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

Marcello Moccia[a,*], Raffaele Palladino[b,c], Antonio Carotenuto[a], Francesco Saccà[a], Cinzia Valeria Russo[a], Roberta Lanzillo[a], Vincenzo Brescia Morra[a]

[a] Multiple Sclerosis Clinical Care and Research Centre, Department of Neurosciences, Reproductive Sciences and Odontostomatology, Federico II University, Via Sergio Pansini, 5 – Building 17, Ground floor, Naples, Italy
[b] Department of Primary Care and Public Health, Imperial College, London, United Kingdom
[c] Department of Public Health, Federico II University, Naples, Italy

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ABSTRACT

Background: Interferon-β has been approved for the treatment of relapsing-remitting (RR) multiple sclerosis (MS), whereas its efficacy in preventing long-term disability and conversion to secondary progressive (SP) MS is still debated. We aim to compare long-term clinical evolution of newly-diagnosed RRMS patients treated with different Interferon-β formulations.

Methods: 507 patients were included in the analysis and followed-up for 8.5 ± 3.9 years. 37.6% were treated with subcutaneous Interferon-β1a 44 mcg, 33.4% with intramuscular Interferon-β1a 30 mcg, and 29.0% with subcutaneous Interferon-β1b 250 mcg. Relapse occurrence, 1-point EDSS progression, reaching of EDSS 4.0 and conversion to SP were recorded as outcome measures. To reduce the selection bias, we calculated the propensity score of receiving the specific treatment considering age (32.7 ± 8.3 years), gender (female 63.1%), disease duration (2.7 ± 2.8 years), and baseline EDSS (1.5, range 1.0–3.5). Propensity score and covariates (age, gender, disease duration and EDSS) were included in the statistical models.

Results: At Cox regression models, the reaching of EDSS 4.0 was not-significantly higher for Interferon-β1b 250 mcg (HR = 1.207; p = 0.063) and for Interferon-β1a 30 mcg (HR = 1.363; p = 0.095), when compared with Interferon-β1a 44 mcg. The rate of SP conversion was higher for Interferon-β1b 250 mcg (HR = 2.054; p = 0.042), and not-significantly higher for Interferon-β1a 30 mcg (HR = 1.884; p = 0.081), when compared with Interferon-β1a 44 mcg.

Conclusions: Patients treated with Interferon-β1a 44 mcg presented with a marginally reduced risk of disability accrual in the long-term, when compared with Interferon-β1b 250 mcg and, at least in part, with Interferon-β1a 30 mcg. Formulation, frequency of administration and dose of Interferon-β might affect the long-term clinical evolution of RRMS.

1. Introduction

Multiple sclerosis (MS) usually starts with a relapsing-remitting (RR) course, and eventually converts to a phase of progressive disability accrual, namely secondary progressive (SP) MS (Lublin et al., 2014). Currently available disease modifying treatments (DMT) have proven to reduce amount and severity of relapses in RRMS (Agenzia Italiana, 2016; Goodin et al., 2012a). However, natural history studies showed a dissociation between relapses and disability progression in the long-term (Scalfari et al., 2010; Río et al., 2017), and, accordingly, the benefit of DMTs on disability progression is still uncertain (Fogarty et al., 2016; Zhang et al., 2015). Evidence of DMT efficacy is based on randomized clinical trials conducted during relatively short observation time, not detecting long-term disease outcomes (Goodin et al., 2012a). Their long-term extension has shed light on the importance of early and continuous treatment, but failed to show any definite comparative result on clinical efficacy, as being open-label (Goodin et al., 2012b; Ebers et al., 2010).

Interferon-β is one of the oldest and still frequently prescribed medications for the treatment of RRMS. Meta-analytic studies found different Interferon-β formulations being similar in efficacy on relapses, whereas no definite results were presented for disability progression (Fogarty et al., 2016; Mendes et al., 2016; Einarson et al., 2017; Kalincik et al., 2015; Newsome et al., 2017). A pooled analysis

* Corresponding author.
E-mail address: moccia.marcello@gmail.com (M. Moccia).

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suggested a reduction of the risk of disability progression for the use of Interferon-β, compared with no treatment (Signori et al., 2016), but 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.

2. Methods

2.1. Study design

The present mono-centric retrospective observational cohort study has been conducted on prospectively collected data, recorded in the clinical database of the Multiple Sclerosis Clinical Care and Research Centre at the "Federico II" University of Naples, Italy. Data were entered by physicians specifically trained in MS and were checked in terms of quality by senior physicians.

In compliance with current Italian applicable laws and regulations, considering that all clinical assessments were part of clinical practice in a university setting and that the retrospective analysis included anonymized data, specific ethics approval was not required. All subjects signed the general informed consent form, authorizing the use of personal data for research purposes, as approved by the Ethics Committee of the "Federico II" University of Naples, Italy. The study was performed in accordance with good clinical practice and Declaration of Helsinki.

2.2. Population

Inclusion criteria were: 1) new diagnosis of clinically-definite RRMS from January 2001 to January 2010 (McDonald et al., 2001); 2) use of Interferon-β as first prescribed DMT after diagnosis, in accordance with the indications for clinical practice of the Italian regulatory agency (Agenzia Italiana, 2016).

Exclusion criteria were: 1) progressive forms of MS at baseline (Lublin et al., 2014); 2) age at diagnosis < 18 years; 3) incomplete clinical records; 4) previous use of DMTs.

2.3. Treatment variables

Newly diagnosed RRMS patients eligible for Interferon-β treatment, received their first medication supply with instructions for the administration from a trained nurse within one month from the diagnosis. No specific criteria were applied in selecting the formulation; patients had the opportunity to discuss pros and cons of available treatments with physicians and nurses, and were given a prescription for the preferred. Clinical evaluations were scheduled according to clinical practice (every 3–6 months). Patients were included in the study up to their last moment of continuous treatment with the same Interferon-β formulation, in order to evaluate the separate contribution of each regimen on the clinical evolution.

Patients were grouped in relation to the prescribed Interferon-β: 1) high-dose high-frequency subcutaneous Interferon-β1a 44 mcg (Rebif 44®) (Interferon-β1a 44 mcg sc); 2) low-dose low-frequency intramuscular Interferon-β1a 30 mcg (Avonex®) (Interferon-β1a 30 mcg); 3) high-dose high-frequency subcutaneous Interferon-β1b 250 mcg (Betaferon®) (Interferon-β1b 250 mcg).

2.4. Clinical outcomes

Clinical assessments were performed by physicians specifically trained in MS and qualified for expanded disability status scale (EDSS) assessments. During the study period, following endpoints of MS evolution were recorded (Runmarker and Andersen, 1993):

- Occurrence of clinical relapses (time to the first relapse on treatment and annualized relapse rate -ARR- during the whole observation period were calculated);
- 1-point expanded disability status scale (EDSS) progression (independently from relapses and sustained for 12 months);
- Reaching of EDSS 4.0 (independently from relapses and sustained for 12 months);
- Transition from RR to SP course (MS was considered SP when a progressive accumulation of disability occurred after an initial relapsing course, and was associated with a worsening of the same functional system, independently from relapse activity) (Lublin et al., 2014).

Observation period was extended to 12 months in order to confirm the reaching of disability outcomes independently from clinical relapses that, if occurring within the period of interest, were required to involve a functional system different from that being involved by progression.

2.5. Statistical analyses

Means and proportions of demographic features and clinical findings were calculated for the MS population, and were compared among DMT subgroups (Interferon-β1a 44 mcg, Interferon-β1a 30 mcg, and Interferon-β1b 250 mcg) with χ^2 test, or analysis of variance (ANOVA) with *post-hoc* Bonferroni Correction, as appropriate. The group of patients treated with Interferon-β1a 44 mcg was considered the reference for statistical analysis.

Time-to-event Cox proportional hazard regression models were performed to estimate differences in rates of relapse occurrence (time to the first relapse), 1-point EDSS progression, reaching of EDSS 4.0, and conversion to SP, in different treatment groups. Hazard ratio (HR) and 95% confidence intervals (95%CI) are presented.

Poisson regression model was used to measure differences in ARR between treatments. Coefficient (Coeff) and 95%CI are presented.

Covariates included in the statistical models were demographic characteristics (age, gender), disease duration (time occurring from first reported symptom to diagnosis and subsequent DMT start), and baseline EDSS.

In order to reduce this source of bias, we estimated three sets of propensity score variables based on the probability of patients being selected for a specific treatment. The propensity score variables were developed using three logistic regression models (Interferon-β1a 44 mcg *vs* Interferon-β1a 30 mcg; Interferon-β1a 44 mcg *vs* Interferon-β1b 250 mcg; Interferon-β1a 30 mcg *vs* Interferon-β1b 250 mcg), entering the following variables in the models: age, gender, disease duration, and baseline EDSS. The propensity score variables were used as additional covariates in the regression models for each study outcome. Considering that we included newly-diagnosed patients, no reliable data were available before baseline visit.

Results have been considered statistically significant if $p < 0.05$. Stata 14.0 has been used for data processing and analysis. Statistician was blind to treatment codes.

3. Results

685 subjects received a new diagnosis of MS during the study period. Among them, 507 RRMS patients were included in the analysis, and followed-up for 8.5 ± 3.9 years. Reasons for exclusion were: first DMT different from Interferon-β (n = 91), progressive disease course at diagnosis (n = 42), age < 18 years (n = 21), incomplete records (n = 23).

Demographic features, clinical findings and treatment variables are presented in Table 1.

At diagnosis, treatment groups were similar in gender distribution ($p = 0.884$), disease duration ($p = 0.522$), and EDSS ($p = 0.320$), but were different in age ($p = 0.007$). Interferon-β1a 44 mcg patients were