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Research Article　　　　　　　　　　　　　　　　　　　　　　**Open Access**

Prospective, Longitudinal, Multicenter Observational Study of Long-term Treatment with Intramuscular Interferon β-1a of Patients with Clinically Isolated Syndrome at High Risk of Conversion

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Abstract

Introduction: Early initiation of treatment with intramuscular (IM) interferon (IFN) β-1a in patients with a single demyelinating event suggestive of multiple sclerosis (MS) has been shown to reduce the risk of a second event. This study investigated the characteristics of patients with clinically isolated syndrome (CIS), conversion to clinically definite MS and quality of life (QoL) in clinical practice.

Methods: Patients eligible for IM IFNβ-1a for CIS were followed for 4 years (1 visit every 6 months, 9 visits in total). Disease progression was assessed using the Expanded Disability Status Scale (EDSS). The rate of conversion, adverse events and laboratory parameters were reported. Patients were administered QoL questionnaires (Functional Assessment of Multiple Sclerosis [FAMS] and EuroQol 5D [EQ-5D]).

Results: Thirty-four patients from 15 Spanish hospitals were included and 18 completed the study. The mean ± SD age of the patients was 32.1 ± 9.08 years and 64% were women. At baseline, the mean EDSS was 0.94 ± 0.85. During follow-up, mean EDSS ranged from 0.89-1.25 and 15 patients (45.5%) converted to CIS. The most common adverse reaction was flu-like syndrome (55%). One patient discontinued treatment due to flu-like syndrome.

The mean score on the visual analogue scale of the FAMS and the EQ-5D remained constant throughout the study (p>0.05 with respect to baseline).

Conclusions: The conversion rate was higher than in the immediate-treatment arm of CHAMPIONS study, which could be expected due to differences in the patient population and delays in treatment initiation.

The added value of the present study lies in the prospective collection of data from the clinical practice in high-risk CIS patients treated with IM IFNβ-1a in Spain. To our knowledge, this is the first study published with these characteristics.

Keywords: Multiple sclerosis; Clinically isolated syndrome; Intramuscular interferon β-1a; Conversion rate; Relapses; Treatment compliance; Quality of life

Introduction

In recent years, our understanding of the early phases of multiple sclerosis (MS) has increased. New imaging techniques make it possible to identify with greater certainty those patients at risk of developing clinically definite MS after an initial demyelinating event suggestive of the disease [1,2].

The better understanding of early phases of the disease prompted studies to investigate whether early interventions could delay the onset of clinically definite MS. For example, in the CHAMPS pivotal study, the effect of intramuscular (IM) interferon (IFN) β-1a on conversion to clinically definite MS in individuals with a first demyelinating event was compared to placebo [3]. The results were encouraging, with a significantly lower cumulative probability of developing clinically definite MS in the IFNβ-1a group compared to the placebo group over the 3-year follow-up period (rate ratio, 0.49; 95 percent confidence interval, 0.33 to 0.73; p<0.001).

In the CHAMPIONS-5 year study, patients from the CHAMPS study were followed to 5years after the initiation of CHAMPS study [4]. The only factors identified as being independently associated with a lower rate of development of clinically definite MS were randomization to the active treatment (early treatment) and younger age of onset of neurologic symptoms, but the size of the effect was modest. Additional studies of the long-term use of IM IFNβ-1a in patients with clinically isolated syndrome (CIS) in clinical practice, with focus not just on efficacy but also on safety and quality of life (QoL), would provide further support for this indication.

The objective of the present prospective study was to report the rates of conversion to clinically definitive MS and the clinical outcomes of patients with clinically isolated syndrome at high risk of conversion who were treated with IM IFNβ-1a for 4 years. The study also aimed to

collect data on the safety and tolerability of IM IFNβ-1a and the QoL in these patients.

Methods

In this prospective study, conducted in 15 Spanish hospitals between December 2004 and December 2010, patients aged 18-45 years who were eligible for IM IFNβ-1a for CIS were enrolled. Eligibility for initiating treatment after the first demyelinating event was determined according to both the Summary of Product Characteristics (SmPC) and the Spanish Committee for the treatment of MS and CIS patients. However, there were regional differences in the approach to treatment due to differences in the criteria of regional committees. Regional differences in approval criteria are outline below:

- Autonomous Communities of Madrid, Murcia, Castilla y León and Asturias: At least 9 T2 lesions and 1 gadolinium enhancing lesion on baseline magnetic resonance imaging (MRI) and 1 new T2 lesion or 1 gadolinium enhancing lesion at 3 months follow-up.

- Autonomous Community of Andalucía: meet one of the two following criteria: 1st. at least 8 T2 lesions on baseline MRI and positive oligoclonal bands in cerebrospinal fluid and / or immunoglobulin (Ig) G intrathecal secretion. 2nd. at least 8 T2 lesions on baseline MRI and a new T2 lesion or a new gadolinium enhancing lesion at 3 months follow-up.

- Autonomous Community of Galicia: At least 9 T2 lesions on baseline MRI and 1 new T2 lesion or 1 gadolinium enhancing lesion at 3 months follow-up.

- Autonomous Community of Canarias: Avonex® SmPC criteria for the early treatment of MS.

Key exclusion criteria were any previous neurological episode lasting more than 24 hours prior to the one indicated in the inclusion criteria as "first demyelination event" that could be attributed to demyelinization in the judgment of the investigator, pregnancy or breastfeeding in women, immunosuppressive therapy within 6 months prior to the neurological event, a history of hypersensitivity to IFNβ, human albumin or any component of the product Avonex®, major depressive disorders or other psychiatric conditions, liver disease, myelo suppression, immune suppression, epilepsy, severe renal or heart disease of any kind, and contraindication of contrast MRI.

Patients remained in the study for 4 years of follow-up only if they did not abandon the treatment within 2 years, switched to another immune modulatory treatment, or developed progressive MS. Other reasons for withdrawal from the study were pregnancy, withdrawal of patient's informed consent and investigator criteria.

We calculated that more than 1000 patients would be eligible for early treatment, based on the incidence of MS in Spain (4-6/100,000), the size of the Spanish population, the ratio patients with a first episode and those with clinically definite MS, and the estimate that 25% of these patients were high risk.

Follow-up procedures

Follow-up procedures consisted of 9 visits over the course of 4 years. These visits corresponded to programmed, standard follow-up visits for patients on IM IFNβ-1a in clinical practice. In these visits, patients underwent a neurological examination. Disease progression (on the Expanded Disability Status Scale [EDSS]) and rate of conversion to

clinically definite MS were assessed (conversion was defined according to the Poser criteria [5]). Adverse events and laboratory parameters were also reported. To investigate QoL, patients were also administered a disease-specific questionnaire, the Functional Assessment of Multiple Sclerosis (FAMS), whose Spanish version has been validated [6], and a general QoL questionnaire, the EuroQol, also validated in Spanish [7]. With the exception of the QoL questionnaires, the procedures performed at study visits corresponded to those that would be performed in normal clinical practice. Compliance and adherence were assessed by questions about whether injections were performed at the frequency stated in the last visit. If the answer was negative, the researcher inquired about the reasons for noncompliance.

Statistical analysis

All analyses were performed on an intention-to-treat basis. Study variables were reported using descriptive statistics. Since this was an exploratory study, no formal statistical hypothesis testing was performed. For comparisons with baseline, a Wilcoxon test was used. The SAS statistical package, version 8.2, was used for all analyses.

Results

Patient population and study disposition

In total, 34 patients were recruited from 15 hospitals throughout Spain, although 1 patient was excluded because IM IFNβ-1a was not actually administered. Therefore, the study population finally analyzed comprised 33 patients. The demographic and baseline characteristics of these patients are presented in Table 1. The mean age of subjects on entering the study was 32 years and almost two-thirds were women.

Clinically isolated syndrome had been diagnosed a mean of 1 year before starting treatment. As per the labelling, all patients had received some form of corticosteroid therapy for the initial demyelinating event.

Demographic characteristics	
Age (years)	32 ± 9.1
Sex Male Female	12 (36.4%) 21 (63.6%)
Family history of multiple sclerosis	2 (6.1%)
CIS characteristics	
Duration (years)	1.0 ± 0.4
Age on diagnosis of CIS (years)	31 ± 9.2
Type of symptoms Unifocal Multifocal Not reported	28 (84.8%) 3 (9.1%) 2 (6.1%)
Type of neurological deficit Sensitive Visual Motor Myelitis Brainstem Cerebellar Others	10 (30.3%) 6 (18.2%) 10 (30.3%) 2 (6.1%) 12 (36.4%) 1 (3.0%) 3 (9.1%)
Corticosteroid therapy	33 (100%)
Intravenous corticosteroid therapy	21 (63.6%)
Oral corticosteroid therapy	12 (36.4%)

CIS: Clinically isolated syndrome
Data presented as mean ± SD or n (%)

Table 1: Demographic and baseline characteristics of the patients included in the study.

On inclusion, patients had between1 and 25 T2 hyper intense lesions (median 10.0), which were mostly supratentorial, and between 0 and 8 T1 gadolinium enhancing lesions (median 1.0). In the 28 patients with analysis of the cerebrospinal fluid, pathological findings with a cell count ≥ 25 were found only in one patient. The median IgG index was 0.83 (range, 0.23-5.82) in the 16 patients with an available IgG index determination and oligoclonal bands were found in 23 out of the 25 in which they were analyzed. Visual evoked potentials were assessed in 23 patients and found to be pathological in 10 (43.5%).

Eighteen patients (54.5%) completed the 4-year follow-up period of the study. Ten patients (30%) withdrew from the study because they switched to another immunomodulator (4 patients due to exacerbations, 1 patient due to tolerability issues and 5 patients due to unknown reasons) while 5 patients withdrew due to pregnancy.

Efficacy

The median score on the EDSS was 1 throughout the study. The mean EDSS score was 0.94 ± 0.85 at baseline visit. During the follow-up visits, the mean EDSS score fluctuated, ranging from 0.89 ± 0.83 (visit 8) to 1.25 ± 0.99 (visit 7). No clear trend was apparent. The only significant difference with respect to baseline was for visit 3 (p=0.0278).

During follow-up, 15 patients (45.5%) had a second relapse (converted to clinically definite multiple sclerosis) and of these, 8 had more than one relapse. Relapses were mostly unifocal (68.2%) and sensory in nature (59.1%). Median time between first event suggestive of MS and second event was 20.4 months (max 59.0 months).Mean EDSS score at the time of the first relapse was 0.89 ± 0.78, 0.94 ± 0.85 at baseline visit and 1.11 ± 0.98 for those who finished the 4 year follow-up. After conversion, nine of the 15 patients switched to another immunomodulator.

Therapeutic compliance

Patients were always compliant until visit 5 (24 months) and for the patients who continued on therapy, the percentage of patients always compliant was always above 90% (Table 2). Considering those patients who withdrew from the study as non-compliant, the percentage of compliant patients was 70%.

Quality of life

As shown in Figure 1, the different components of the FAMS questionnaire showed little change over time (higher scores indicate worse QoL). Likewise, the overall score showed little variation, with mean values ranging from 60.9 ± 15.9 at baseline to 69.8 ± 27.2 at visit 9. Of note is that throughout the study, higher scores were obtained for general mood and family and social environment than for the
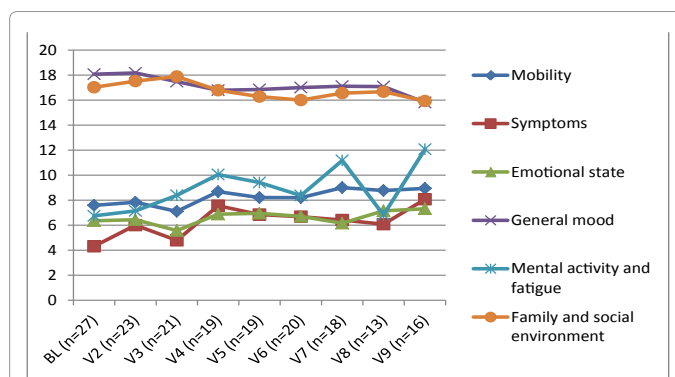

Figure 1: Mean scores on the different components of the Functional Assessment of Multiple Sclerosis (FAMS).

other components. The part of the FAMS questionnaire that deals with "other concerns" (and which does not form part of the overall score) showed that patients were not particularly bothered by the side effects of treatment (mean score never more than 2 at any given visit) while relationship issues and concerns about the disease in general were more worrying (mean score above 3 for components such as "feeling of closeness to your partner", "doctor explains your doubts satisfactorily" and "worried that the disease will worsen"). The non-disease-specific EQ-5D also showed little variation throughout the study (mean score on the visual analogue scale ranged from 84.4 ± 14.2 at baseline to 76.7 ± 17.6 at visit 7 [higher values indicate better QoL]).

Tolerability

Twenty-nine patients (88.0%) had at least one adverse drug reaction during the study and, in total, there were 127 adverse drug reactions. These were mainly mild in severity (71%). Only one severe event was reported (lung cancer, not considered as related to IFNβ therapy) and only one adverse event led to withdrawal of study drug (flu-like syndrome). Among the adverse events reported, 66.7% were considered probably, possibly or certainly related to IFNβ therapy. Most of the reactions considered certainly related were flu-like syndrome and pyrexia.

In the safety laboratory tests, the mean uric acid level did not change significantly between baseline and subsequent visits (ranging from 5.03 ± 1.41 mg/dl at the baseline visit to 4.38 ± 1.38 mg/dl at visit 5). No more than 3 patients had abnormal values at any given time during follow-up, the same number as at baseline. Few patients had hematological abnormalities (never more than 2 patients per parameter at a given study visit). Alanine transaminase abnormalities were the most frequently reported biochemistry abnormalities throughout the study and indeed such abnormalities were often reported as an adverse drug reaction (9 patients [27%], the second most frequently reported adverse drug reaction after flu-like syndrome). However, these adverse events did not lead to discontinuation of IFNβ therapy.

Discussion

Over the last decade, there has been a shift towards earlier treatment in patients considered at risk developing clinically definite MS after a first demyelinating event suggestive of MS (that is, with lesions apparent in brain MRI) [8]. In addition to the CHAMPIONS study with IM IFNβ-1a mentioned earlier [4], studies of early interventions with disease-modifying therapy have been conducted with glatiramer acetate [9], IFNβ-1b [10] and subcutaneous IFNβ-1a [11]. In all cases, the results supported an early intervention with disease-modifying

	Always compliant	Sometimes incompliant
Visit 1 (n=33)	33 (100%)	-
Visit 2 (n=32)	32 (100%)	-
Visit 3 (n=28)	28 (100%)	-
Visit 4 (n=26)	26 (100%)	-
Visit 5 (n=23)	21 (91.3%)	2 (8.7%)
Visit 6 (n=21)	20 (95.2%)	1 (4.8%)
Visit 7 (n=20)	20 (100%)	-
Visit 8 (n=19)	18 (94.7%)	1 (5.3%)
Visit 9 (n=18)	17 (94.4%)	1 (5.6%)

Table 2: Summary of compliance.

therapy. However, at the time when this study began (2004), IM IFNβ-1a was the only disease-modifying therapy authorized in Spain after a first demyelinating event. The aim of the study was to see when and how frequently a second relapse occurred (clinical conversion to MS) and to assess changes in QoL scales resulting from initiation and maintenance of immunomodulatory therapy in patients at early stage of the disease, before the conversion to clinically definite MS.

In the CHAMPIONS-5 year study, the cumulative probability of development of clinically definite MS was 36% in immediate treatment group (those randomized to active treatment in the CHAMPS) compared to 49% in the group who received IFNβ-1a later (those randomized to placebo in CHAMPS and who started active treatment after a median time of 29months) (HR adjusted=0.57; p=0.008) [4]. This conversion rate is comparatively lower than the 45.5% conversion rate at 4 years of in our study. Nevertheless, there are substantial differences between our study population and the population in the CHAMPIONS study, in particular the MRI lesion load and the delay in starting treatment. For example, in that study, patients were randomized within 27 days of the first demyelinating event suggestive of MS whereas our patients waited a mean of 1 year before initiating therapy. It is conceivable that an earlier intervention in the case of our study patients would have shown a conversion rate more in line with that found in the "delayed treatment" arm of the CHAMPIONS study. The delay is in part due to the need for all Spanish patients to be evaluated by a local MS committee to ensure eligibility according to the officially approved indication of these committees, which hindered the enrolment since many patients have already converted to clinically definite MS before the committee approved the treatment. While the approval process undoubtedly ensures that individuals are not unnecessarily exposed to treatment, it does delay start of treatment. Ten-year follow-up data are now available for the CHAMPIONS-10 year study [12,13], which further support the need for early intervention (the cumulative probability of developing clinically definite MS was significantly lower in patients who received immediate treatment, with an adjusted hazard ratio of 0.61 [95% CI, 0.45-0.82], P=0.001).

When patients are being treated in the long-term with disease-modifying therapies, it is important to consider aspects such as adherence to treatment and QoL when assessing the value of treatment, particularly when short-term benefit is often intangible, reducing the motivation to continue to take the therapy. As a result, QoL is receiving increasing recognition as an important outcome in multiple sclerosis therapy [14,15]. It is not just physical disability per se, but also other aspects such as cognitive decline and visual impairment that have an impact on QoL [16]. In the early stages of the disease, the effects can be subtle. Concern about the treatment, side effects, compliance, and the impact in the future should also be taken into consideration in order to avoid false expectations. In our study, scores on FAMS, the disease-specific instrument used in this study, and the generic EuroQoL-5D tended to remain stable. However, worse scores on the FAMS were obtained for general mood and family and social environment than for components pertaining to symptoms or physical aspects of the disease. Patients also expressed concerns about worsening disease.

A stable score on the FAMS questionnaire was also found in the 3-year follow-up of the BENEFIT study of early versus late IFNβ-1b in clinically isolated syndrome [17]. In another study of IFNβ-1a IM in patients with MS, overall QoL did not change significantly over the 12-month follow-up period [18]. Where changes were apparent, these generally correlated with disability progression. As the mean EDSS hardly changed at all in our study, it is not surprising that no changes in QoL were observed.

As mentioned above, adherence to treatment is another important consideration for patients with CIS likely to receive long term immunomodulatory treatment, especially as short-term benefits are often less visible, reducing the motivation to follow the treatment administered. Compliance was generally high in our study, with more than 90% reporting that they had always been compliant in the preceding 6 months throughout the study. In our study, of 4 years duration, 54.5% completed the study.

Pregnancy was one of the most common reasons for withdrawal from treatment in our study. MS is a disease that primarily affects young women, many of whom will have a desire to become pregnant [19]. If a woman should become pregnant while taking the drug, the labelling suggests that she be warned of the potential hazards and that discontinuation of the therapy should be considered [20]. Indeed, in our study, becoming pregnant was a withdrawal criteria.

Our study provided a detailed characterization of patients who initiate IFNβ-1a therapy for clinically isolated syndrome in Spain. As required by the labelling, disease activity was apparent in the imaging studies and, of note, almost 93% of patients had pathological findings in the analysis of cerebrospinal fluid. The presence of oligoclonal bands is thought to be a predictor for developing clinically definite MS [13]. Although not all untreated patients with clinically isolated syndrome develop MS the high prevalence of abnormalities in the cerebrospinal fluid samples confirms that the patients included in our study were generally at a high risk of conversion.

IM IFNβ-1a was well tolerated and the adverse events reported were in line with those described in the SmPC, both in terms of frequency and intensity.

This study is subject to a number of limitations. First and foremost, there is no control arm for our rates of conversion. Nevertheless, the study did provide the opportunity to collect detailed data on the baseline characteristics of patients who entered treatment with IM IFNβ-1b in clinical practice. Another weakness is that relatively few patients were enrolled. One explanation for this is the existence of the aforementioned barriers to starting treatment (discussed above). Another possible reason is the heterogeneity of existing criteria in different parts of the country due to the decentralized health system. Such heterogeneity hinders data integrity in an observational study of this type. Of note is that some Spanish regions did not participate in the study and that some patients who were potential candidates for treatment converted to clinically definite MS during the authorization process to initiate treatment so were not finally included in the study.

Without a control arm and with such a small sample size, we cannot make firm affirmations about efficacy. Nevertheless, this study is of interest in that it provides long-term and prospectively collected data in a cohort of CIS patients at high risk of conversion treated in Spain with IM IFNβ-1a.

In summary, IM IFNβ-1a was well tolerated and patients showed high levels of compliance. QoL in both the generic and disease-specific questionnaires remained stable in the follow-up period.

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