Multiple Sclerosis and Related Disorders 10 (2016) 90–96

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard

Predictors of long-term interferon discontinuation in newly diagnosed relapsing multiple sclerosis

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ARTICLE INFO

Keywords:
Multiple sclerosis
Interferon
Persistence
Discontinuation
Longitudinal

ABSTRACT

Background: Interferon-β has long-term safety and efficacy profiles for Relapsing Remitting Multiple Sclerosis (RRMS). However, the increasing number of available treatments requires to improve patient profiling and to perform individualized clinical decisions. Therefore, the present study investigated predictors of Interferon-β discontinuation.

Methods: The present retrospective observational cohort study included 499 newly diagnosed, drug naïve RRMS subjects receiving Interferon-β as first disease modifying treatment (DMT), during a 7.9 ± 3.8 year period, up to treatment discontinuation. Possible markers of interest were recorded at the time of diagnosis (age, gender, disease duration, baseline EDSS) or during follow-up as variables of disease evolution (relapse occurrence, annualized relapse rate -ARR-, 1-point EDSS progression, reaching of EDSS 4.0) or of treatment (high-dose Interferon-β1a, low-dose Interferon-β1a, or Interferon-β1b).

Results: 217 patients (43.5%) discontinued the treatment during the follow-up period, with an incidence of 5% person-years (95%CI=4.6–5.9%). A multivariate Cox regression model showed an increased rate of Interferon-β discontinuation for female gender (p=0.019; HR=1.428), higher baseline EDSS (p=0.026; HR=1.346), relapse occurrence (p=0.009; HR=1.618), higher ARR (p < 0.001; HR=5.269), and Interferon-β1b treatment (p=0.019; HR=1.506); and a reduced rate for occurrence of EDSS progression (p < 0.001; HR=0.299).

Conclusions: Most of the factors associated with Interferon-β discontinuation are not modifiable, and are part of demographic features (i.e. gender), or of disease characteristics (i.e. disability at diagnosis), but should be taken into account when prescribing the first DMT for MS. Noteworthy, the use of Interferon-β1b is associated with 50% increased risk of discontinuation, compared with high-dose Interferon-β1a, highlighting the importance of drug formulations in treatment persistence.

1. Introduction

Clinical trials and real life studies have been showing that Interferon-β1a and Interferon-β1b provide multiple sclerosis (MS) patients with remarkable benefits on long-term disability outcomes (Trojano et al., 2009; Bates, 2011; Plosker, 2011), and have acceptable safety profiles (Reder et al., 2010; Sørensen, 2011; Saida et al., 2016; Signori et al., 2016). Accordingly, neurologists are usually confident in prescribing Interferon-β as a first-line treatment for the vast majority of patients who develop Relapsing-Remitting (RR) MS (Sørensen, 2011). Nevertheless, Interferon-β possibly might also reduce the risk of conversion to secondary progressive MS (SPMS) (Trojano et al., 2007).

However, most patients may still present signs of disease activity, sometimes requiring more aggressive and expensive therapeutic strategies (Goodin, 2008; Sørensen, 2011; Moccia et al., 2016b). Furthermore, considering the need for long term use of disease modifying treatments (DMTs), tolerability and adverse events can represent a significant concern, with substantial effects on treatment adherence (Goodin et al., 2012; Reder et al., 2014; Lanzillo et al., 2015; Moccia et al., 2015). In addition, the development of new therapies for MS, with different benefits and risks, requires an accurate evaluation of factors possibly predicting optimal long-term response, in order to use the most appropriate and individualized treatment (Sørensen, 2011;

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http://dx.doi.org/10.1016/j.msard.2016.09.011
Received 8 June 2016; Received in revised form 25 September 2016; Accepted 27 September 2016

Sormani and De Stefano, 2013; Hartung et al., 2015). Indeed, if the presence of a therapeutic window of opportunity is assumed, the identification of early predictors (i.e. demographic features or clinical characteristics) of poor response to Interferon-β is expected to facilitate treatment decisions, possibly also reducing future disability accrual (Bermel et al., 2010; Du Pasquier et al., 2014; Hartung et al., 2015; Ziemssen et al., 2016).

Therefore, the possibility to predict Interferon-β discontinuation remains an unmet need in MS clinical care and research, and, so far, has been investigated only in two long-term studies (Evans et al., 2012; Zhornitsky et al., 2015). However, these investigations recruited heterogeneous MS populations with different courses of the disease, with the use of variable diagnostic criteria, and occasionally dating from periods without many therapeutical options. Nevertheless, only a limited number of demographic features (age, gender) and disease characteristics (disease duration, EDSS at first DMT) have been evaluated (Evans et al., 2012; Zhornitsky et al., 2015), whereas nowadays different markers of long-term disease evolution and treatment response have been identified (Sormani and De Stefano, 2013). In view of this, the present retrospective study has been conducted in a longitudinal cohort of newly diagnosed, drug naïve RRMS patients with an average follow-up of 8 years, and aims at evaluating predictors of Interferon-β discontinuation that have been determined at the time of the diagnosis and during the course of MS.

2. Methods

2.1. Study design

The present retrospective observational cohort study evaluated markers associated with the risk of discontinuing Interferon-β treatment among newly diagnosed, drug naïve MS subjects.

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. The study was performed in accordance with good clinical practice and Declaration of Helsinki.

2.2. Patients

Inclusion criteria were: 1) new diagnosis of RRMS from January 2001 to January 2010, at the MS Clinical Care and Research Centre of the Federico II University Hospital (Naples, Italy), according to McDonald 2001 criteria (McDonald et al., 2001; Lublin et al., 2014); 2) prescription of Interferon-β1a (high-dose or low-dose) or Interferon-β1b as first DMT for MS; 3) presence of at least 5 year clinical follow-up or discontinuation of the first DMT before that period; 4) age at baseline > 18.

Exclusion criteria were: 1) progressive forms of MS at the time of enrolment (Lublin et al., 2014); 2) pregnancy during the study period. Indeed, pregnancy does not only cause Interferon-β discontinuation, but can also result in a more benign clinical course, possibly affecting study results (Jokubaitis et al., 2016).

Due to the retrospective nature of the study, all MS subjects underwent DMTs, which were possibly discontinued during the study period, in accordance with the European Medicines Agency indications for clinical practice (EMA, 2015), and, so, as a consequence not only of suboptimal treatment effect but also of adverse events or low tolerability. Follow-up visits were scheduled at three-month intervals, or on the occasion of relapse.

2.3. Discontinuation of Interferon-β1a/b

Discontinuation of Interferon-β1a/b treatment was defined as a > 90-day interruption in therapy, a switch to another first- or second-line therapy (i.e. Glatiramer acetate, Natalizumab, or Fingolimod), or complete discontinuation (i.e. no further record of medication initiation). The cohort was categorized as discontinuing or not the first DMT. To be more precise, switching from one Interferon-β1a dose to another was considered as discontinuation (i.e. from low-dose once weekly regimen, to high-dose three times a week). Switching between different branded versions of Interferon-β1b was not considered as discontinuation. Switching from Interferon-β1a to β1b formulations was considered as discontinuation (Evans et al., 2012; Zhornitsky et al., 2015).

Within 1 month from the diagnosis, patients were suggested to start a DMT by the physician, and received their first drug supply with instructions for the administration from a trained nurse, according to clinical practice (baseline visit). The time occurring between DMT start and discontinuation was calculated (time to discontinuation). The discontinuation date was the last day that a patient received a dose, as reported in clinical records (Evans et al., 2012; Zhornitsky et al., 2015).

2.4. Markers of interest for discontinuation of Interferon-β1a/b

Possible predictors of Interferon-β1a/b discontinuation were either recorded at the time of the diagnosis (early markers), or during follow-up visits (long-term markers).

In particular, at the time of the diagnosis, demographic characteristics (age, gender), and disease duration were collected. The Kurtzke's Expanded Disability Status Scale (EDSS) was recorded to estimate the MS-related disability at diagnosis (baseline) (Kurtzke, 1983).

In addition, patients were classified into three groups according to the first DMT received (high-dose Interferon-β1a, low-dose Interferon-β1a, or Interferon-β1b).

Finally, MS subjects were evaluated for 4 different long-term markers of MS evolution, recorded in the most recent visit or, conversely, up to Interferon-β1a/b discontinuation:

- Occurrence of clinical relapse: number of relapses occurring during the study period was recorded, and annualized relapse rate (ARR) was subsequently calculated; patients were further categorized as being relapse free or not during the treatment period; relapsing patients presented a range of motor/sensory symptoms and met commonly used standards for relapse as determined by clinical neurologists (McDonald et al., 2001);
- 1-point EDSS progression: the cohort was subsequently categorized as experiencing or not EDSS progression;
- Reaching of EDSS 4.0: the cohort was subsequently categorized according to the reaching of EDSS 4.0 (EDSS≥4.0) or not (EDSS < 4.0);
- Transition from RR to SP course: MS was retrospectively 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); the cohort was subsequently categorized in converting to SP (RR→SP) or not (RR→RR).

Long term disability markers (EDSS progression, reaching of EDSS 4.0 and converting to SP), were chosen because clinically important and unlikely to remit once sustained (Runmarker and Andersen, 1993; Sormani and De Stefano, 2013; Moccia et al., 2016a). For their evaluation, the observation period was extended to 12 months in order not to misestimate disability accrual (Kalincik et al., 2015).

2.5. Statistical analyses

Means and proportions of demographics and clinical features were calculated for MS patients discontinuing or not Interferon-β1a/b treatment, and compared with *t*-test, χ^2 test, or Fisher's exact test, as