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Clinical Study

# Predictors of first-line treatment persistence in a Portuguese cohort of relapsing-remitting multiple sclerosis

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ABSTRACT

Treatment persistence in first-line injectable disease-modifying therapies (DMT) for relapsing-remitting multiple sclerosis (RRMS) is an important indicator of effectiveness. Identifying predictors of treatment discontinuation is important as there are other therapies currently available and a growing range of emerging drugs. We report a retrospective study of RRMS and clinically isolated syndrome patients followed in a University Hospital during a 13-year period with the objective of identifying predictors of treatment persistence. An evaluation of persistence on the first DMT, rates of DMT discontinuation, and reasons and predictors of discontinuation was performed. A total of 410 patients were included, 69% female, with mean disease duration of 37.8 months, mean age of 34.2 years and mean follow-up time of 6.1 years. The first DMT was glatiramer acetate (GA) in 27.56% of patients, interferon (IFN) β-1a intramuscular in 26.34%, IFNβ-1b in 26.10%, IFNβ-1a22 in 13.66% and IFNβ-1a44 in 6.34%. Treatment was discontinued in 16.34% of patients after 1 year of treatment and in 50.24% of patients in the total follow-up time, with a mean time for discontinuation of 39.80 months. Higher baseline Expanded Disability Status Scale score was an independent predictor of treatment discontinuation (hazard ratio 1.35, $p = 0.002$). After the first year, treatment persistence was 90.74% for IFNβ-1a-IM, 88.46% for IFNβ-1a44, 83.18% for IFNβ-1b, 83.19% for GA and 69.64% for IFNβ-1a22 ($p = 0.014$). Lower frequency of administration was associated with higher persistence rates. The most common reason for treatment discontinuation was lack of efficacy in all DMT subgroups.



## 1. Introduction

Treatment effectiveness encompasses the effect of treatment under everyday conditions of care, resulting from a combination of efficacy, safety, tolerability and patient satisfaction. Therefore, treatment persistence is considered an important indicator of effectiveness.

Injectable disease-modifying therapies (DMT) were, until recently, the only first-line treatments approved for relapsing-remitting multiple sclerosis (RRMS). In the pivot clinical trials of this drugs, the rates of DMT persistence at the end of first year ranged from 90% to 97% [1–4]. However, these results may not be adequately extrapolated to the real world population, as lower rates of treatment persistence have been reported in post-marketing studies, with real-world studies describing rates of treatment persistence from 78.5% to 90% after one year and dropping to 59% to 72% between the third and fifth year of treatment, with discontinuation occurring mainly due to side effects and lack of efficacy [5–8].

In this article, we present a retrospective study of RRMS and clinically isolated syndrome (CIS) patients with the objective of assessing treatment persistence for the first DMT and evaluating the reasons and possible predictors of treatment discontinuation.

## 2. Materials and methods

This is a retrospective study including patients with RRMS, according to McDonald Criteria of 2010, and CIS, followed in the multiple sclerosis (MS) outpatient clinic of a university hospital.

The study included treatment naïve patients who were started on first line DMT between 2000 and 2013. The following subgroups of DMT were used: glatiramer acetate (GA), Interferon (IFN) β-1a intramuscular (IM), IFNβ-1a22, IFNβ-1a44 or IFNβ-1b.

Exclusion criteria included previous exposure to other treatments, including immunosuppressive drugs (such as azathioprine, mycophenolate mophetil, cyclophosphamide, mitoxantrone or

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methotrexate) and other DMT approved for RRMS (such as natalizumab, fingolimod or alemtuzumab), and previous inclusion in clinical trials.

Clinical evaluation of the patients was performed in the outpatient clinic with 6-month intervals and all the data collected was recorded in our MS consultation database using the program iMED®.

Data collected comprised demographic data, including sex, age at diagnosis and age at first treatment, clinical data, including disease duration, clinical presentation,relapses and disability score assessed by the Expanded Disability Status Scale (EDSS) and treatment data, including first DMT used and treatment adverse events. First DMT treatment persistence, defined as months of continuous use of the first DMT, and reasons for treatment discontinuation were assessed.

Treatment discontinuation due to lack of efficacy was defined by the treating physician in a standard manner, and considered when there was disability progression, relapses or increase in MRI lesion load. Treatment discontinuation due to adverse events was considered when treatment was stopped or switched due to important systemic or local reactions or infections. Pregnancy was considered a reason for treatment discontinuation in patients who stopped treatment because of pregnancy or while attempting conception.

Accurate annualized relapse rate previous to the first DMT was not available in many patients and therefore was not included in the analysis.

Demographic characteristics are presented as means and standard deviations for continuous variables, and as frequencies and percentages for categorical variables. Patient EDSS is described as mean and standard deviation.

In our sample all the variables have a non-normal distribution, except for age at MS diagnosis and age at DMT start, therefore non-parametric tests were used. Wilcoxon Signed Ranks Test was used to compare related samples, the Mann–Whitney Test to compare different groups of patients and multivariable survival analyses were used to identify predictors of treatment discontinuation. Statistical significance was considered when $p < 0.05$, and 95% confidence intervals (CI) were used in the graphs. IBM SPSS Statistics® (version 20.0) (IBM, Armonk, NY, USA) was used for the statistical analysis.

## 3. Results

From a global population of 966 patients followed in our MS outpatient clinic, 410 RRMS and CIS treatment-naïve patients were started on a first line DMT between 2000 and 2013 and were included in the study.

### 3.1. Patient demographics

All the patients had Caucasian background, 68.54% (n = 281) were female, the mean disease duration at treatment start was 37.8 months and the mean age at first treatment was 34.2 years. The mean follow-up time was 6.1 ± 4.0 years.

Table 1 presents more details about the patient demographics and also clinical presentation and EDSS at baseline.

The first treatment was glatiramer acetate (GA) in 113 patients (27.56%), Interferon β (IFNβ)-1a intramuscular (IFNβ-1aIM) in 108 patients (26.34%), IFNβ-1b in 107 patients (26.10%), IFNβ-1a22 in 56 patients (13.66%) and IFNβ-1a44 in 26 patients (6.34%).

Comparing the DMT subgroups, it was noted a tendency to lower age at disease onset of GA patients (31.17 ± 10.54 years, $p = 0.051$) and a higher baseline EDSS in the IFNβ-1b (2.56 ± 1.12) and IFNβ-1a22 (2.33 ± 0.98) subgroups ($p < 0.001$) (Table 1).

**Table 1**
Baseline characteristics of patients with RRMS commencing first-line treatment with DMT

| | All DMT (n = 410) | GA (n = 113) | IFNβ-1aIM (n = 108) | IFNβ-1b (n = 107) | IFNβ-1a22 (n = 56) | IFNβ-1a44 (n = 26) | p value |
|---|---|---|---|---|---|---|---|
| Follow-up time, years (SD) | 6.07 (±3.98) | 5.56 (±4.11) | 5.98 (±3.48) | 6.34 (±4.11) | 6.80 (±4.12) | 6.04 (±4.48) | 0.375 |
| Female, n (%) | 281 (68.54) | 87 (76.99) | 71 (65.74) | 66 (61.68) | 39 (69.64) | 18 (69.23) | 0.162 |
| Age at RRMS diagnosis, years (SD) | 34.30 (±14.02) | 31.17 (±10.54) | 35.66 (±10.78) | 36.51 (±20.73) | 34.04 (±10.70) | 33.81 (±8.43) | 0.051 |
| Age at first treatment, years (SD) | 34.78 (±10.46) | 32.54 (±10.22) | 36.42 (±10.72) | 35.32 (±10.56) | 35.13 (±10.67) | 34.69 (±8.49) | 0.085 |
| Disease duration since diagnosis at treatment start, months (SD) | 4.23 (±14.03) | 5.36 (±14.65) | 3.68 (±13.01) | 1.59 (±3.45) | 7.50 (±23.30) | 5.42 (±15.07) | 0.549 |
| EDSS at treatment start (SD) | 2.14 (±0.96) | 1.98 (±0.95) | 1.86 (±0.67) | 2.56 (±1.12) | 2.33 (±0.98) | 1.95 (±1.12) | <0.001[#] |
| Presentation[*], n (%) | | | | | | | |
| Supratentorial | 59 (18.61) | 18 (18.75) | 14 (17.95) | 12 (15.0) | 14 (29.79) | 1 (6.25) | 0.191 |
| Optic pathways | 69 (21.77) | 25 (26.04) | 14 (17.95) | 17 (21.25) | 7 (14.89) | 6 (37.50) | |
| Infratentorial | 76 (23.97) | 23 (23.96) | 27 (34.62) | 16 (20.0) | 8 (17.02) | 2 (12.50) | |
| Spinal | 77 (24.29) | 19 (19.79) | 18 (23.08) | 25 (31.25) | 10 (21.28) | 5 (31.25) | |
| Multiple systems | 36 (11.36) | 11 (11.46) | 5 (6.41) | 10 (12.50) | 8 (17.02) | 2 (12.5) | |

[#] p value <0.05 was considered statistically significant.
[*] Incomplete data.
DMT = disease-modifying therapy, EDSS = Expanded Disability Status Scale, GA = glatiramer acetate, IFN = interferon, IM = intramuscular, n = number, RRMS = relapsing-remitting multiple sclerosis, SD = standard deviation.