RESEARCH ARTICLE

Interferon Beta-1b for the Treatment of Multiple Sclerosis – More than 10 Years of Experience

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Objective: Interferon beta-1b (IFNβ-1b) was the first disease-modifying agent (DMT) used for the treatment of multiple sclerosis (MS). We aimed to evaluate the first patients with MS that started treatment in our clinic. **Methods**: An observational, retrospective study was performed on 78 patients that had continuous treatment with IFNβ-1b for more than 10 years. The collection of the demographical data and periodical clinical evaluation was performed on all patients. The disability was quantified using the Expanded Disability Status Scale (EDSS), creating two groups of patients, G1: EDSS < 4.0 and G2: EDSS ≥ 4.0. The hallmarks of the disability evolution were gathered by direct patient interview, such as the symptoms at onset and relapse frequency. **Results**: After more than 17 years of disease evolution, more than half (65.38%) of the patients present a mild disability score. The majority (54.90%) started treatment in the first three years after the onset, while the patients in G2 started treatment after more than 3 years from the onset. The initiation of IFNβ-1b lead to a significant reduction of the relapse rates. A reduced number of patients (<25%) transitioned from RRMS to SPMS. **Discussion**: Continuous evaluation of MS patients allows us to assess the possibility of prolonged treatment with IFNβ-1b and to differentiate the responders from non-responders. The clear reduction in relapse rates and disability progression, notably in patients that started treatment early ensure us into continuing administering this medication. Compared to historical cohorts, our lot had a slower disability evolution and a significant proportion hadn't reach an important disability score.

Keywords: multiple sclerosis, interferonβ-1b, disability, evolution, disease-modifying therapy

Introduction

Multiple sclerosis (MS), a chronic, immune-mediated disease of the central nervous system (CNS), which predominantly affects the young adults, is one of the most frequent causes of neurological disability in the modern world. Relapsing-remitting MS (RRMS) is the most common form of evolution, which accounts for most of the cases and usually converts into the secondary-progressive MS (SPMS) in 10 to 15 years. [1, 2] Accumulation of disability in MS is secondary to both inflammatory and neurodegenerative processes. From a clinical perspective, active inflammation will trigger a relapse and recovery may be complete or partial, resulting in neurological sequelae. Neurodegenerative processes will lead to progressive disability and mark the onset of the SPMS [3]. The available treatments for MS exert their actions mainly in the inflammatory phase by modulating the immune response, thus being known as disease-modifying therapies (DMT).

The interferons were discovered by accident in 1957 by Alick Isaacs and Jean Lindenmann, two British researchers who were actively following the viral response to the Influenza viruses in animal models (chicken embryos) [4]. While the interferon gamma was the first agent used for the treatment of MS, it proved to have a contrasting effect by incrementing the relapse rates and overall augmenting the disease evolution [5], being quickly replaced by the interferon beta. One of the most studied DMTs - the interferon beta was the first immunomodulatory agent used for the treatment of MS, with a well-known safety profile and a good impact upon the general clinical evolution of the patients. The interferon beta-1b (IFNβ-1b) was approved for the treatment of RRMS in USA in 1993, and in EU in 1995 [6], and shortly after, in 1999, it was approved for use in SPMS [7] after extensive studies that focused upon disease's evolution determined that it also reduces the disability progression and [8] controls the relapse rates in patients with an SPMS [9, 10].

Despite the increasing number of DMTs appearing on the market, the IFNβ-1b remains one of the most prescribed agents for MS' treatment. Whether this drug can significantly delay the disability accumulation when being used for long periods of time is still under dispute, but due to its worldwide availability, the increasing number of long-term treated cohorts of patients starts to answer one question at the time. In order to bring our contribution to the MS world, we examined the clinical impact of IFNβ-1b in MS patients treated continuously for more than 10 years.

Methods
Lot selection

For this study, patients treated with IFNβ-1b subcutaneously once every two days were selected. In our clinic we treat more than 400 patients with MS, from which 140 are treated with IFNβ-1b.

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An observational, retrospective study was performed on 78 patients that had continuous, uninterrupted treatment with IFNβ-1b for more than a decade. Data collection and patient evaluation took place between 2016-2017. The patients have been followed ever since the treatment was instituted in the Neurology 1 Clinic of the Emergency Clinical County Hospital of Targu Mures, Romania. All the patients that are included in the MS treatment programme were evaluated every six months or when needed in case of relapses or other symptoms, as well as brain and spinal cord magnetic resonance imagining (MRI) together with complete neurological follow-ups, as per diagnosis protocol based on the revised McDonalds criteria (2010). [11]

The inclusion criteria were: a) patients diagnosed with MS based on McDonalds criteria revised in 2010, b) were treated continuously for more than 10 years with IFNβ-1b, c) had no prior immunomodulatory treatment and d) consented to regular follow-ups and to be a part of the study. The exclusion criteria were applied for the remaining 62 patients, as following: a) patients interrupted at one point, either voluntarily (pregnancy) or because of adverse effects the treatment with IFNβ-1b, b) had prior immunomodulatory treatment with other DMT, c) they did not consent to be a part of the study, d) had less than 10 years of continuous treatment with IFNβ-1b.

Lot evaluation
The patient's demographical and clinical data, including date of the clinical onset, symptoms at onset, relapses and disability were recorded at the first visit and historical information about the course of the disease was retrospectively collected and analysed. The neurological disability was quantified using the *Expanded Disability Status Scale* (EDSS) [12], actively following the disability progression and moment of conversion from a RR to a SP. The functional systems (FS) affected at onset were noted as optic (O-FS): onset with optic neuritis, pyramidal (P-FS): onset with pure motor deficit, brainstem (B-FS): onset with diplopia or alternate syndromes, cerebellar (C-FS): onset with coordination impairment and instability, sensory (S-FS): onset with either paraesthesias or loss of sensibility and polysymptomatic onset(X-FS).

The total number of relapses was calculated as annual relapse ratio (ARR), by using the following formula: ARR = number of relapses/number of treatment years. ARR was defined as the total number of relapses, ARR_0 as relapses before the treatment respectively, ARR_1, relapses on treatment. A relapse was considered as the sudden onset of new neurological symptoms with a concomitant worsening of the clinical picture, that occurred in the absence of fever or any other kind of active infection. The events lasted more than 24 hours and alleviated spontaneously or with the use of corticosteroids [13].

The disability score was noted according to EDSS, and to simplify the patient selection two groups were defined: G1 – patients with an EDSS < 4.0 and G2 – patients with an EDSS ≥ 4.0 at the study inclusion. The patients' evolutions were followed accordingly, thus the progression was subsequently assessed by consulting the old records, mainly the transition from a lesser EDSS to a score of 4.0 or 6.0. The milestones 4.0 and 6.0 were chose because of the impact they have upon the disability progression. Thus, an irreversible EDSS of 4.0 marks the first clinical signs of ambulatory restriction, limiting the walking perimeter within 500 meters (without any physical aid), and the EDSS of 6.0 is defined by the necessity of unilateral assistance for ambulation. By evaluating the patient files, we were able to indicate, when applicable, the moment of progression, keeping in mind that the ambulatory capacity is the main determinant for the EDSS. The EDSS at the start of the treatment is $EDSS_0$, respectively at the study inclusion $EDSS_1$.

Statistical Analysis
The data was centralized using the Excel Platform incorporated in Microsoft Office 2016 and the statistical analysis was performed using Graph Pad Prism 6. We used mean and standard deviation (SD) when assessing gaussian population, and median and range defined by 25%-75% percentile when analysing non-gaussian populations. The normality tests used were Shapiro-Wilk and Kolmogorov-Smirnov, and the correlations were performed using Spearman or Pearson test, after assessing the normality distribution. The statistical significance was defined when p<0.05.

Results
A total of 78 MS patients that had continuous treatment with IFNβ-1b for more than 10 years were evaluated. Patient demographic and general clinical data are presented in *Table I*. At the moment of study inclusion, 51 (65.38%) of the patients had an EDSS lower than 4.0, while 27 (34.61%) had a disability score higher or equal to 4.0. The female gender is dominant in both groups, 68.62% in G1 and 70.37% in G2. There was no statistically significant difference (p=0.259) when comparing the age at onset of the disease for both groups, (*Fig.1*) but statistical significant data was found when comparing the age at the beginning of the treatment between the two groups (p<0.0001), with a median for G1 of 35 years, respectively 42 years for G2 (*Fig 1*). Most of the patients in G1 (54.90%) started treatment between 1 and 3 years from the onset of the symptoms, while in G2, most of them started treatment after 3 years (70.22%).

From the cohort of patients, 63 (80.75%) started treatment with an EDSS between 0 and 3.5 and 48 (76.16%) of them still have an EDSS < 4.0 at the moment of study inclusion, signifying that more than three quarters of the patients with a mild/moderate degree of disability still have a good clinical course. 15 (23.80%) patients converted to SPMS.

The patients had been treated with IFNβ-1b approximately 13 years for both groups. The mean duration of

Table I. Demographic and clinical data of the patients

	All patients - G n= 78	EDSS < 4.0 - G1 n= 51 (65.38%)	EDSS ≥ 4.0 - G2 n= 27 (34.61%)	EDSS ≤ 2.0 n=29 (38.46%)
Female	54 (69.23%)	35 (68.62%)	19 (70.37%)	23 (79.31%)
Male	24 (30.76%)	16 (31.37%)	8 (29.62%)	6 (20.68%)
Mean age at the MS' onset (years)				
< 20 years old	4 (5.12%)	3 (5.88%)	1 (3.70%)	1 (3.44%)
20-30 years old	35 (44.87%)	21 (41.17%)	14 (51.85%)	13 (44.82%)
31-40 years old	30 (38.46%)	26 (50.98%)	4 (14.81%)	12 (41.37%)
> 41 years old	9 (11.53%)	1 (1.96%)	8 (29.62%)	3 (10.34%)
Mean age at the beginning of treatment (± SD*) (years)	36.73 ± 8.53	29.82 ± 7.19	42.04 ± 7.52	29.72 ± 7.26
Mean duration of the disease (years) (± SD)	18.90 ± 7.10	16.90 ± 5.43	22.67 ± 8.36	16.10 ± 5.010
Mean treatment duration (years) (± SD)	13.08 ± 2.46	12.80 ± 2.38	13.59 ± 2.59	12.34 ± 2.05
Start treatment				
Same year	9 (11.53%)	7 (13.72%)	2 (7.40%)	2 (6.89%)
1-3 years	34 (43.58%)	28 (54.90%)	6 (22.22%)	18 (62.06%)
> 3 years	35 (44.87%)	16 (31.37%)	19 (70.22%)	9 (31.03%)
FS at onset				
Optic (O-FS)	16 (20.51%)	13 (25.49%)	3 (11.11%)	9 (31.03%)
Pyramidal (P-FS)	19 (24.35%)	12 (23.52%)	7 (25.92%)	5 (17.24%)
Cerebellar (C-FS)	6 (7.69%)	2 (3.92%)	4 (14.81%)	1 (3.44%)
Sensory (S-FS)	11 (14.10%)	8 (15.68%)	3 (11.11%)	5 (17.24%)
Brainstem (B-FS)	20 (25.64%)	13 (25.49%)	7 (25.92%)	6 (20.68%)
Polysymptomatic (X-FS)	6 (7.69%)	3 (5.88%)	3 (11.11%)	3 (10.34%)
Median EDSS_0 (25%-75% percentile)	2.0 (1.0 – 3.0)	1.5 (1.0 – 2.5)	3.5 (2.5 – 4.5)	1.5 (1.0 – 2.0)
Median EDSS_1 (25% - 75% percentile)	3.5 (2.0 – 5.5)	2.0 (1.5 – 3.5)	6.0 (5.0 – 6.5)	1.5 (1.0 – 2.0)

*SD: standard deviation

Age at onset of the disease for G1 and G2
(Mann Whitney test)

Age at beginning of the treatment for G1 and G2
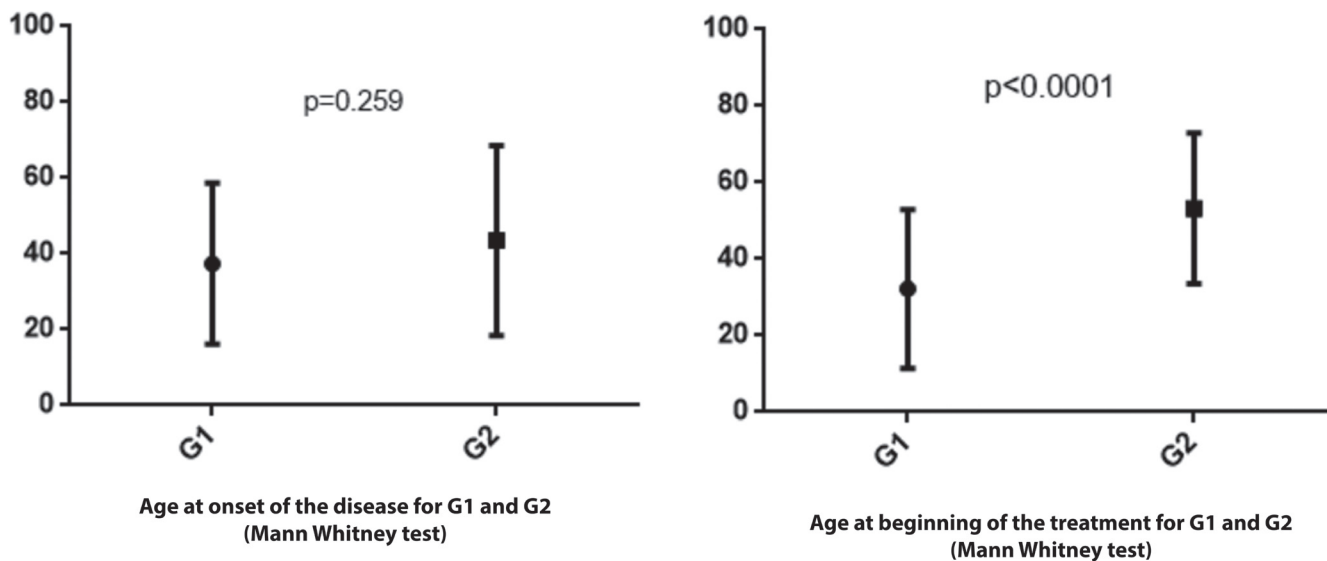**(Mann Whitney test)**

Fig. 1. Age values analysis for G1 and G2, based on the onset and moment of treatment initiation

the disease was 16.90 years for G1 and 22.67 years for G2. Most of our patients in G1 presented at onset with B-FS and O-FS (25.49%) symptoms, while in G2, the predominance was between B-FS and P-FS (25.92%). The EDSS_0 ranged from 1.5 in G1 to 3.5 in G2. At the study inclusion, the EDSS_1 for G1 was 2.0, while for G2 was 6.0.

By comparing the ARR before and after the treatment was instituted, statistical significance was found for all the groups: G, G1, and G2, but with a stronger p-value for G1 (p<0.0001), signifying a reduced relapse ratio after treatment with IFNβ-1b was started (Fig 2).

The overview of the clinical evolution of the patients is presented in *Table II*. This included the 15 patients that converted to an SPMS during the treatment. We did not

account for patients that already had a higher disability level when they started treatment, because of the difficulty in correctly assessing the moment of conversion historically. The median time from the MS' onset to an EDSS of 4.0 was 12 years and for an EDSS of 6.0 was 16 years. The mean treatment duration was 15 ± 2.63 years. This can be interpreted as following in our study: a patient will reach

Table II: Conversion of the RRMS patients into SPMS

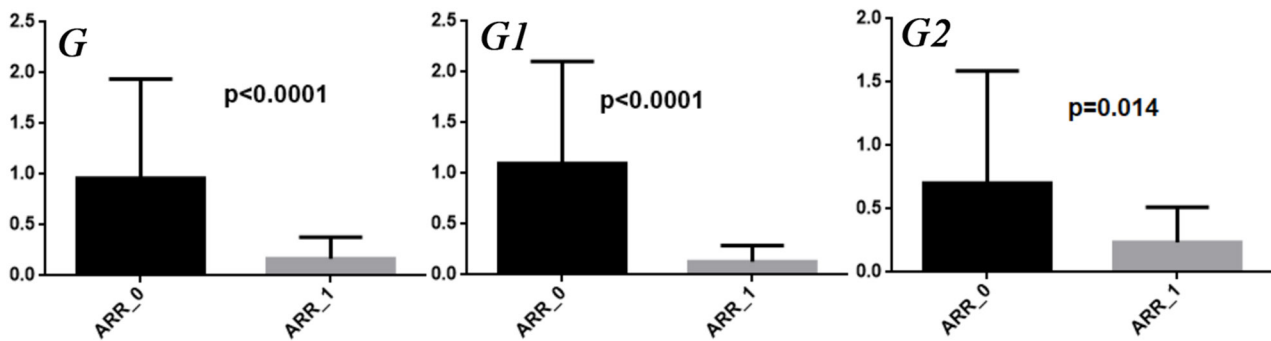| n=15	EDSS 4.0	EDSS 6.0
MS' onset (years) Median (25% - 75% percentile)	12 (8 – 17)	16 (9 – 22)
Start of treatment (years) Median (25% - 75% percentile)	5 (1 – 7)	6 (1.5 – 10)

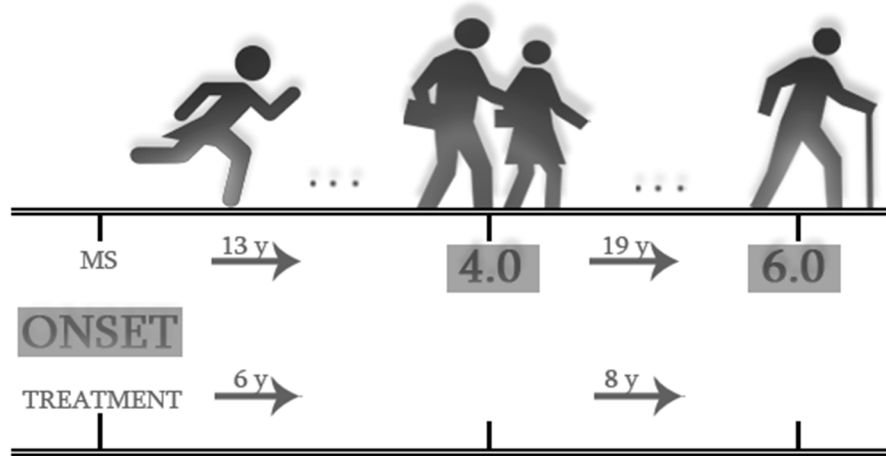Fig. 2. Analysis of the relapse rates using Wilcoxon matched paired signed ranked test.

Fig. 3. Representation of the evolution of disability

an irreversible EDSS of 6.0 in 4 years after the start of the progressive phase. The median time from the start of the treatment to an EDSS of 4.0 was 5 years and to an EDSS of 6.0 was 6 years. The evolution towards an SP phase is represented in Fig.3.

The patients were evaluated every 6 months for the entire duration of the treatment. The retrospective information allowed us also to explore the subgroup with the lesser degree of disability and to assess the clinical data (*Table I*). 29 (38.46%) patients present with an EDSS < 2.0 at the moment of study inclusion. Their mean age at MS' onset, the mean age at the beginning of the treatment, mean duration of the disease and mean treatment duration were similar between the G1 and G2. Most of the patients started IFNβ-1b in the first three years from the onset (62.06%) and the dominant FS present at onset was O-FS (31.03%), followed by B-FS (20.68%). The median EDSS_0 was equal to EDSS_1, with a low disability score of 1.5.

Discussion

The efficiency of IFNβ-1b has been the subject of numerous individual and collective studies, mainly due to its availability and ease of monitoring. Ever since its approval in 1993, numerous extensions followed, which demonstrated that continuous administration has a persistent effect upon relapse rate reduction [14], thus diminishing the disability accumulation. In our present study, we focused on clinically evaluating those patients that started the treatment as soon as it became available in our country, know-

ing that IFNβ-1b was first DMT approved in Romania in our center in 2000 for the RRMS and, shortly after, for the SPMS.

The pathophysiological mechanisms of MS, though not being fully understood yet, are characterized by two entwining processes: demyelination and neurodegeneration, defining MS as a two-stage disease [15]. Demyelination is the result of an over-active auto-immunity and is characteristic for the active form of the disease, RRMS, where inflammation is the dominating pathophysiological process and usually manifests as clinical relapses. The available DMTs will exert their action modulating the inflammation and have a modest effect on the second stage, the neurodegeneration, marked by axonal loss. But the evolution of disability in the first phase seems to be independent than the progression that manifests in the second phase of the disease [16].

IFNβ-1b mechanism of action is partially known, but it's main effects are targeted against lymphocyte T proliferation and a reduction of endogenous IFN-gamma. It also blocks the class II major histocompatibility complex (MHC) and reduces the subsequent expression of the antigen presentation, blocking the activity of the adhesion molecules, reducing thus the inflammation in the CNS [17]. At a umoral level, the agents act upon reduction of the pro-inflammatory cytokines and augment the expression of anti-inflammatory agents [18].

The demographic data of our patients were similar to the results reported by other studies. The obvious dominance

was for female patients [19]. There is a genetic susceptibility for female patients to have a higher risk of developing auto-immune conditions [20], some linked to MHC genes on chromosome 6 [21] and some explained by the various HLA complexes [22]. We found no significant differences between the age of the patients at the MS onset. What was expected was the strong statistical significance when we evaluated the age of patients at the start of the treatment for both groups, knowing that the onset in younger patients tends to be correlated with a better evolution [23, 24].

The importance of early treatment was easily stratified in the present study. More than half of the patients from the G1 started treatment in the first 3 years, while for the G2, most of the patients started treatment over 3 years after onset. Considering the times, it was not uncommon, due to the absence of DMTs in our country when most of our patients presented their first symptoms, but it is clear that early treatment equals better evolution, from the perspective of relapse reduction and disability control [10, 25]

Probably one of the most important effects that IFNβ-1b exerted was the reduction in the relapse rates, noticed for both groups but with a stronger statistical significance for the G1. Subsequent relapses will favor disability burden and thus, disability progression, therefore, by controlling relapse rates one can delay the conversion to an SP phase. Several studies hold unto the idea that relapses will increment disability progression [26] while others affirm that the data cannot be validated in order to reproduce this argument [27]. But it is certain that being relapse free is wished for in clinical practice.

IFNβ-1b proved its efficiency in significantly delaying the conversion from clinically isolated syndrome (CIS) to clinically defined MS [28]. IFNβ-1b effects are also beneficial upon patients with an SP form [17] because even though the effects are mainly anti-inflammatory, by adequately modulating the immune response the agents act upon the residual inflammation that is also present in the second phase of the MS, dominated by neurodegeneration. One study reported a reduction in ARR in SP patients up to a 43% [29].

The conversion rate from RRMS to SPSM was low, less than 25% from the patients with RRMS progressed to SPMS. Our patients reached a moderate disability, an EDSS of 4.0 in a median of 12 years and 6.0 in 16 years from the MS' onset. Studies upon the evolution of the disease mention a rate of conversion as high as 54% [3] with a median time of evolution of 19 years. These patients had a mean time of treatment of 13 years, so we would have anticipated a higher conversion rate. Another study comparing disabilities showed that MS patients will normally reach an EDSS of 6.0 after approximately 17 years of evolution [30], and in our case, this happened at 16 years after the first symptom. The natural history of MS states that, in about 11 years from the onset of the disease, the progression is unavoidable [31]. The mean age of patients that converted to SP in early historical studies was around 40

years [32], but in our study, the patients progressed and reached an irreversible EDSS close to 48 years of age, finding consistent to other international studies on cohorts of long term treated patients [33].

Depending on the onset of the disease, for the G1 the clinical picture was dominated by optic and brainstem symptoms, while the G2 patients the predominance was pyramidal and brainstem symptoms. It has been reported that the onset with ocular [34] or sensory symptoms [35] is usually associated with a lesser degree of disability. A polysymptomatic onset is usually an indicator of a poor prognosis [36].

Seeing how in some of the cases we are faced with a slow or steady evolution, we hypothesized about *benign MS*. Even though the diagnosis of a benign MS can be made only after a long evolution of the disease and many authors still disapprove of the concept, it's important to evaluate this specific lot of patients in order to at least determine the favourable predictors. *Razzolini L et al* implied that to maintain a benign MS status, the EDSS should be lower than 2.0 and the diseases' evolution should exceed 10-12 years. Also, brain volume as measured in T1 is an important biomarker that can aid in the diagnosis of a truly benign MS [37]. The selected patients from our cohort with a mild disability level had no significantly different demographic data compared to the whole G1/G2 groups, most of them presented at onset O-FS and B-FS symptoms and they started treatment early in the first 3 years from the onset. The only clinical difference was their EDSS level, at study inclusion their mean EDSS was 1.5, signifying only signs of disability, with no clinical impact. While we cannot say that we have obtained new prognostic factors to aid in the definition of benign MS, the follow-up of the abovementioned patients including imaging studies will aid us into completing the missing diagnosis pieces.

Being one of the most used MS treatment, the safety profile of IFNβ is well known. One study that followed patients treated with IFNβ-1b for over 16 years [38] showed that adverse effects (AE) tend to diminish with time. The most frequent AE are local inflammatory reactions such as pain or tenderness around the area of injections and flu-like syndrome, both of which are easily manageable with intermittent anti-inflammatory medications [39]. Comparing the IFNβs, IFNβ-1b with subcutaneous administration is better tolerated than IFNβ-1a with subcutaneous/intramuscular administration. [40, 41].

The limitations of our study are represented by the classical method of determining the neurological status of our patients, the EDSS. This scale mainly implies the physical disability and mobility and doesn't quantify the whole clinical picture of an MS patient, such as fatigue, depression, anxiety etc, given the fact that disability might not always be perceived by the patient as the inability to walk. The clinical data of our patients from the first moment they entered the clinic is accurate, as trained MS specialists were performing the clinical evaluations, but the be-

fore clinical status of the patients, most importantly the ones that joined us already in an SP phase is being left to speculation, since we cannot exactly pinpoint the moment of conversion. An important characteristic of the present study is the uninterrupted IFNβ-1b treatment in a rather homogenous population which displays a heterogeneous response.

Conclusions

Long-term treatment with IFNβ-1b for MS patients remains a safe and optimal option. It's well-known safety profile and ease of monitoring, manageable AE and good tolerability makes it one of the most widely prescribed agents for the treatment of MS.

By reducing the relapse rates and disability progression, IFNβ-1b will delay the evolution of the disease, focusing its effects mainly in the inflammatory phase. It is important to start IFNβ-1b treatment as early as possible, ideally when the diagnosis of MS has been established, this being universally recommended for any other kind of DMT. Extension of the indication for the treatment of not only RRMS but SPMS makes IFNβ-1b an excellent first-line treatment.

However, one must always remember that clinical monitoring it's essential and that if our patients show signs of progression or bad tolerance, either a switch or an escalation of therapy is mandatory in order to ensure the best quality of medical care.

Authors'contribution

Laura Iulia Barcutean, MD (Conceptualization; Investigation; Methodology; Writing – original draft; Data analysis)
Smaranda Maier, MD, PhD (Reviewing)
Zoltan Bajko, MD, PhD (Statistical analysis of the data)
Anca Motataianu, MD, PhD (Writing – review & editing)
Andreea Romaniuc, MD (Investigation)
Sebastian Razvan Andone, MD (Investigation; Writing – review & editing)
Rodica Ioana Balasa, MD, PhD, Professor (Conceptualization; Investigation; Writing –review & editing)

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Conflict of interest

The authors have no conflict of interests.

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