analysis presenting powerful evidences including 23 randomized controlled study and 9096 RRMS patients in total indicated in the favor of high dose frequent interferon use to prevent relapses. It was also emphasized that clinical effects of these treatments were not clear after 2 years (21). Our efficacy results on relapses showed similarity with the results of this meta-analysis.

According to our results, patient rates with deteriorating disability scores in IFN-B-1b and GA groups were lower than the patient without any change in their disability scores. In IFN-B-1a sc group, a mild decrease was detected in disability scores of 11 patients at the end of the second year. Khan et al. showed significant decrease in EDSS values of patients treated by IFN-B-1b and GA (9). In our data, majority of patients without EDSS increase were in IFN-B-1b and GA groups, and this was consistent with aforesaid study.

It was shown in studies that immunomodulatory drugs partially slowed the progression of the disease by decreasing the number of the relapses (4,5,6,7). In our cohort, no difference was determined in mean EDSS scores between the first and second years of treatment among four drugs. It is known that immunomodulatory drugs have effects on relapse frequency rather than the disability.

Although immunomodulatory drugs are well tolerated, and they have good safety profiles, some side effects including injection site reaction, flu-like symptoms, leukopenia, and abnormal liver function tests might be observed during the treatment. The most commonly encountered side effects are flu-like symptoms and injection site reaction. In our study, flu-like symptoms were noted in approximately half of patients on treatment while it was reported in none in GA group. These findings were consistent with the results of EVIDENCE and INCOMIN studies (8,12). We found no statistically significant difference in terms of injection site reaction between drugs. When we evaluated flu-like symptoms and injection site reaction , it was observed that none of patients discontinued the treatment due to side effects. Although these side effects sometimes lasted longer than expected, the intensity was generally mild.

Abnormal liver function tests and leukopenia side effects in our study were observed only in high dose IFN-B-1b and IFN-B-1a sc groups, and they were consistent with the literature. This might be explained by using these treatments at high doses, and frequent administrations, as well as their high immunological effects.

Evoked potential studies are used in diagnosis in multiple sclerosis, and they are useful to show electrophysiological transmission defects of CNS with/without clinical symptoms and signs. In different series, EP disorders were reported as 25-38% (26). VEP shows abnormalities at higher rates especially in EP examinations (27). In our study, VEP abnormality was the most commonly encountered defect. EPs have been used to investigate natural progression of diseases, and efficacies of treatment methods (28,29,30,31,32,33). While some studies reported weak or no correlation between clinical and EP changes, some studies reported moderate correlations (28,29,30,33).

Studies investigating effects of treatment on EP are limited in number, and in general, EP changes were secondary endpoints. The reason of having limited number of EP study may be explained as common use of MRI in diagnosing MS has caused less importance of EP in the practice. In a study performed in the period before widely usage of immunomodulatory drugs, it was proposed that azathioprine caused changes in VEP and SEP one year before any clinical changes in chronic progressive MS. In another study where methylprednisolone effects were investigated, a relationship between the changes in disability and EP scores was suggested (32,34).

There is no head-to-head study comparing effects of immunomodulatory drugs on EP. In a study in which MSEP, TSEP, and VEP values of 10 patients who received IFN-B-1a 22 mcg treatment were evaluated before treatment, and months 2, 4, 6, and 9 of treatment, no significant difference was found (35). In a randomized, prospective study, no significant VEP changes were observed by administration of IFN-B-1a for 12 months (36). In a study where effects of IFN-B-1b treatment were investigated on VEP changes, improvement after treatment was determined in 5 out of 10 patients who had VEP latency delay before the treatment (37). As no significant deteriorations were observed in VEP changes in patients receiving IFN-B-1b, it was interpreted in the favor of the drug (38). However, it is impossible to draw strong evidences out of these studies about effects of IMTs on EPs.

In our study, VEP abnormality was the most common EP abnormality, and no significant difference was found between the impact of drugs on EPs. Since there is no head-to-head comparison study evaluating effects of IMT on EP in the literature, we are unable to compare our data regarding EPs.

Cranial and spinal MRI examinations have gained indispensable significance in diagnosing and differential diagnosing in MS especially in terms of showing the distributions and numbers of demyelinating lesions, possible axon loss and atrophy. Relationships between the number of lesions in imaging methods and clinical characteristics are debatable, and its prognostic significance has not been definitely defined. Axon loss and presence of atrophy, and presence of contrast enhanced active lesions have been defined as bad prognostic factors in many studies (39). Atrophy and neurodegeneration are conditions, which are encountered in advanced stages of the disease, and they are related to progression. It has been shown radiologically that long-term uses of IMTs may decrease atrophy (40,41,42). Early period data (the first 2 years) were included in our study, so atrophy was not evaluated.

In the present study, no marked increase in total numbers of T2 lesions was determined in four groups. This data indicates that each drug is radiologically effective correlating to the clinical progression and number of relapses. As active lesion development was not evaluated as a radiological parameter in our study, it is impossible to compare our results with approval studies of IFN-B-1b and IFN-B-1a sc in RRMS, which reported that high dose and frequent administration was more effective than low dose administration in active lesion development in MRI examination, and results of INCOMIN and EVIDENCE, which reported that more marked decrease was observed in high and frequent dose administration group when compared with low dose administration once in a week. Since there was no significant increase in number of T2 lesions in MRI examinations in all drug groups, outcomes of their effectiveness on MRI activities were consistent with the pivotal studies. It was also observed that efficacies of all drug groups on number of T2 lesions in MRI examination were not superior to each other.

Radiological effectivity of immunomodulatory drugs may contribute to delay in disease progression, and decrease in number of relapses. There are studies in the literature, which are showing that development of no new lesion may affect clinical progression relatively better (43). One of the causes of clinical improvement (decrease in number of relapses, absence of marked increase in disability) in our study may be due to this effect of immunomodulatory drugs.

Radiological effectivity is the most prominent limitation of our study as only the number of T2 lesions in MRI was evaluated. Further studies are

required to investigate possible effects of long-term immunomodulatory drug use on both, atrophy and neurodegeneration, and the effects of this neurodegeneration on clinical picture.

In conclusion, since treatment periods between patient groups vary, the present study evaluated the clinical, radiological and electrophysiological data for the initial 2-year term post-treatment in order to achieve an unbiased comparison.

Despite noticeable limitations in study design such as non-homogeneous groups resulting from the lack of randomization due to study's non-blinded and retrospective nature as well as the inability to perform MRI examinations of evoked potentials regularly in all patients during the first and second years of treatment, our results provide meaningful and valuable data for clinicians.

Predominantly, all IMTs were found to be effective upon reduced frequency of relapses in patients with RRMS. The results of this retrospective, non-randomized and non-blinded study are similar to the observations of more comprehensive, randomized and controlled studies. While the study results demonstrate that higher doses and frequent administration are more effective in reducing the frequency of relapses, there is no difference among the drugs in terms of the radiological and electrophysiological efficacies.

Although new agents keep being introduced in the treatment of MS, immunomodulatory drugs, which we have a better understanding and broader experience particularly as regards to their efficacy and long term adverse effects in clinical practice seem to be preserving their status in the treatment of MS also in the future.

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