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ORIGINAL ARTICLE

Long-term disability outcomes in relapsing-remitting multiple sclerosis: a 10-year follow-up study

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Abstract

Objective The aim of this study is to assess the impact of interferon (IFN) beta treatment on the development of worsening disability in relapsing-remitting (RR) multiple sclerosis (MS) patients in the single-center observation cohort.

Method This is a prospective study of 236 IFN-beta-treated and 183 untreated RRMS patients recruited consecutively at the Clinic of Neurology in Belgrade (Serbia). Out of this original cohort, 10-year follow-up data were available for 233 IFN-beta-treated and 131 untreated subjects. The median time since recruitment was 9.7 years.

Results IFN-beta treatment significantly delayed ($p < 0.001$) the time to reach each of the clinical outcomes (secondary progression-SP, EDSS scores 4 and 6) since recruitment. Time from the first visit to SP was reached after 9.7 years for IFN-beta-treated vs. 7.8 years for untreated patients. The delay for the development of EDSS score ≥ 4 from the first visit was 1.6 years (8.7 years for IFN-beta-treated vs. 7.1 years for untreated patients). Time from the first visit to EDSS score of 6 was reached after 9.8 years for IFN-beta-treated vs. 8.8 years for untreated patients. The IFN-beta-treated group showed significant reduction ($p < 0.001$) in the risk of conversion to SP when compared with untreated patients (HR = 0.22). There was also a significant difference in reaching EDSS scores 4 and 6 ($p < 0.001$), in favor of the IFN-beta-treated group (HR = 0.40 and HR = 0.27, respectively).

Conclusion Comparison of outcomes in our IFN-beta-treated vs. untreated RRMS patients suggests that this treatment may delay development of long-term disability in MS.

Keywords Multiple sclerosis · Interferon beta · Disability · Prediction · Long-term follow-up · Relapse rate

Introduction

The natural history of multiple sclerosis (MS) is characterized by a marked variation when it comes to the gradual progression of disability [1]. It has been demonstrated that about one-half to two-thirds of relapsing-remitting (RR) MS patients would develop severe neurological disability 11 to 23 years from disease onset [2, 3]. Additionally, 2–3% of patients per year will convert to secondary progressive (SP) phase of the disease [4, 5].

Interferon (IFN) beta 1b was the first disease-modifying therapy (DMT) to be approved for the treatment of RRMS, and afterwards, additional IFN-beta formulations have become available [6]. Up to now, several randomized clinical trials (RCTs) have shown that IFN-beta reduced relapse frequency, relapse-related accumulation of disability, and new inflammatory lesions as demonstrated by magnetic resonance imaging (MRI) [7]. However, patient cohorts included in RCTs are not representative of real-world practice and, additionally, those controlled trials which last only 2–3 years are primarily focused on short-term outcomes [8–10]. Furthermore, evidence from RCTs and extension open-label IFN-beta studies for preventing or delaying long-term

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neurologic disability is incomplete [11, 12]. In contrast to RCTs, observational longitudinal studies, which can be used for long-term outcomes, are burdened by significant biases [13]. Until now, a few observational studies have been performed which provided potentially significant information on the long-term impact of IFN-beta [14–16]. However, their results are inconsistent and although in two of these studies [14, 16] association between IFNs and delay of long-term disability has been demonstrated, it was not confirmed in the remaining Canadian study [15].

Having in mind all abovementioned, the aim of our study was to assess the impact of IFN-beta treatment on the worsening disability in IFN-beta-treated RRMS patients in comparison with untreated ones in the single-center observation cohort, under "real-world" conditions.

Material and methods

Cohort of the 419 RRMS (236 IFN-beta-treated and 183 untreated) RRMS patients (McDonald criteria, 2001) [17] was recruited at the Clinic of Neurology, Clinical Center of Serbia, Belgrade, which is a national referral center for MS. Fifty-six percent ($n = 133$) of 236 IFN-beta-treated patients were treated with IFN-beta 1a 44 mcg, and 44% ($n = 103$) received IFN-beta 1b. Firstly, all these patients were followed up for up to 7 years (data presented elsewhere) [16]. Then, out of this original cohort, 10-year follow-up data were available on 364 (233 IFN-beta-treated and 131 untreated) subjects.

The baseline demographic and clinical characteristics of subjects who participated in the long-term follow-up (9–10 years) were recorded according to standardized protocols of our hospital-based MS registry.

The date of the first visit corresponded to the date of the first IFN-beta administration for the IFN-beta-treated patients. For untreated patients, the date of the first assessment at the Clinic of Neurology was used as the date of the first visit.

The IFN-beta-treated cohort comprised patients who were exposed to IFN-beta therapy for up to 10 years. The total exposure time to treatment divided by the follow-up time was used to calculate the proportion of days covered by treatment. The proportion of days covered by IFN-beta treatment was of 82.8% in our treated cohort.

Patients eligible to start IFN-beta treatment had to fulfill the following criteria: diagnosis of MS (McDonald criteria) [17], maximum Expanded Disability Status Scale (EDSS) score [18] 3.5, active RR form of the disease, with at least two relapses within the last 2 years, and age ≥ 18 years. Majority of our untreated RRMS patients were not treated because of the restrictive policy of the Health Insurance Fund (HIF). In the Republic of Serbia, great majority of inhabitants have public insurance, and due to the poor economic conditions, our HIF has a very limited resources for financing MS treatment. Therefore, the number of MS patients who are treated is limited. The remaining subjects were not treated because they voluntarily refused this therapy, planned to get pregnant, or had comorbidities (i.e., liver diseases, hematological disorders, or severe depression).

Treatment with IFN-beta was recorded for each patient, including the start and stop dates. The majority of IFN-beta-treated patients had a short break (less than a month), which we considered not to influence the benefit from therapy. In this study, we assumed that both IFN-beta formulations had equivalent impacts on disability progression. Thus, no adjustment by specific therapeutic intervention was performed.

Two groups were compared with respect to the following clinical outcomes over 10 years: proportion of patients reaching EDSS score ≥ 4.0, ≥ 6.0, and developing SP, and time to reach these outcomes. A disability score was defined as confirmed if it persisted for at least 6 months, and all the subsequent scores assessed during the follow-up of the patient were either equal to or higher than that score. The SP phase was defined as initial RR disease course followed by progression for at least 12 months with or without relapses [19] and confirmed EDSS progression defined as an increase in EDSS score of ≥ 1.0 points (≥ 0.5 points if the baseline score was ≥ 6.0) over at least 6-month duration. The EDSS score was recorded at baseline and at least every 6 months subsequently to determine the level of disability, based on the neurological examination performed by experienced MS neurologists (JD, SM, ID) who were not blinded to patient's treatment status. These three neurologists (JD, SM, ID) checked database case by case, and EDSS scores were recorded at baseline and at each visit at every 6 months subsequently in order to define the timing of an increase in EDSS score of ≥ 1.0 points (≥ 0.5 points if the baseline score was ≥ 6.0) which was consequently maintained after 6 months, thus defining the existence of the confirmed disability progression. Since subsequent amelioration of the EDSS may occur, the EDSS progression was confirmed also at the last follow-up visit, in all patients. However, EDSS scoring was performed without knowledge of the baseline and previous EDSS scores in the total patient cohort.

Prognostic factors for clinical outcomes

In order to assess predictor variables for long-term disability outcomes, following baseline characteristics were investigated as potential demographic and clinical prognostic/predictive factors: gender, age at onset, age at the start of IFN-beta therapy/first visit, disease duration, number of relapses during 1 year prior to the start of IFN-beta therapy/first visit, and baseline EDSS score dichotomized as follows: ≤ 3.0 vs. ≥ 3.5.

The composite predictor, no evidence of clinical disease activity (NEDA), was defined as no relapses and no clinically significant increase in EDSS from baseline to 24 months.

The study was approved by the Ethics Committee of the Faculty of Medicine University of Belgrade. Participants provided informed consent.

Statistical analysis

Baseline characteristics for the IFN-beta-treated group and the untreated control group were compared with the χ^2 and Mann–Whitney U tests depending on the type of variables (categorical vs. continuous).

Time-to-event variables were analyzed using Cox proportional hazards models. These models adjusted for the numbers of relapses in the last year before the start of IFN-beta therapy/first visit were used to assess the differences between the two groups for the three endpoints. Adjustment for other baseline variables was not performed because the difference between the treated and untreated group was detected for no other variable except for the numbers of relapses in the last year before the start of IFN-beta therapy/first visit. Results are expressed as hazard ratios (HR) and 95% confidence intervals (CI). p-values less than 0.05 were considered significant.

Propensity score analysis was performed in order to minimize the baseline difference. To compare the two groups, propensity score 1:1 exact matching method was used, with a caliper of 0.05. Covariates used for propensity score estimation were the following variables: gender, age, duration of disease, baseline EDSS, and the numbers of relapses in the last year before the start of IFN-beta therapy/first visit.

The Kaplan–Meier method to draw curves for each of three clinical endpoints (times to reach SP, EDSS 4.0, EDSS 6.0) was used, and the log-rank test to assess the difference between the two groups comprising participants retained after propensity score matching.

The prognostic/predictive factors were tested in univariate models also using Cox proportional hazards regression models for reaching clinical outcomes (SP, EDSS 4.0, EDSS 6.0). In all three separate Cox proportional hazard model analyses, start of IFN-beta therapy for treated patients and first assessment visit for untreated persons with MS, respectively, were defined as zero time. The endpoint time in these analyses was conversion to SP, reaching EDSS 4.0 and EDSS 6.0. As a final step, the variables that had reached significance at the 0.05 (alpha level) in the univariate analysis were further analyzed in three multivariate Cox proportional hazard regression models. The selected predictors are combined into a model by using a forward stepwise method.

The SPSS 17.0 statistical software package (SPSS Inc., Chicago, IL, USA) was used in the statistical analysis.

Results

The baseline demographic and clinical characteristics of subjects who participated in the study are presented in Table 1.

There were no significant differences between the IFN-beta-treated and untreated MS patients for any of the baseline variables, except for the number of relapses in the last year before the first visit. In the IFN-beta-treated group, a number of relapses were higher compared with the untreated control group ($p < 0.001$). Only three patients from the baseline IFN-beta-treated group were lost to follow-up because of the displacement. Higher attrition rate was registered in the untreated group, since out of the total number, for the majority (85%) of lost cases, DMTs were offered and they started with treatment, and the remaining (15%) were displaced. The baseline characteristics of untreated MS patients who were retained in the study compared with those lost to follow-up were similar, except for the disease duration which was longer for those retained in the study (Table 2).

The median follow-up time in the total cohort was 9.7 years since recruitment. The time from disease onset to the first visit was 7.0 ± 5.5 years for treated patients and 3.6 ± 4.6 years for untreated.

The percentage of patients that reached SP after 10 years of follow-up was 45.8% for the untreated patients versus 14.2% for IFN-beta-treated patients. The time from the start of IFN-beta therapy/first visit to SP was reached with a delay of 1.9 years in IFN-beta-treated patients (9.7 years for IFN-beta-treated vs. 7.8 years for untreated patients). The percentage of untreated patients who had reached an EDSS score ≥ 4.0 was 51.1% compared with 27.9% of the IFN-beta-treated group. The delay for the development of EDSS score ≥ 4.0 from the start of IFN-beta therapy/first visit was 1.6 years (8.7 years for IFN-beta-treated vs. 7.1 years for untreated patients). For the endpoint EDSS score ≥ 6.0, 33.6% of untreated patients compared with 11.6% of IFN-beta-treated group reached an EDSS score ≥ 6.0. Time from the start of IFN-beta therapy/first visit to EDSS score of 6.0 was reached with a delay of 1 year (9.8 years for IFN-beta-treated vs. 8.8 years for untreated patients).

The time from disease onset to SP was 16.6 ± 8.1 years for IFN-beta-treated versus 11.3 ± 6.3 years for untreated patients. The development of EDSS score ≥ 4.0 from the onset of disease occurred 15.6 ± 7.1 years in IFN-beta-treated group and 10.7 ± 6.3 years in the untreated group. Finally, the time from disease onset to the development of EDSS score ≥ 6.0 was 16.7 ± 8.0 years for IFN-beta-treated versus 12.5 ± 5.8 years for untreated patients.

We recruited 233 IFN-beta-treated patients and 131 untreated. After propensity matching, we retained 131 patients in each group with comparable demographic and clinical characteristics. The results of the Cox proportional hazard models after propensity score analysis for the risk of each of the three

Table 1 Baseline characteristics of relapsing-remitting multiple sclerosis patients according to the treatment group ($n = 364$)

Variable	IFN-beta-treated group	Untreated control group	All patients	p
Number	233	131	364	
Age at first visit (years)				
Mean ± SD	31.5 ± 7.8	32.1 ± 8.7	31.7 ± 8.1	0.201
Median (range)	31.0 (22.0–56.0)	32.0 (18.0–66.0)	31.0 (18.0–66.0)	
Age at onset (years)				
Mean ± SD	27.5 ± 7.3	28.5 ± 8.4	27.7 ± 7.6	0.228
Median (range)	27.0 (13.0–57.0)	27.0 (12.0–57.0)	27.0 (12.0–57.0)	
Gender*				
Male	69 (29.6)	40 (30.5)	109 (29.9)	0.854
Female	164 (70.4)	91 (69.5)	255 (70.1)	
Disease duration (years)				
Mean ± SD	10.7 ± 5.7	9.9 ± 5.2	10.4 ± 5.6	0.165
Median (range)	9.0 (1.0–32.0)	9.0 (2.0–29.0)	9.0 (1.0–32.0)	
EDSS score				
Mean ± SD	1.9 ± 0.8	1.9 ± 0.7	1.9 ± 0.8	0.601
Median (range)	2.0 (0.0–4.0)	1.5 (1.0–4.0)	2.0 (0.0–4.0)	
Number of relapses**				
Mean ± SD	1.6 ± 0.9	0.8 ± 0.6	1.3 ± 0.9	< 0.001
Median (range)	1.0 (0.0–5.0)	1.0 (0.0–2.0)	1.0 (0.0–5.0)	

*Number (%);**During 1 year prior to the start IFN-beta therapy/first visit

clinical outcomes are presented in Table 3. The IFN-beta-treated group showed a highly significant reduction ($p < 0.001$) in the risk of SP when compared with untreated patients. There was also a significant difference ($p < 0.001$) in favor of the IFN-beta-treated group for reaching both EDSS score ≥ 4.0 (reduced for 56%) and for the EDSS score ≥ 6.0 (reduced risk 75%). The Kaplan–Meier curves for each of three clinical endpoints (times to reach SP, EDSS 4.0, EDSS 6.0) showed that IFN-beta treatment significantly delayed the time to each of the three clinical outcomes in participants retained after propensity score matching (Figures 1–3, Supplementary files).

The composite predictor, no evidence of clinical disease activity (NEDA-2), from baseline through the second year of the study was detected in 60.9% IFN-beta-treated and 7.6% untreated patients ($p < 0.001$). The increase in EDSS from baseline to year 2 occurred in 7.3% IFN-beta-treated and 15.3% untreated patients ($p = 0.015$). The annualized relapse rate (ARR) from the baseline to year 2 was 0.3 ± 0.5 in IFN-beta-treated and 0.9 ± 0.6 in untreated patients ($p < 0.001$).

Predictive factors were examined separately in both cohorts (Tables 4, 5, and 6). In univariate models, baseline EDSS score (≤ 3.0 vs. ≥ 3.5), baseline to year 2 increase in EDSS, ARR from baseline to year 2, and NEDA-2 were significant predictors for SPMS conversion, and likelihood of confirmed EDSS worsening up to scores ≥ 4 and ≥ 6, in IFN-beta-treated group. In the untreated group, all those variables were significant predictors for all endpoints, except ARR from baseline to year 2 and only for confirmed EDSS worsening up to score ≥ 6, NEDA-2. Independent variables that were predictive in multivariate models for all three outcomes were dichotomized baseline EDSS and increases in EDSS score over 2 years, in both patient groups (Tables 4, 5, and 6). Only in IFN-beta-treated group, ARR from the baseline to year 2 was an independent predictor for all three outcomes (Tables 4, 5, and 6).

Discussion

In this study, we compared 233 IFN-beta-treated with 131 untreated patients, followed up for up to 10 years, and demonstrated beneficial effect of therapy on long-term disability.

The IFN-beta-treated group showed a highly significant ($p < 0.001$) reduction in the risk of reaching SP, EDSS scores of 4.0 and 6.0, when compared with untreated patients. All of these clinical outcomes were developed with significant delays estimated by the times from the first visit in favor of treated patients. In our IFN-beta-treated cohort, the percentage of patients who converted to SP was 14.2%; 27.9% of patients reached EDSS score 4.0, and 11.6% EDSS score 6.0. These findings are in accordance with those from the first large observational study [14] which examined a cohort of 1504 RRMS patients receiving different IFN-beta formulations for up to 7 years in order to analyze its impact on disability. Authors have demonstrated that the IFN-beta-treated group showed a highly significant reduction in proportion of patients who developed SP (8%), reached EDSS scores 4.0 (20.5%)

Table 2 Comparison of baseline characteristics of untreated MS patients retained in the study versus those lost to follow-up ($n = 181$)

Variable	Untreated retained	Untreated lost to follow-up	All untreated patients	*p*
Number	131	50	181	
Age at first visit (years)				
Mean ± SD	32.1 ± 8.7	29.9 ± 7.0	31.5 ± 8.3	0.100
Median (range)	32.0 (18.0–66.0)	29.0 (18.0–46.0)	30.0 (18.0–66.0)	
Age at onset (years)				
Mean ± SD	28.5 ± 8.4	27.1 ± 6.9	28.1 ± 8.0	0.311
Median (range)	27.0 (12.0–57.0)	26.0 (16.0–44.0)	27.0 (12.0–57.0)	
Gender*				
Male	40 (30.5)	14 (28.0)	54 (29.8)	0.739
Female	91 (69.5)	36 (72.0)	127 (70.4)	
Disease duration (years)				
Mean ± SD	9.9 ± 5.2	7.7 ± 4.3	9.3 ± 5.1	0.010
Median (range)	9.0 (2.0–29.0)	6.5 (2.0–20.0)	8.0 (2.0–29.0)	
EDSS score				
Mean ± SD	1.9 ± 0.7	1.7 ± 0.5	1.8 ± 0.7	0.178
Median (range)	1.5 (1.0–4.0)	1.5 (1.0–4.0)	1.5 (0.0–4.0)	
Number of relapses**				
Mean ± SD	0.8 ± 0.6	0.8 ± 0.8	0.8 ± 0.7	0.716
Median (range)	1.0 (0.0–2.0)	1.0 (0.0–4.0)	1.0 (0.0–4.0)	

*Number (%); **During 1 year prior to the first visit

and 6.0 (7.7%), after the first visit, when compared with untreated patients. In another observational cohort study, IFN-beta group was not associated with statistically significant difference in reaching EDSS score 6.0 compared with two untreated cohorts [15]. In this study, the authors compared three MS patient cohorts: 868 patients treated with IFN-beta, 829 patients who were not treated with IFN-beta, and 959 patients in the historical cohort.

Observational studies are the method of choice for "real-world" evaluation of MS DMT efficacy and for the assessment of their long-term outcomes, since RCTs are limited by short duration. However, it is generally accepted that observational studies are burdened with numerous biases. The design of an observational study comparing treated vs. untreated is one of the most challenging, due to the difficulty in defining time zero, in assessing immortal time bias and adjusting for time-dependent confounders [20]. One of the crucial principles in the design of randomized trials is the specification of time zero of follow-up as the time when the eligibility criteria are met and a treatment strategy is assigned. Several methodological techniques have been suggested in order to overcome these issues [21]. Trojano at al. used in their study [14] the propensity score analysis which is the most common technique currently used in observational studies in order to reduce biases [22]. In our study, although our groups differed significantly in only one baseline variable, the number of relapses during 1 year prior to the start of IFN-beta therapy/first visit, propensity score analysis was also performed.

It has been emphasized that indication-to-treat bias should be adequately addressed in certain observational studies in order to obtain relevant conclusions [15, 23]. In our study, it was not necessary to consider the influence of indication-to-

Table 3 Results of analysis of the effects of interferon beta treatment to reach the three clinical endpoints in relapsing-remitting multiple sclerosis patients using the propensity score-adjusted Cox proportional hazard models

	Clinical endpoints					
	SP		EDSS score 4		EDSS score 6	
	HR* (95%CI)	*p*	HR* (95%CI)	*p*	HR* (95%CI)	*p*
IFN-beta treatment	0.22 (0.14–0.36)	< 0.001	0.40 (0.27–0.59)	< 0.001	0.27 (0.16–0.47)	< 0.001

SP, secondary progression; *EDSS*, Expanded Disability Status Scale; *HR*, hazard ratio; *95%CI*, confidence interval

*Adjusted by age at the first visit, the disease duration, gender, the number of relapses before the first visit, and the treatment status

Table 4 Predictive factors for secondary progression in relapsing-remitting multiple sclerosis (MS) patients using the Cox proportional hazard models

	Univariate analysis			Multivariate analysis		
	Variable			Variable		
	HR	95% CI	*p*	HR	95% CI	*p*
Interferon beta-treated MS patients						
Gender	0.89	0.42–1.87	0.751			
Age at onset	1.00	0.96–1.06	0.845			
Age at first visit	1.02	0.98–1.07	0.260			
Disease duration	1.03	0.98–1.09	0.266			
Number of relapses during 1 year prior to the start of IFN-beta therapy	0.99	0.69–1.44	0.998			
Baseline EDSS score (≤ 3.0 vs. ≥ 3.5)	5.87	2.77–12.44	*< 0.001*	6.30	2.93–13.52	*< 0.001*
Annualized relapse rate*	2.44	1.61–3.70	*< 0.001*	2.88	1.24–6.68	*0.014*
EDSS worsening**	7.49	3.45–16.24	*< 0.001*	2.89	1.16–7.21	*0.023*
NEDA***	2.99	1.47–6.09	*0.002*			
Untreated MS patients						
Gender	0.72	0.42–1.24	0.233			
Age at onset	1.03	1.02–1.06	*0.036*			
Age at first visit	1.04	1.01–1.07	*0.016*			
Disease duration	1.01	0.96–1.07	0.608			
Number of relapses during 1 year prior to the first visit	0.74	0.50–1.11	0.144			
Baseline EDSS score (≤ 3.0 vs. ≥ 3.5)	3.91	1.78–8.56	*0.001*	4.42	1.89–10.33	*0.001*
Annualized relapse rate*	1.05	0.69–1.62	0.805			
EDSS worsening**	3.66	2.05–6.54	*< 0.001*	5.94	3.13–3.93	*0.009*
NEDA***	2.27	1.02–5.06	*0.044*			

HR, hazard ratio; *95%CI*, 95% confidence interval. Italicized values denote statistical significance

*From baseline to year 2; **Baseline to year 2 increase in EDSS; ***No evidence of clinical disease activity, baseline to year 2

treat bias, since we were not able to offer treatment to the majority of our untreated patients, during the course of regular neurological 10-year follow-up.

Having in mind the potentially confounding biases which result from the patients excluded from the analysis, we paid special attention to this issue. Only three patients from our IFN-beta-treated group were lost to follow-up. Significantly higher attrition rate ($N = 50$) was registered in the untreated group, but the baseline characteristics of those who were retained in the study compared with those 50 patients lost to follow-up were similar.

Based on RCTs, it is not possible to assess the impact of IFN-beta on long-term outcomes. Therefore, extension trials and exploratory studies have been performed for various formulations of this drug [10, 24–28]. Recently, the results from an exploratory study of the correlation between cumulative exposures to Rebif with long-term clinical outcomes in RRMS patients have been published [8]. Patients were invited to a follow-up visit 15 years after randomization, and the findings from an extension study [24] were confirmed. In the maximum cumulative dose group, about 20% of patients converted to SPMS during 15 years, which is rather similar to our findings demonstrating that SPMS developed in about 14% of cases after 10-year follow-up. Consistently, after 7–8 [24] and 15-years of follow-up [25], it has been demonstrated that change in EDSS score from baseline to 24 months was predictor for higher likelihood of confirmed EDSS progression and SPMS conversion. Similarly, in 16-year follow-up study after the pivotal IFN-beta 1b RCTs, the change in EDSS score over the first 2 years, as well as ARR, in this period were demonstrated to be independent predictors of physical outcome [8, 11, 27]. MRI measures of atrophy and lesion burden were not demonstrated to be independent predictors of physical outcome in any of the abovementioned trials.

In our study, it has been demonstrated that patients with RRMS transitioned to SPMS after a mean time of 16.6 years for IFN-beta-treated and 11.3 years for untreated patients. Additionally, IFN-beta-treated patients developed an EDSS score of 6.0 after 16.7 years and untreated patients after 12.5 years. These findings are very similar to those from the recently published large, prospective study of 517 MS patients enrolled in a single tertiary referral center, followed over a 10-

Table 5 Predictive factors for reaching EDSS score ≥ 4.0 in relapsing-remitting multiple sclerosis (MS) patients using the Cox proportional hazard models

	Univariate analysis			Multivariate analysis		
	Variable			Variable		
	HR	95% CI	*p*	HR	95% CI	*p*
Interferon beta-treated MS patients						
Gender	1.26	0.72–2.22	0.419			
Age at onset	1.00	0.97–1.04	0.750			
Age at first visit	1.05	1.01–1.08	*0.003*			
Disease duration	1.06	1.02–1.10	*0.001*			
Number of relapses during 1 year prior to the prior to the start of IFN-beta therapy	0.98	0.76–1.28	0.910			
Baseline EDSS score (≤ 3.0 vs. ≥ 3.5)	4.84	2.66–8.82	*< 0.001*	4.26	2.31–7.86	*< 0.001*
Annualized relapse rate*	2.58	1.87–3.56	*< 0.001*	2.75	1.37–5.51	*0.004*
EDSS worsening**	8.15	4.45–14.95	*< 0.001*	3.18	1.61–6.31	*0.001*
NEDA***	3.26	1.97–5.40	*< 0.001*			
Untreated MS patients						
Gender	0.74	0.44–1.24	0.256			
Age at onset	1.03	0.99–1.06	0.094			
Age at first visit	1.03	0.99–1.06	0.056			
Disease duration	1.01	0.97–1.06	0.628			
Number of relapses during 1 year prior to the first visit	0.82	0.56–1.19	0.285			
Baseline EDSS score (≤ 3.0 vs. ≥ 3.5)	3.02	1.39–6.53	*0.005*	3.45	1.58–7.55	*0.002*
Annualized relapse rate*	1.04	0.68–1.60	0.849			
EDSS worsening**	3.19	1.80–5.63	*< 0.001*	3.70	2.07–6.63	*< 0.001*
NEDA***	2.33	1.10–4.91	*0.027*			

HR, hazard ratio; *95%CI*, 95% confidence interval; Italicized values denote statistical significance

*From baseline to year 2; **Baseline to year 2 increase in EDSS; ***No evidence of clinical disease activity, baseline to year 2

year period [29]. Included in this study were patients with all MS phenotypes, out of which about 40% were not treated with DMTs, and the great majority of the remaining with moderate efficacy DMTs. After a median time of 16.8 years since disease onset, 11.3% of relapsing MS patients of this cohort transitioned to SPMS during the course of the study. At the same time point, 10.7% of patients had reached an EDSS ≥ 6.0 [29].

During the last 20 years, a significant number of DMTs for RRMS were introduced on the basis of their high efficacy in RTCs. Unfortunately, controlled trials provide limited data about the comparative efficacy of DMTs [30, 31]. Until now, no DMT has shown to be effective in all persons with MS. Rapid detection of suboptimal response to a DMT is thus very important, in order to switch to an alternative highly efficacious agent. Therefore, we assume that in the certain proportion of patients in our cohort, a switch to some of the highly efficacious therapies should be considered in the near future.

We have decided to perform analysis using dichotomized baseline EDSS score as follows: ≤ 3.0 vs. ≥ 3.5 since it has been assumed that in MS, disability progression is a two-stage process with the first phase defined by the period until irreversible EDSS score 3.0 [32]. In accordance with the abovementioned findings from IFN-beta observational, extension and exploratory studies, in our treated and untreated groups, independent variables for all three outcomes were baseline EDSS score higher than 3 and the increase in EDSS over the first 2 years [25, 26, 33]. Additionally, it has to be emphasized that value of EDSS score 3.0 is not only clinically relevant for neurologists, patients, and healthcare providers but that also indicates exhaustion of compensatory mechanisms due to structural damage [34]. It has been demonstrated that ARR was clinically significant predictor for all three endpoints only in IFN-beta-treated group. This indicates that ARR correlated with worsening disability, and additionally since observed only in IFN-beta-treated cohort, this parameter seems to be a sensitive marker of the IFN-beta treatment response. Finally, having in mind these findings, it could be suggested that it might be important that in the choice of a first- or second-line treatment, a cut-off in the EDSS score should be also considered, and not only clinical or MRI activity.

Table 6 Predictive factors for reaching EDSS score ≥ 6.0 in relapsing-remitting multiple sclerosis (MS) patients using the Cox proportional hazard models

	Univariate analysis			Multivariate analysis		
	Variable			Variable		
	HR	95% CI	*p*	HR	95% CI	*p*
Interferon beta-treated MS patients						
Gender	0.73	0.33–1.64	0.451			
Age at onset	0.98	0.92–1.04	0.449			
Age at first visit	1.01	0.97–1.06	0.560			
Disease duration	1.03	0.97–1.10	0.297			
Number of relapses during 1 year prior to the start of IFN-beta therapy	1.00	0.67–1.51	0.990			
Baseline EDSS score (≤ 3.0 vs. ≥ 3.5)	4.28	1.73–10.35	*0.001*	6.38	2.45–16.59	*< 0.001*
Annualized relapse rate*	2.89	1.85–4.51	*< 0.001*	6.81	2.84–16.31	*< 0.001*
EDSS worsening**	8.70	3.86–19.58	*< 0.001*	3.13	1.21–8.11	*0.019*
NEDA***	2.83	1.30–6.19	*0.009*			
Untreated MS patients						
Gender	0.90	0.47–1.73	0.757			
Age at onset	1.03	0.99–1.06	0.110			
Age at first visit	1.04	1.00–1.70	*0.048*			
Disease duration	0.98	0.92–1.05	0.654			
Number of relapses during 1 year prior to the first visit	0.76	0.47–1.22	0.261			
Baseline EDSS score (≤ 3.0 vs. ≥ 3.5)	2.84	1.11–7.25	*0.029*	3.42	1.30–9.02	*0.013*
Annualized relapse rate*	1.42	0.87–2.34	0.164			
EDSS worsening**	3.81	2.01–7.24	*< 0.001*	4.43	2.30–8.55	*< 0.001*
NEDA***	1.98	0.77–5.07	0.155			

HR, hazard ratio; *95%CI*, 95% confidence interval; Italicized values denote statistical significance

*From baseline to year 2; **Baseline to year 2 increase in EDSS; ***No evidence of clinical disease activity, baseline to year 2

Our study has certain limitations that have to be addressed. It is generally accepted that observational study design is strongly affected by an immortal time bias. Thus, our study is affected by a selection bias due to the exclusion of the immortal time. Preferably, the baseline date should have been the same for both groups and then the treatment should be included as a time-dependent covariate in the time-to-event models. Additionally, this single-center observation cohort is moderate in size. Furthermore, in our study, the attrition rate was high (27.6%) in the untreated group. However, untreated patients lost to follow-up were generally similar to those maintained in the study. Finally, it has to be emphasized that brain MRI parameters have not been available in our study. Although they are the most widely studied short-term variables to predict long-term response to IFN-beta, findings related to their predictive value are inconsistent [35].

In conclusion, even though until now the findings related to the association between IFN-beta therapy and long-term disability are not completely consistent, this observational study might further support its beneficial effect on natural history via delaying clinical worsening in RRMS patients, already demonstrated in a number of previous studies [14, 16, 24, 25, 27, 28]. Detection of prognostic factors that may predict a beneficial long-term outcome is warranted in order to conduct a successful decision-making process.

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Compliance with ethical standards

The study was approved by the Ethics Committee of the Faculty of Medicine University of Belgrade. Participants provided informed consent.

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