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

Gençer GENÇ¹, Şeref DEMİRKAYA², Semai BEK³, Zeki ODABAŞI²

¹Department of Neurology, Gümüşsuyu Military Hospital, İstanbul, Turkey

²Department of Neurology, Gülhane Training and Research Hospital, Ankara, Turkey

³Department of Neurology, Başkent University Adana Practicing and Research Center, Adana, Turkey

ABSTRACT

Introduction: Although it has been shown that immunomodulatory therapies (IMTs) in multiple sclerosis (MS) can modify the course of the disease by reducing the relapse rate and delaying the progression 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: We studied a cohort of 85 MS patients who were followed up for at least 2 years and had complete charting, including pre-treatment and post-treatment clinical, radiological, and electrophysiological findings. We compared the 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, and 0.5 for IFN-B-1a im ($p=0.01$). The percentages of relapse-free patients after one year were 54.5% for IFN-B-1a im and GA,

82.9% for IFN-B-1a sc, and 86.4% for IFN-B-1b, and after two years the percentages were 27.3% for IFN-B-1a im, 54.5% for GA, 72.7% for IFN-B-1b, and 78% for IFN-B-1a sc ($p<0.05$). Disability scores after 2 years increased for IFN-B-1a im, decreased for IFN-B-1a sc (with a 0.1-point increase compared to the first year), and did not change for IFN-B-1b or GA compared to before treatment. Within the 2-year treatment period, no significant increase in the number of magnetic resonance T2 lesions was observed. No significant differences were found for any of the therapies in terms of evoked potentials.

Conclusion: Our results revealed that high dose and more frequent regimens were more effective in terms of reducing the relapse rate, whereas there were no differences 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

INTRODUCTION

Multiple sclerosis (MS) is an autoimmune inflammatory demyelinating disease of the central nervous system (CNS) usually presenting with episodes of relapses and remissions, and sometimes progression of the disease can be triggered by environmental factors and the genetic background (1). Magnetic resonance imaging (MRI) provides significant data in MS regarding diagnosis, demonstration of the clinical-lesion relationship, disease activity and treatment follow-up (2). Examination of evoked potentials (EPs) is a simple and non-invasive method that is important in confirming clinical signs and symptoms as well as revealing silent lesions and multisystem involvement. Visual evoked potentials (VEPs), brainstem auditory evoked potentials (BAEPs), and somatosensory evoked potentials (SEPs) are used to electrophysiologically define lesions in CNS afferent pathways, and they reveal the multifocal characteristics of the disease.

Because episodes might 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 an Expanded Disability Status Scale (EDSS) score <5.5 who have had two or more episodes lasting longer than 24 hours with new symptoms or deterioration of previous symptoms and no fever. Debates as to which agent should be selected for which patient, the time to start treatment, the duration of treatment, and the roles of side effects in efficacy are ongoing. We aimed to compare these agents in terms of clinical, radiological, and electrophysiological measurements and to determine whether these agents showed any differences in efficacy or side effects.

METHODS

Study Population

We chose a cohort of 85 patients older than 18 years of age who applied to the MS outpatient clinic of the Gülhane Military Medical Academy between April 2006 and April 2009 and who were being followed up with a "Clinically Definite MS" diagnosis according to the Poser and

Correspondence Address: Gençer Genç, Gümüşsuyu Asker Hastanesi, Nöroloji Bölümü, İstanbul, Türkiye
E-mail / E-posta: gencerg@gmail.com

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McDonald criteria. These patients had relapsing-remitting type and were receiving immunomodulatory therapy (IMT) for at least 2 years, and they had been followed up regularly for at least 2 years by clinical, radiological, and electrophysiological evaluation.

Study Design

In the present retrospective study, the effects of four IMT agents (IFN-B-1a intramuscular (im), IFN-B-1a subcutaneous (sc), IFN-B-1b, and GA) used in treating RRMS were investigated in terms of annual relapse rates, mean relapse numbers before and after 1 and 2 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 every 6 months. Neurological examinations and routine biochemistry tests were also performed. EDSS scores and side effects of these drugs were also recorded. Relapse was defined as the emergence of a non-existent finding or deterioration of a previous finding lasting longer than 24 hours and the absence of a disorder such as infection, fever, or metabolic disorder that might be the cause. For relapses developing during treatment periods, the relapses with examination findings determined at our center and the relapses that had been filed in other centers' records were taken into consideration.

Electrophysiologically, VEP, median nerve SEP (MSEP), tibial nerve SEP (TSEP), and BAEP values before treatment and after the first and second years of treatment were evaluated, and normal values from our neurophysiology laboratory were used for determining the abnormal EPs values

for the study. In the examination of EPs, pathological values were accepted as elongations of P100 latency of more than 120 msec for VEP or an intra-ocular latency difference of 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 upon MRI were evaluated when treatment was started and after the first and second years of treatment.

Local ethics committee approval was obtained for the present study. Since this was a retrospective study based on the screening of medical records, an informed consent could not be obtained.

Statistical Analysis

Non-parametric tests were used for comparisons. Pairwise comparisons were performed for multiple group comparisons. A chi-square test was used for percentage comparisons of groups.

RESULTS

Of 85 participants included in the study, 60 were females and 25 were males with an age range between 21 and 58 years (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 the groups in terms of age at recruitment to the study, age at onset of the disease, or gender. The mean disease duration was 8-10 years, and no differences in disease duration were seen between the different groups.

Efficacy on Relapses

There were no significant differences in mean total relapse numbers before treatment between groups, but it was determined that total relapse

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							
IFN-B-1a im: interferon-beta 1a intramuscular; IFN-B-1a sc: interferon-beta 1a subcutaneous; IFN-B-1b: interferon-beta 1b; GA: glatiramer acetate							

Table 2. Pairwise comparisons of the number of relapses in the first and second years of treatment

Pairwise comparison	p*	Pairwise 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)			
IFN-B-1a im: interferon-beta 1a intramuscular; IFN-B-1a sc: interferon-beta 1a subcutaneous; IFN-B-1b: interferon-beta 1b; GA: glatiramer acetate			

numbers in the IFN-B-1a sc and IFN-B-1b groups before treatment were higher when compared with those in the IFN-B-1a im and GA groups (Table 1).

The mean number of relapses in the first year was 0.5 for IFN-B-1a im, 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 the 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 pairwise 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, Figure 1).

When annual relapse rates over 2 years were evaluated, it was found that annual relapse rates were 0.1 for IFN-B-1a sc, 0.2 for IFN-B-1b, 0.3 for GA, and 0.5 for IFN-B-1a im ($p=0.017$) (Table 3, Figure 2). This difference was due to the comparison of IFN-B-1a sc to IFN-B-1a im ($p=0.002$), and no differences were seen between the other groups.

In the first year, the percentage of relapse-free patients was 86.4% for IFN-B-1b, 82.9% for IFN-B-1a sc, and 54.5% for both IFN-B-1a im and GA ($p=0.044$). In the second year, the percentage of relapse-free patients was 78% for IFN-B-1a sc, 72.7% for IFN-B-1b, 54.5% for GA, and 27.3% for IFN-B-1a im ($p=0.011$) (Figure 3). When the percentages of relapse-free patients between groups were compared according to years, 3 out of 6 patients in the IFN-B-1a im group who had no relapse in the first year remained without any relapses in the second year. In the GA group, all 6 patients who had no relapse in the first year remained without any relapses in the second year. In the IFN-B-1b group, 16 out of 19 patients had no relapse in the second year, and in the IFN-B-1a sc group 32 out of 34 patients remained without any relapses. No significant differences were seen in these comparisons (McNemar's test).

Efficacy on Disability, Side Effects, and Drug Compliance

The mean EDSS scores before treatment were 0.5 in the IFN-B-1a im group, 0.9 in the IFN-B-1a sc group, 0.8 in the IFN-B-1b group, and 0.7 in

the GA group. The mean EDSS scores after the first year of treatment were 0.6 in the IFN-B-1a im group, 0.8 in the IFN-B-1b group, and 0.7 in both the IFN-B-1a sc and GA groups. Thus there was a 0.1 increase in the IFN-B-1a im group in the first year of treatment, no change was observed in either the IFN-B-1b or GA groups, and there was a mean EDSS decrease of 0.2 in the IFN-B-1a sc group. In the second year of treatment, disability scores continued to increase in the IFN-B-1a im group, and the mean EDSS score was 0.9 at the end of the second year. Although a decrease was seen in the IFN-B-1a sc group when compared with the time before treatment, an increase of 0.1 points was seen when compared with the first year. No changes were observed in the mean EDSS scores in the IFN-B-1b or GA groups. Disability scores were unchanged in the first two years in the IFN-B-1b and GA groups, there was a decrease of 0.1 points in IFN-B-1a sc group at the end of the second year when compared with the time before the treatment, and there was a 0.4 point increase in the IFN-B-1a im group. There were no significant differences in the mean EDSS scores in the IFN-B-1a sc, IFN-B-1b, or GA groups, but there was a significant increase in the IFN-B-1a im group ($p=0.022$) (Table 4, Figure 4).

In terms of EDSS scores, the drug groups were compared in two ways: Mean EDSS scores and the presence of 1-point change in EDSS scores. Latter was classified as deterioration by 1 point, improvement, or remaining unchanged in the second year of therapy compared to before treatment, EDSS values remained unchanged in 6 patients (54.5%) in the IFN-B-1a im group, in 23 patients (56.1%) in the IFN-B-1a sc group, in 19 patients (86.4%) in the IFN-B-1b group, and in 9 patients (81.8%) in the GA group, and there was no change in disability in the majority of cases in the IFN-B-1b and GA groups. At the end of the second year, a 1-point deterioration in disability score was seen in 5 patients (45.5%) in the IFN-B-1a im group, in 7 patients (17.1%) in the IFN-B-1a sc group, and in 1 patient (4.5% and 9.1%, respectively) in both the IFN-B-1b and GA groups. The ratio of patients whose disability scores deteriorated was lower in the IFN-B-1b and GA groups, whereas the ratio of patients without any change was higher. Mild decreases in disability scores were identified in 11 patients in the IFN-B-1a sc group at the end of the second year (Table 5, Figure 5).

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

Figure 2. Annual relapse rates in the immunomodulatory treatment groups

Table 3. Pairwise comparisons of the mean annual relapse rates

Pairwise comparison	p*	Pairwise 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)

IFN-B-1a im: interferon-beta 1a intramuscular; IFN-B-1a sc: interferon-beta 1a subcutaneous; IFN-B-1b: interferon-beta 1b; GA: glatiramer acetate

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

Figure 4. Mean EDSS scores in the immunomodulatory treatment groups

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

Drug	N	Mean	Std. Deviation	Median	Minimum	Maximum	p*
Before treatment							
IFN-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	
Dependent comparison	p*	p**		p***		p****	
IFN-B-1a im	0.022	0.157		0.034		0.102	
IFN-B-1a sc	0.214						
IFN-B-1b	0.368						
GA	1.000						

*Kruskal-Wallis test

*Friedman test (Before treatment vs. Year 1 of treatment vs. Year 2 of treatment)

**Wilcoxon test (Before treatment vs. Year 1 of treatment), Level of significance=0.0167

***Wilcoxon test (Before treatment vs. Year 2 of treatment), Level of significance=0.0167

****Wilcoxon test (Year 1 of treatment vs. Year 2 of treatment), Level of significance=0.0167

EDSS: Expanded Disability Status Scale; IFN-B-1a im: interferon-beta 1a intramuscular; IFN-B-1a sc: interferon-beta 1a subcutaneous; IFN-B-1b: interferon-beta 1b; GA: glatiramer acetate

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

Effects on Evoked Potentials

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

Table 5. Changes in EDSS

Before treatment - year 2 of treatment						
Drug			Deterioration (+)	No change	Improvement (+)	
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	100.0
	Percentage	17.1	56.1	26.8	100.0	
IFN-B-1b	Number	1	19	2	22	100.0
	Percentage	4.5	86.4	9.1	100.0	
GA	Number	1	9	1	11	100.0
	Percentage	9.1	81.8	9.1	100.0	
Entire group	Number	14	57	14	85	100.0
	Percentage	16.5	67.1	16.5	100.0	

Chi-square test (Monte-Carlo method was utilized)

EDSS: Expanded Disability Status Scale; IFN-B-1a im: interferon-beta 1a intramuscular; IFN-B-1a sc: interferon-beta 1a subcutaneous; IFN-B-1b: interferon-beta 1b; GA: glatiramer acetate

Figure 5. Comparisons of EDSS scores for 1 point of deterioration, improvement, or no change in year 2 of treatment compared to before treatment **Figure 6.** Side effects of immunomodulatory treatments

When the four groups were compared for MSEP abnormality, no significant differences were seen at the 2-year follow-up (Figure 8).

When immunomodulatory drugs were evaluated for TSEP abnormality, no significant difference was determined during the 2-year follow-up (Figure 9). Based on these findings, sensorial pathways were similarly and progressively affected during the treatment period.

When immunomodulatory drugs were evaluated for BAEP abnormality, no significant differences were seen (Figure 10). Although BAEP abnormality was determined in fewer patients than the other evoked responses, it was observed that hearing pathways in the brainstem were similarly affected during treatment, and the disorder continued to progress. When patient records were reviewed, it was observed that

Figure 7. Effects of immunomodulatory treatments on VEP **Figure 8.** Effects of immunomodulatory treatments on MSEP **Figure 9.** Effects of immunomodulatory treatments on TSEP

the cases followed up for BAEP were mostly patients with brain stem involvements.

Effects on MRI Findings

The number of T2 lesions before, in the first year, and in the second year of treatment were 15.6, 14.8, and 15.2 in the IFN-B-1a im group; 16.7, 17.4, and 16.9 in the IFN-B-1a sc group; 18.4, 16.6, and 16.6 in the IFN-B-1b group; and 18.3, 18.3, and 22.2 in the GA group, respectively. There were no differences between groups before treatment or after the first year of treatment. At the end of the second year, the numbers of T2 lesions were similar in the IFN-B-1a im and IFN-B-1a sc groups, but they had decreased in the IFN-B-1b group and increased in the GA group. However, none of these changes were statistically significant. The effects of each drug were similar with regard to the number of T2 lesions, and no significant differences were observed in the 2 years of follow-up (Figure 11).

Figure 10. Effects of immunomodulatory treatments on BAEP

Figure 11. Effects of immunomodulatory treatments on MRI findings

DISCUSSION

The aim of the treatment in MS is to suppress disease activity, to decrease the number of relapses to the minimum, and to prevent or delay the progression of the disease's natural course. It is known that widely used immunomodulatory drugs impart their clinical and radiological effects via the immune system, but the differences between their efficacies have caused 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, or electrophysiological changes.

In the present study, there were no statistically significant differences in total relapse numbers or in electrophysiological or radiological findings before treatment between the groups. Because 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 the long-term effects of the drugs. Because it was known that inefficacy due to neutralizing antibodies had developed after the second year of treatment, we assumed that there were no neutralizing antibody effects of drugs in our study.

The IFN-B-1a sc, IFN-B-1b, and GA groups had lower numbers of relapses than the IFN-B-1a im group. Our data indicates that the efficacy of these drugs was more prominent and continued in the second year of treatment. Because no differences between the numbers of relapses in the first and second years of treatment were seen for any of the drugs, we interpreted this to mean that all drugs continued their first-year efficacies into the second year.

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

In the EVIDENCE trial, relapse rates in the 24th week were 0.29 for the IFN-B-1a sc group and 0.40 for the IFN-B-1a im group, and the 27% difference in favor of the IFN-B-1a sc group was statistically significant ($p=0.022$). In Week 48, a 16% difference was seen 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 to be relatively low. Indeed, there are publications in the literature showing that GA efficacy has been observed later than for other drugs (7,10). In contrast, Khan et al. showed that the efficacy of IFN-B-1b appeared immediately and it continued (9). Haas and Firzlaß proposed that the effects of GA on decreasing relapse rates starts at the sixth month and that its clinical efficacy is not delayed (11). The difference between our study and their study regarding the effects of GA on relapse rates might result from our cohort, the absence of criteria for patient and drug selection, and the absence of randomization between the groups in our study. However, because Haas and Firzlaß did not include a 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 reduced by high doses and more frequent dose administration. This result supports previous data indicating that high dose and frequent administration are more effective for decreasing the number of relapses (8,12). Because we did not have a placebo group, we could not determine the decrease rate in relapse number. However, when we consider the pre-treatment total relapse numbers, it is clear that the number of relapses decreased. Furthermore, our study affirms the fact that immunomodulatory agents are beneficial in decreasing the number of relapses in RRMS patients. However, because we did not include data from patients who did not receive this treatment, we are not able to state the amount of this benefit exactly.

In the present study, annual relapse rates in the 2-year treatment period were 0.1 in the IFN-B-1a sc group, 0.2 in the IFN-B-1b group, 0.3 in the GA group, and 0.5 in the IFN-B-1a im group. Annual relapse rates in the IFN-B-1a sc group were significantly lower than in the IFN-B-1a im group. This 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, a significant difference in efficacy was identified in favor of the high-dose group (5). In the 5-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, the 44 mcg group was superior to the 22 mcg group ($p=0.046$) (14). In the 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, the annual relapse rate in the treatment group was significantly lower than the placebo group (4). Annual relapse rates of GA in RRMS were found to be lower when compared with the placebo group (7,10).

There are few studies in the literature comparing the effects of immunomodulatory drugs on annual relapse rates. Carra et al. (15) study has similarities with our study in terms of significant decreases in annual relapse rates in all four drug groups and the absence of this effect in the IFN-B-1a

im group. In the QUASIMS study, no significant difference was determined in annual relapse numbers between the groups (16).

Consequently, annual relapse rates were found to be lower in the high dose and frequent administration groups in our study, and these results are similar to the results of approval studies of IFN-B-1b and IFN-B-1a sc in RRMS and the results of the 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 to the absence of randomization in our study and the inclusion of patients who were at relatively early stages of the disease.

When we evaluated the effects of treatments on the percentage of relapse-free patients, 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 continued into the second year. When the percentage of relapse-free patients was examined after the first and second year of treatment, 3 out of 6 patients who had no relapse in the first year of IFN-B-1a im treatment experienced relapses in the second year, whereas none of the 6 patients who had no relapse in the first year of GA treatment experienced any relapses in the second year. This suggests a different mechanism of action for GA and its probable neuroprotective effect.

On the other hand, it was observed that the percentage of relapse-free patients was similarly high in the IFN-B-1b and IFN-B-1a sc groups. After 2 years of treatment, approximately three fourths of the patients receiving IFN-B-1b and IFN-B-1a sc and one fourth of the patients receiving IFN-B-1a im remained without any relapses. These results are consistent with the pivotal study of IFN-B-1a sc for RRMS and the EVIDENCE and INCOMIN studies. (6,8,12). In terms of the percentage of relapse-free patients, our results were different from 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 the study design.

A meta-analysis of randomized controlled studies reported high levels of evidence that IFN-B-1a sc is superior to other treatments when compared to placebo in preventing clinical relapses within a 24 month period. The meta-analysis presented a moderate level of evidence for IFN-B-1b, and it was concluded that IFN-B-1a im had an unfavorable benefit/risk ratio for RRMS. Results of this meta-analysis presented powerful evidence, including 23 randomized controlled studies and 9096 RRMS patients in total, in favor of high dose and frequent interferon use to prevent relapses. It was also emphasized that the clinical effects of these treatments were not clear after 2 years (17). Our efficacy results on relapses showed similarity with the results of the meta-analysis.

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

Previous studies have shown that immunomodulatory drugs partially slow the progression of MS by decreasing the number of relapses (4-7). In our cohort, no difference was seen in mean EDSS scores between the first and second years of treatment among the 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 the patients on treatment, while they were reported in no patients in the GA group. These findings were consistent with the results of the EVIDENCE and INCOMIN studies (8,12). We found no statistically significant difference in terms of injection site reaction between the four drugs. When we evaluated flu-like symptoms and injection site reaction, it was found that none of the patients discontinued the treatment due to side effects. Although these side effects sometimes lasted longer than expected, their intensity was generally mild.

Abnormal liver function tests and leukopenia side effects in our study were observed only in the 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 in addition to their strong immunological effects.

Evoked potential studies are used in the diagnosis of MS, and they are useful to show electrophysiological transmission defects in the CNS either with or without clinical symptoms and signs. In a different series, EP disorders were reported to be 25-38% (18). VEP has also been shown to have abnormalities at higher rates, especially in EP examinations (19). In our study, VEP abnormality was the most commonly encountered defect. EPs have been used to investigate the natural progression of diseases and the efficacies of treatment methods (20,21,22,23,24,25). While some studies reported weak or no correlation between clinical and EP changes, some studies reported moderate correlations (20,21,22,25).

Studies investigating the effects of treatment on EP are limited in number, and in general EP changes were secondary endpoints. The reason for the limited number of EP studies might be explained by the common use of MRI in diagnosing MS that has led to reduced importance for EP in practice. In a study performed during the period before the wide usage of immunomodulatory drugs, it was proposed that azathioprine causes changes in VEP and SEP one year before any clinical changes in chronic progressive MS. In another study where the effects of methylprednisolone were investigated, a relationship between the changes in disability and EP scores was suggested (24,26).

There are no head-to-head studies comparing the effects of immunomodulatory drugs on EP. In a study in which the MSEP, TSEP, and VEP values of 10 patients who received 22 mcg IFN-B-1a treatment were evaluated before treatment and after 2, 4, 6, and 9 months of treatment, no significant differences were found (27). In a randomized, prospective study, no significant VEP changes were observed after administration of IFN-B-1a for 12 months (28). In a study where the effects of IFN-B-1b treatment were investigated in terms of VEP changes, there was an improvement after treatment in 5 out of 10 patients who had VEP latency delay before the treatment (29). Because no significant deteriorations were observed in the VEP changes in patients receiving IFN-B-1b, this was interpreted in favor of the drug (30). However, it is impossible to draw strong conclusions from these studies about the effects of IMTs on EPs.

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

Cranial and spinal MRI examinations are now indispensable 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 the prognostic significance of the number of lesions has not been definitely defined. Axon loss and the presence of atrophy, along with the presence of contrast-enhanced active lesions, have been defined as poor prognostic factors in many studies (31). Atrophy and neurodegeneration are conditions that are encountered in advanced stages of MS, and they are related to progression of the disease. It has been shown radiologically that long-term use of IMTs might decrease atrophy (32,33,34). Only 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 the total numbers of T2 lesions were seen for the four groups. This indicates that each drug is radiologically effective in correlation to the efficacy on clinical progression and the number of relapses. Because active lesion development was not evaluated as a radiological parameter in our study, it is impossible to compare our results with the 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, or to the results of INCOMIN and EVIDENCE, which reported that a more marked decrease was observed in the high and frequent dose administration group when compared with low dose administration once a week. Because there was no significant increase in the number of T2 lesions upon MRI examination in any of the drug groups, the outcomes of their effectiveness on MRI activities were consistent with the pivotal studies. It was also observed that the efficacies of all drug groups on the number of T2 lesions upon MRI examination were not superior to each other.

The radiological effectivity of immunomodulatory drugs might contribute to a delay in disease progression and a decrease in the number of relapses. There are studies in the literature showing that the development of no new lesion might be associated with relatively slower clinical progression (35). One of the causes of clinical improvement (a decrease in the number of relapses and an absence of marked increase in disability) in our study might be due to this effect of immunomodulatory drugs.

Radiological effectivity is the most prominent limitation of our study because only the number of T2 lesions upon MRI was evaluated. Further studies are required to investigate the possible effects of long-term immunomodulatory drug use on both atrophy and neurodegeneration and the effects of this neurodegeneration on the clinical picture.

Because treatment periods between patient groups vary, the present study evaluated the clinical, radiological, and electrophysiological data for the initial 2 years 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 the study's non-blinded and retrospective nature as well as the inability to regularly perform MRI examinations of evoked potentials in all patients during the first and second years of treatment, our results provide meaningful and valuable data for clinicians.

All four IMTs were found to be effective in reducing the 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 their radiological or electrophysiological efficacies.

Although new agents are being introduced for the treatment of MS, immunomodulatory drugs, which we have a better understanding of and broader experience with, particularly with regards to their efficacy and long-term adverse effects in clinical practice, seem to be retaining their usefulness in the treatment of MS and will likely continue to be used in the future.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Gülhane Training and Research Hospital.

Informed Consent: Informed consent was not received due to the retrospective nature of the study.

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