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Why are the First-Line Therapies Used as Injections Discontinued in the Treatment of Multiple Sclerosis?

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Sedat ŞEN[1a], Murat TERZİ[1b]

[1]Ondokuz Mayıs University, Faculty of Medicine, Department of Neurology, Samsun, Turkey
ORCID ID: [a]0000-0001-8048-6845, [b]0000-0002-3586-9115

Abstract:

Objective: Immunomodulatory therapies are used in the treatment of multiple sclerosis considering their efficacy and safety. Although other effective treatments have been used in recent years, the use of immunomodulatory therapies continues. In this study, we aimed to reveal the reasons for the discontinuation of immunomodulatory therapies used as injections.

Method: Immunomodulatory therapies data of 1464 patients were collected and analysed from the Imed database, where 20-year data of the patients were entered by us. Groups were divided as; Interferon beta-1a subcutaneous, interferon beta-1a intramuscular, glatiramer acetate and Interferon beta-1b. Age, gender, duration of illness, types of disease onset, time to start the injection, duration of injection therapy, and reason for discontinuation of patients were analysed.

Results: The most common reason for discontinuation of treatments was found to be disease progression (20.13%, 28.14%, 19.64%, 23.87%). Side effects, increased relapse frequency, patient demand, disease activity detection in imaging methods, and pregnancy planning followed the disease progression respectively.

Conclusion: Immunomodulatory therapies as an injection form are used in the treatment of multiple sclerosis, considering their effectiveness and reliability. The most common reason for discontinuing treatment is disease progression.

Keywords: *Multiple sclerosis, immunomodulatory therapy, interferon beta, glatiramer acetate*

Corresponding author: E-mail: sedatsen83@hotmail.com

Introduction

Multiple Sclerosis (MS) is a chronic disease of the central nervous system that progresses with loss of myelin and axon damage [1]. Immunomodulatory therapies (IMTs) were currently used to control this disease. Interferon beta-1b (IFN-β1b), approved in 1993, is the first IMT agent for MS treatment. This was followed by intramuscular form of interferon beta-1a intramuscular (IFN-β1a IM) in 1995, glatiramer acetate (GA) in 1996, and interferon beta-1a subcutaneous (IFN-β1a SC) in 1998 [2]. MS disease has been tried to be controlled with the help of these treatments for many years. Although oral, intravenous and monoclonal new treatment options have started to be used in the last 10 years, the molecules used in the form of injection in the traditional MS treatment still maintain their place in the treatment.

IMTs are applied in an algorithm according to their effectiveness and reliability, taking into account the clinical demographics of the patients. In addition to stepwise treatment, the use of high-efficacy treatments is another option at the initial stage [2]. The most decisive limitation for the use of high-efficacy treatments is the side effects. The immunosuppression caused by these treatments may also cause additional problems [3]. For these reasons, injection treatments still maintain their validity and effectiveness, although they do not create high efficacy compared to new treatment options.

For MS patients using injection therapies, it may be necessary to switch to higher-level therapies in cases such as inability to cope with side effects, inadequate relapse control, and disease progression. In the present study, the reasons for discontinuation of IMTs as an injection form during MS treatment are discussed in detail.

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Materials and Methods

After the Ethics Committee of Ondokuz Mayıs University (Samsun, Turkey) approved the protocol of the study (2021/489), previously entered data by expert neurologist to the IMed database were obtained and analysed. The data of 2456 patients followed up in Ondokuz Mayıs University Faculty of Medicine MS Unit of Neurology Department between January 2001 - January 2021 were scanned for the study. Among these patients, 1464 patient-injection therapy matches were identified and included in the study. Age, gender, disease duration, disease onset patterns, injection initiation time, duration of injection therapy, and treatment discontinuation reason of patients were analysed.

Statistical analysis

Data were analysed with IBM SPSS V25 statistical package program. A chi-Square test was used to determine the presence of a significant difference between the treatment groups. One-way analysis of variance (ANOVA) and post-hoc Tukey-Kramer tests were used to compare the duration of discontinuation of treatment among groups. Data are given as mean ± standard deviation or percent (%).

Result

Table 1 reveals demographic profiles on age and disease duration. When this table was analysed, it was determined that there was a similarity among injection groups and there was no significant difference.

Table 1. *Demographic profiles of study participants.*

IMT	Age (years)				Disease duration (years)			
	IMT starting		Current		IMT starting		Current	
	Mean (SD)	Min-Max	Mean (SD)	Min-Max	Mean (SD)	Min-Max	Mean (SD)	Min-Max
IFN-β1a SC	31,95 (9,98)	11,43-61,73	41,01 (11,08)	17,14-72,16	1,98 (3,57)	0-19,84	11,12 (6,35)	0,31-29,44
IFN-β1a IM	31,26 (9,95)	11,01-61,32	42,56 (11,65)	16,37-73,33	1,54 (2,69)	0-13,51	13,47 (5,83)	0,81-30,38
GA	35,54 (10,66)	18,07-60,23	43,93 (11,48)	20,12-73,04	3,05 (4,70)	0-20,64	11,91 (6,62)	0,11-35,78
IFN-β1b	33,44 (10,04)	15,71-63,71	44,54 (11,69)	21,89-74,41	2,15 (3,52)	0-17,77	12,28 (7,25)	0-31,27

IMT: Immunomodulatory therapy, IFN-β1a SC: Interferon beta-1a subcutaneous, IFN-β1a IM: Interferon beta-1a intramuscular, GA: glatiramer acetate, IFN-β1b: Interferon beta-1b.

The number of patients whose IMT treatment was continued or discontinued is shown in table 2. When the number of patients whose treatment was discontinued and continued, Chi-square test revealed no significant difference among treatment groups. The rate of continuation of treatment in IFN-β1a SC, IFN-β1a IM, GA and IFN-β1b groups were %27.4, %27.1, %31.3, and %19.0, respectively. In patients whose treatment was discontinued, there was no significant difference in terms of duration of drug use. The duration of discontinuation of treatment in IFN-β1a SC, IFN-β1a IM, GA and IFN-β1b groups were 4.33±4.61, 4.78±4.48, 4.02±4.44, and 4.51±4.42 years respectively.

Table 2. *Number of patients continuing/discontinuing IMTs treatment and the duration of IMTs treatment.*

IMT	**Total IMT** n (%)	**Continuing IMT** n (%)	**Discontinuing IMT** n (%)	**Duration of IMT (years)** Mean ± SD
IFN-β1a SC	423 (100)	116 (27,40)	308 (72,60)	4.33 ± 4.61
IFN-β1a IM	384 (100)	104 (27,10)	280 (72,90)	4,78 ± 4.48
GA	383 (100)	120 (31,30)	263 (68,70)	4.02 ± 4.44
IFN-β1b	274 (100)	52 (19,00)	222 (81,00)	4.51 ± 4.42

IMT: Immunomodulatory therapy, IFN-β1a SC: Interferon beta-1a subcutaneous, IFN-β1a IM: Interferon beta-1a intramuscular, GA: glatiramer acetate, IFN-β1b: Interferon beta-1b.

Table 3 shows reasons for discontinuation of treatment. It was observed that treatment was discontinued most frequently due to increase in disease progression-disability. This was followed by side effects, increased frequency of relapses, patient request, improvement in imaging findings, pregnancy status and other reasons.

Table 3. *Reasons for Discontinuing IMTs.*

IMT	Total	Disease progression	Side effects	Relapse frequency	Patient demand	MRI activity	Pregnancy	Others	Unknown
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
IFN-β1a SC	308 (100)	62 (20,13)	63 (20,45)	22 (7,14)	22 (7,14)	19 (6,17)	20 (6,49)	31 (10,06)	69 (22,40)
IFN-β1a IM	280 (100)	55 (19,64)	33 (11,79)	16 (5,71)	29 (10,36)	25 (8,93)	12 (4,29)	45 (16,07)	65 (23,21)
GA	263 (100)	74 (28,14)	46 (17,49)	19 (7,22)	11 (4,18)	13 (4,94)	4 (1,52)	40 (15,20)	56 (21,29)
IFN-β1b	222 (100)	53 (23,87)	44 (19,82)	15 (6,76)	15 (6,76)	14 (6,31)	4 (1,80)	38 (17,129	39 (17,57)

IMT: Immunomodulatory therapy, IFN-β1a SC: Interferon beta-1a subcutaneous, IFN-β1a IM: Interferon beta-1a intramuscular, GA: glatiramer acetate, IFN-β1b: Interferon beta-1b. MRI: magnetic resonance imaging

Discussion

In the last 20 years, there have been rapid developments in the treatment of MS disease. Although the disease cannot be completely cured, the number of relapses can be reduced, the increase in disease progression and brain atrophy can be prevented with the current drugs [2]. Apart from these parameters, *no evidence of disease activity* (NEDA) [4] and progression independent of relapse activity (PIRA) [5] concepts have come into prominence. As in previous years, waiting for a long time in low-efficacy treatments is replaced by starting high-effective treatments as soon as possible [6,7]. IMTs used as injections are still used and the effects that expected from IMTs are increasing day by day in the treatment of MS.

There are not major safety problems for the first-line IMTs used as injections [2]. Thanks to the experience accumulated over many years, almost all the side effects that may occur during the use of these treatments have been observed and management strategies have been determined. However, it is very difficult to cope with the side effects and to manage the ineffectiveness-disease progression state. Our study revealed that the treatments used in this way were most frequently

discontinued due to disease progression and side effects. This result is in parallel with the current MS treatment strategies.

The interesting aspect of our study is that gender distribution, age and disease duration are similar in all four IMTs groups. In addition, a similar duration of treatment was observed in all treatment groups. The fact that IFN-β1a IM treatment, which provides lower disease activity control than other injection treatments, has similar findings with other treatments, may possibly be related to the initiation of the patient group with lower activity. For preventing disease progression, the most effective strategy applied today is known as switching to a high-efficiency treatment rather than switching within the first-line treatments [6]. From this point of view, it can be said that this is the most obvious reason for reducing the use of first-line injection treatments.

Side effects are another problem for IMTs injection treatments. Patient compliance has a great impact on treatment effectiveness [8,9]. Correct application of IMDs by patients is of great importance in terms of avoiding side effects. Minor changes in the way of the administration of the IMTs may improve compliance [10, 11]. In this respect, it is very important to give injection trainings to patients by MS professionals. The occurrence of side effects, which was the second most common reason of discontinuation in our study, can be the sign of this reason. The best way to optimize success in MS treatment is through the appropriate administration of treatments that meet the NEDA criteria. For this reason, it is necessary to consider the parameters such as efficacy, reliability, patient compliance [2, 12]. Although we can say that the problem of safety for first-line injection treatments has been overcome, efficacy and management of side effects are still among the most basic problems.

Apart from the inability to control the disease activity, it is seen that the treatments are also discontinued for patient request and pregnancy planning. For MS patients with pregnancy planning, first-line IMTs appear to be safe compared to other treatment options [13]. Although this can be seen as an advantageous situation, the discontinuation of the treatment with the patient request approaching 10 percent should not be ignored. It is very important to evaluate this pregnancy planning patient group in more detail, to reveal the situation that caused the discontinuation of the treatment and to reorganize it in an appropriate way.

Conclusion

Similar results for IFN and GA treatments indicate that the most common reasons of discontinuation of IMTs are disease progression and side effects. For optimal MS treatment,

individualized patient-specific approaches should be applied. From this point of view, first-line injection treatments can be continued to be used, considering efficacy, safety and side effects.

Conflict of interest

The authors declare no conflict of interest.

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