# A 8-year retrospective cohort study comparing Interferon-β formulations for relapsing-remitting multiple sclerosis

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## Introduction

Interferon-β is one of the oldest and still frequently prescribed medications for the treatment of relapsing-remitting (RR) multiple sclerosis (MS). Meta-analytic studies found different Interferon-β formulations being similar in efficacy on relapses, whereas no definite results were presented for disability progression. However, long-term studies directly comparing the three main Interferon-β formulations have never been conducted so far. Therefore, the present propensity score-adjusted cohort study evaluated the clinical evolution of newly diagnosed RRMS patients during 8-year treatment with different Interferon-β formulations.

## Methods

The present mono-centric retrospective observational cohort study has been conducted on prospectively collected data.
Inclusion criteria: 1) new diagnosis of clinically-definite RRMS from January 2001 to January 2010; 2) use of Interferon-β as first prescribed DMT after diagnosis, in accordance with the indications for clinical practice of the Italian regulatory agency.
Exclusion criteria: 1) age at diagnosis <18 years; 2) incomplete clinical records; 3) previous use of DMTs.
Treatment groups: 1) high-dose high-frequency Interferon-β1a 44mcg sc (Rebif 44®); 2) low-dose low-frequency Interferon-β1a 30mcg (Avonex®); 3) high-dose high-frequency Interferon-β1b 250mcg (Betaferon®).
Clinical outcomes: occurrence of clinical relapses, annualized relapse rate (ARR), 1-point expanded disability status scale (EDSS) progression, reaching of EDSS 4.0, transition from RR to secondary progressive (SP) MS.
Statistical analyses: Cox proportional hazard regression models were used to estimate the rate of clinical outcomes, in different treatment groups. Poisson regression model was used to measure differences in ARR between treatments. Covariates were age, gender, disease duration and baseline EDSS. Also, we estimated three sets of propensity score (PS) variables based on the probability of patients being selected for a specific treatment, which were used as additional covariates. The PS variables were developed using three logistic regression models entering the following variables in the models: age, gender, disease duration, and baseline EDSS. Results have been considered statistically significant if $p<0.05$. Stata 14.0 has been used for data analysis. Statistician was blind to treatment codes.

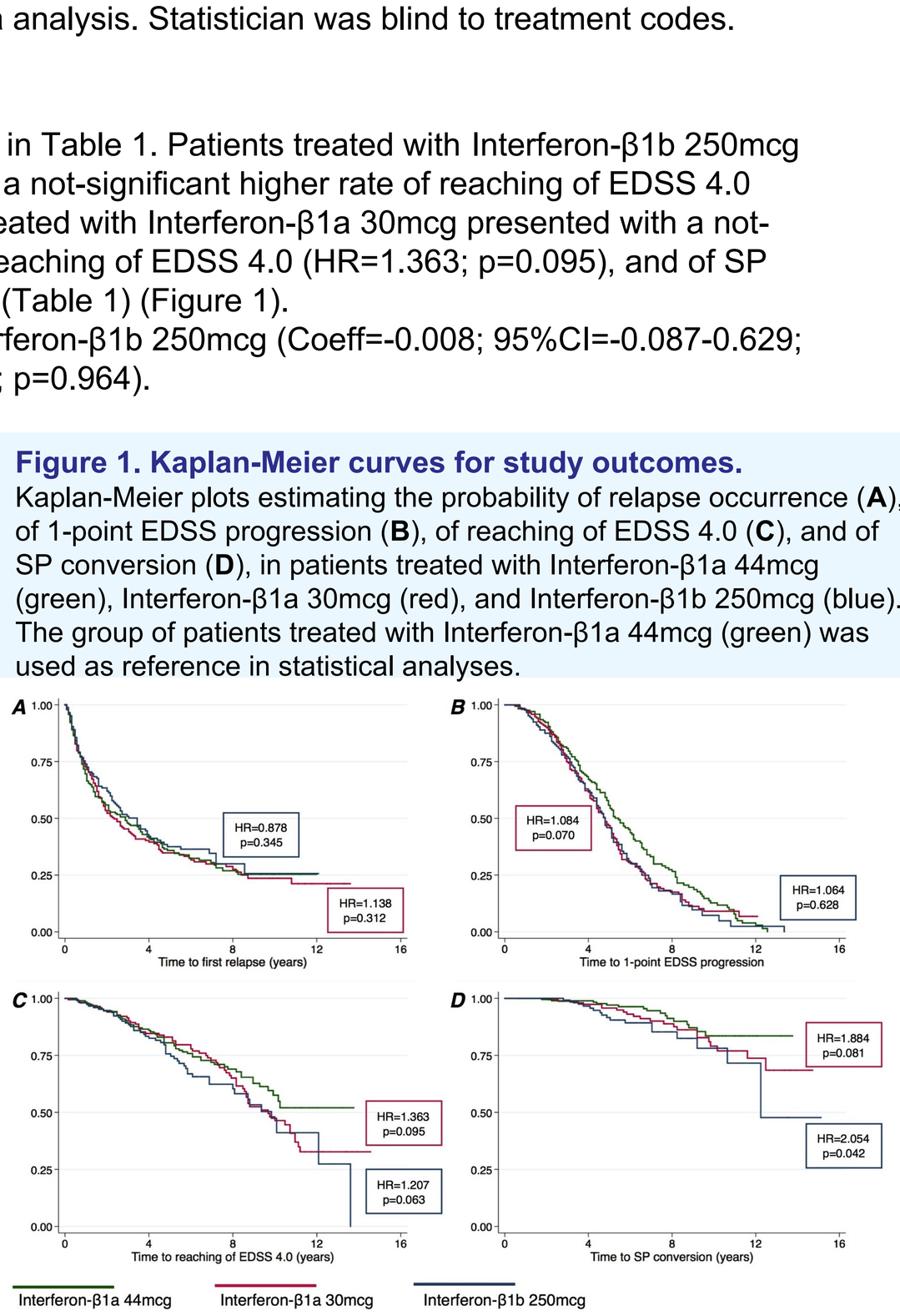
## Results

Demographic features, clinical findings and treatment variables are presented in Table 1. Patients treated with Interferon-β1b 250mcg presented with a higher rate of SP conversion (HR=2.054; p=0.042), and with a not-significant higher rate of reaching of EDSS 4.0 (HR=1.207; p=0.063), when compared with Interferon-β1a 44mcg. Patients treated with Interferon-β1a 30mcg presented with a not-significant higher rate of 1-point EDSS progression (HR=1.084; p=0.070), of reaching of EDSS 4.0 (HR=1.363; p=0.095), and of SP conversion (HR=1.884; p=0.081), when compared with Interferon-β1a 44mcg (Table 1) (Figure 1).
ARR of patients treated with Interferon-β1a 44mcg was not different from Interferon-β1b 250mcg (Coeff=-0.008; 95%CI=-0.087-0.629; p=0.139), and from Interferon-β1a 30mcg (Coeff=0.002; 95%CI=-0.389-0.372; p=0.964).

**Table 1. Demographic features and clinical findings.**

| | Interferon-β1a 44mcg (reference) (n=191, 37.6%) | Interferon-β1a 30mcg (n=168, 33.4%) | HR | 95%CI Lower | 95%CI Upper | p-values | Interferon-β1b 250mcg (n=148, 29.0%) | HR | 95%CI Lower | 95%CI Upper | p-values |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Age**, *years* | 32.3±7.8 | 34.2±8.5 | | | | | 31.4±8.3 | | | | |
| **Gender**, *female (%)* | 123 (64.4%) | 104 (61.9%) | | | | | 93 (62.8%) | | | | |
| **Disease duration at diagnosis**, *years* | 2.7±2.8 | 2.8±2.7 | | | | | 2.5±2.7 | | | | |
| **EDSS at diagnosis**, *median (min-max)* | 1.5 (1.0-3.5) | 1.5 (1.0-3.5) | | | | | 1.5 (1.0-3.5) | | | | |
| **Study duration**, *years* | 9.0±4.3 | 8.8±3.6 | | | | | 8.4±3.7 | | | | |
| **Annualized relapse rate** | 0.32±0.59 | 0.35±0.43 | | | | | 0.34±0.47 | | | | |
| **Relapse occurrence** *(%)* | 131 (68.5%) | 120 (71.0%) | 1.138 | 0.885 | 1.464 | 0.312 | 93 (62.8%) | 0.878 | 0.671 | 1.149 | 0.345 |
| **Time to first relapse**, *years* | 4.3±4.2 | 4.1±3.4 | | | | | 3.9±3.2 | | | | |
| **1-point EDSS progression** *(%)* | 154 (81.0%) | 135 (80.3%) | 1.084 | 0.827 | 1.369 | 0.070 | 104 (70.2) | 1.064 | 0.827 | 1.369 | 0.628 |
| **Time to 1-point EDSS progression**, *years* | 6.6±3.4 | 5.8±3.2 | | | | | 5.5±2.7 | | | | |
| **Reaching of EDSS 4.0** *(%)* | 60 (31.4%) | 65 (38.5%) | 1.363 | 0.947 | 1.963 | 0.095 | 51 (34.6%) | 1.207 | 0.828 | 1.761 | 0.063 |
| **Time to reaching of EDSS 4.0**, *years* | 8.5±3.9 | 7.1±3.4 | | | | | 7.1±3.7 | | | | |
| **SP conversion** *(%)* | 16 (8.3%) | 22 (13.0%) | 1.884 | 0.925 | 3.834 | 0.081 | 17 (11.5%) | 2.054 | 1.026 | 4.110 | 0.042* |
| **Time to SP conversion**, *years* | 9.3±4.1 | 7.9±3.4 | | | | | 7.3±3.5 | | | | |

**Figure 1. Kaplan-Meier curves for study outcomes.**
Kaplan-Meier plots estimating the probability of relapse occurrence (**A**), of 1-point EDSS progression (**B**), of reaching of EDSS 4.0 (**C**), and of SP conversion (**D**), in patients treated with Interferon-β1a 44mcg (green), Interferon-β1a 30mcg (red), and Interferon-β1b 250mcg (blue). The group of patients treated with Interferon-β1a 44mcg (green) was used as reference in statistical analyses.




## Conclusions

The present study compared the clinical efficacy of different labeled formulations of Interferon-β, and showed that patients treated with Interferon-β1a 44mcg presented with a marginally reduced risk of disability accrual in the long-term, when compared with Interferon-β1a 30mcg and Interferon-β1b 250mcg. Formulation, frequency of administration and dose of Interferon-β might affect the long-term clinical evolution of RRMS. Therefore, in the clinical practice, MS physicians, patients and caregivers have to balance the more convenient and possibly better tolerated low-dose low-frequency regimen, with the long-term risk of disease evolution.

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