Disability progression markers over 6-12 years in Interferon-β-Treated Multiple Sclerosis Patients

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Abstract

Objective: To investigate the association between activity during interferon beta therapy (IFNβ) and disability outcomes in patients with relapsing–remitting multiple sclerosis (RRMS).

Methods: A longitudinal study based on two previously described cohorts of IFNβ treated RRMS patients was conducted. Patients were classified according to clinical activity after 2 years (clinical cohort) or to clinical and radiological activity after one year (MRI cohort). Multivariate Cox models were calculated for early disease activity predicting long-term disability.

Results: A total of 516 patients from two different cohorts were included in the analyses. Persistent clinical disease activity during the first 2 years of therapy predicted severe long-term disability (clinical cohort). In the MRI cohort, Modified Rio score, and no or minimal evidence of disease activity (NEDA / MEDA) did not identify patients with risk of EDSS worsening. However a Rio score ≥2 (HR 3.3 95% CI 1.7-6.4), ≥3 new T2 lesions (HR 2.9 95% CI 1.5-5.6) or ≥2 Gd-enhancing lesions (HR 2.1 95% CI 1.1-4) were able to identify patients with EDSS worsening.

Conclusions: Although early activity during IFNβ therapy is associated with poor long-term outcomes, minimal degree of activity does not seem to be predictive of EDSS worsening over 6.7 year mean follow-up.

Introduction

Interferon beta (IFNβ) has been demonstrated to reduce clinical and radiological activity (1-6). However, in the last years, new therapeutic approaches for the management of MS have appeared. In this scenario, it will be necessary to obtain early factors that predict long-term outcomes with the objective of optimizing therapy and of facilitating evidence-based therapeutic decision-making (7).

Studies have shown a positive association between early clinical and radiological activity during treatment with IFNβ and short- and long-term disability (8-16). In previous work, we demonstrated that isolated clinical activity during the first two years of treatment with IFNβ was predictive of an increase in disability after six years of follow-up (17), and we subsequently described an association between clinical and radiological activity during the first year of treatment with IFNβ and the presentation of new activity in the next two years (12). Thus, the combination of clinical and radiological measures seems to be the best strategy for predicting IFNβ treatment outcomes. Several scores that combine clinical and MRI markers have been proposed (12, 13, 18, 19, 20). However, these scoring systems have been tested only over short follow-up periods, and their long-term predictive value is currently unknown.

Therefore, based on the above premises, the objectives were the following: 1) to evaluate the impact of early activity on long-term disease evolution in treated patients and 2) to compare the predictive value of different treatment monitoring

scoring systems including the Rio score, modified Rio score, no or minimal evidence of disease activity (NEDA or MEDA), to identify which patients will attain clinically meaningful disability outcomes in the long term.

Patients and Methods

Study design and patient disposition

This was a single-centre, longitudinal, observational study based on two previously described prospective cohorts of patients with MS who had received IFNβ (Figure 1). All patients were fully naive of any disease modifying drugs before starting IFNβ (12, 17). Our first cohort (clinical cohort) included patients treated with IFNβ between 1995 and 2001. The second cohort (clinical and MRI cohort, for ease termed the MRI cohort from here on) included patients who began IFNβ between 2001 and 2005. The reason for studying these two consecutive cohorts separately lies in the different monitoring protocols. For the first and oldest cohort, no MRI data were available. In contrast, in the second cohort, MRI data were obtained. The local ethical committee approved the study, and all patients provided their informed consent.

Measures of early disease activity during treatment

In the clinical cohort, based on a previous study (17), we defined a number of clinical activity measures during the first two years of treatment (17) (Figure 1). In that study, we demonstrated that EDSS worsening, the presence of relapses, and the combination of both measures in the first two years of therapy were

significant predictors of irreversible disability after 6 years of follow-up, displaying very good specificity and sensitivity. Therefore, in the present study, we tested the value of the same measures to predict long-term disability. As previously described (17), an increase in the EDSS score after the first 2 years of treatment was defined as an EDSS worsening of at least 1 point confirmed at 6 months and sustained up to the end of follow-up. If the EDSS score was 0 at baseline, an increase was defined as an EDSS score change of 1.5 or more, while a change in the EDSS score of 0.5 was defined as an increase in patients with scores greater than 5.0. Neurologists trained in EDSS scoring performed neurological assessments. A relapse was defined as the occurrence, recurrence or worsening of symptoms of neurological dysfunction lasting more than 24 hours and then stabilizing or eventually resolving either partially or completely.

In the MRI cohort, patients were classified according to their clinical and MRI activity in the first year of therapy (12) (Figure 1). We considered activity after one year based on the following: the presence of relapses, sustained EDSS worsening, and new T2 or gadolinium (Gd)-enhancing lesions. Different scores were assigned and analysed according to different combinations of these measures of activity (11-14, 18), namely, the Rio score (RS), modified Rio score (MRS), and no evidence of disease activity (NEDA) scale score. The RS was obtained after the first year of therapy as follows: (i) MRI criterion, 1 point for patients with ≥3 new T2 and/or Gd-enhancing lesions; (ii) relapse criterion, 1 point for patients with ≥1 relapse; and (iii) EDSS criterion, 1 point for patients with an EDSS score increase of ≥1 point, sustained at the end of follow-up. The MRS was obtained after the first year of therapy as follows: (i) MRI criterion, 1

point for patients with ≥5 new T2 lesions and (ii) relapse criterion, 1 point for patients experiencing 1 relapse and 2 points for patients experiencing ≥2 relapses. A total score (0–3) was calculated for each scoring system, and patients were classified into one of two categories: low (score 0–1) or high (score 2–3) risk. NEDA was defined as the absence of relapses, lack of EDSS worsening, and absence of MRI activity (new T2 or Gd-enhancing lesions). As NEDA aims to predict good evolution on therapy and the RS and MRS are scores aimed at predicting poor evolution on therapy, the term EDA (any evidence of disease activity) has been used to enable comparison between scores.

Long-term disability outcomes

Considering the different follow-up periods, i.e., 12 years for the clinical cohort and 8 years for the MRI cohort, we established different long-term outcomes for the two cohorts.

For the clinical cohort after the first two years of treatment, we established the following outcomes: A) developing secondary progressive MS (SPMS), B) attaining a confirmed EDSS score of 7.5, and C) exhibiting an increase of at least 5 EDSS steps at the end of follow-up EDSS at month 24 was used as the starting point to evaluate progression. We defined progressive disease as a continuing deterioration (for at least one year) without substantial remissions or exacerbations (21). SPMS onset was assessed retrospectively, at least one year after the onset of the gradual worsening.

Previous studies have shown that, as an outcome measure, looking at the increase in the number of EDSS steps is less dependent on baseline EDSS

than the more commonly used reaching EDSS 6 (17). Given the long period of follow up, we also chose the clinical meaningful endpoints of reaching EDSS 7.5 and time of conversion to SPMS.In the MRI cohort, due to the shorter follow-up time, the endpoint after the first year of treatment was the occurrence of sustained EDSS worsening of at least 2 points that was confirmed at the end of the follow-up period.

MRI protocol

The number of active lesions on the 12-month MRI scan was visually assessed by two experienced neuroradiologists who were blinded to the patients' clinical data by direct comparison with the baseline scan, according to previously published guidelines (22).

Statistical analysis

Descriptive statistics were used to assess the demographic and clinical data. To identify differences between groups for each of the clinical activity definitions analysed, we used Student's *t*-test for continuous variables and the chi-square and Fisher's exact tests for categorical variables.

We calculated the diagnostic properties (sensitivity, specificity, PPV, NPV, and accuracy) to identify patients who reached the pre-defined long-term outcomes. The 95% confidence intervals (CIs) of each of these indices for each parameter or scoring system were calculated.

Kaplan-Meier survival analyses were used to estimate the cumulative risk of developing endpoints of EDSS worsening according to the presence or absence of active disease based on the above-mentioned parameters and score

systems after the beginning of therapy. We performed uni- and multivariate logistic regression and Cox proportional hazards analyses to study the prognostic value of early clinical disease activity for the prediction of long-term disability outcomes. In these analysis, it has been considered “time zero” the beginning of treatment plus 2 years (clinical cohort) or plus 1 year (MRI cohort). Statistical analysis was performed with SPSS 20.0 (SPSS Inc., Chicago, IL), SAS (SAS Institute Inc., Cary, NC), and G-Stat (GlaxoSmithKline S.A., Spain) statistical software packages. The level of statistical significance was set at $p<0.05$.

Results

A total of 516 patients were included in the main analyses; specifically, 283 formed the clinical and 233 formed the MRI cohort of patients (Figure 2).

As shown in Figure 2, in the clinical cohort, 234 (83%) patients (163 females, 71 males) were identified as having at least 12 years of follow-up. The mean clinical follow-up in this cohort was 11.5 (SD 3.1) years (range 2-17.3 years). There were no significant baseline differences in terms of age, gender, disease activity and EDSS between the patients lost to follow-up and those who underwent a full assessment (data not shown). Twelve (4%) patients died (5 patients died due to respiratory infection, 2 patients died due to lung cancer, and the other deaths were due to urinary sepsis, a car accident, suicide, cerebral haemorrhage, and leukaemia), and 37 (13%) patients were lost to follow-up. The mean age in this cohort at treatment onset was 32.7 (SD 9.4) years, with a mean disease duration of 6.2 (SD 5.3) years. The mean number of

relapses in the 2 years before treatment was 2.7 (SD 1.3), and the median EDSS score at study entry was 2 (range 0-5.5). In the MRI cohort, 209 (90%) patients (152 females, 57 males) were identified as having at least 8 years of follow-up. The mean clinical follow-up in this cohort was 6.75 (SD 0.8) years (range 1-13.2 years). One (0.5%) patient died due to a pancreatic neoplasm, and 12 (5%) were lost to follow-up. The patients had a mean age of 34.2 years (SD 9.7; range 18-69) at the beginning of treatment and a mean disease duration of 4.7 years (SD 5.4; range 1- 47). The median EDSS score at baseline was 2 (range 0-5.5). Patients had a mean number of relapses over the previous two years of 1.9 (SD 0.9; range 1-5).

Early clinical activity and long-term disability in the clinical cohort

In this cohort, 120 patients (51%) were clinically active during the first 2 years, 107 (46%) had at least one relapse, 44 (19%) had EDSS worsening, and 31 (13%) had relapses and EDSS worsening.

During the follow-up period, 77 (31%) patients had developed SPMS, 62 (25%) had an EDSS worsening of at least 5 points, and 39 (16%) had reached an EDSS score of 7.5. No patient reached these outcomes during the first 2 years of treatment. As shown in figure 3 all studied measures of clinical activity after two years of treatment confer a significant risk of achieving the long-term outcome. However, it is important to note that the presence of one relapse without changes in EDSS during the first two years of treatment did not confer a significant risk of developing long-term disability (OR 1.6; 95% CI 0.6-3.8 for SPMS and OR 2.2; 95% CI 0.7-6.8 for 5-step EDSS worsening) compared with the risk in patients without relapses.

The sensitivity, specificity, predictive values, and accuracy values for the different clinical activity measures at two years used to predict relevant outcomes at 12 years are shown in Table 1.

Early clinical and MRI activity and long-term disability in MRI cohort

In this cohort, 51 patients (23%) had ≥1 relapse, 33 (15%) had at least one point of EDSS worsening, 132 (59%) had at least one new T2 lesion and 63 (28%) had at least one Gd-enhancing lesion on the MRI performed 12 months after initiating therapy. One hundred and forty-seven patients (76%) had some evidence of disease activity (EDA). During the follow-up period, 44 patients (20%) had an EDSS worsening of at least 2 points. No patient reached the outcome during the first year of treatment.

Figure 4 shows the risk of developing an EDSS worsening during the follow-up period in patients with clinical or MRI activity in the first year of treatment adjusted for age, gender, and baseline EDSS. From a clinical point of view, the presence of ≥1 relapse during had a marginal effect on the risk of long-term disability (HR 1.5, 95% CI 0.8-2.9). From a MRI perspective, the presence of at least 3 new T2 lesions (HR 2.9, 95% CI 1.5-5.6) or of at least 2 Gd-enhancing lesions (HR 2.1, 95% CI 1.1-4) was able to identify patients with EDSS worsening. In contrast, the presence of MEDA (<3 new T2 lesions or <2 Gd-enhancing lesions) did not properly identify patients with a risk of EDSS worsening. Additionally, MEDA defined by the presence of one relapse with 0 or 1-2 new T2 lesions had only a marginal effect on the risk of long-term disability (HR 2.2, 95% CI 0.7-7.4). However, a RS ≥2 (HR 3.3, 95% CI 1.7-6.4)

conferred a significant risk of long-term disability. By contrast, neither the MRS (0-1 versus 2-3) nor EDA predicted EDSS worsening (figure 5). As shown in table 2, EDA and ≥1 new T2 lesion were the most sensitive measures; however, both showed the lowest specificity. The combined scores had acceptable specificity but poor sensitivity. A RS ≥2 showed the best balance between sensitivity and specificity.

Discussion

Although IFNβ showed a positive effect, the accumulated data (23, 24) indicate that some patients will present long-term disability despite therapy; therefore, the early identification of these patients is important to optimize the benefit of treatment and to determine the best course of therapy. Our study demonstrates that the presence of early significant clinical or MRI activity during treatment with IFNβ is a relevant predictor of the long-term worsening of the disability.

Although it has been demonstrated that the long-term prognosis could be better in treated patients compared with untreated patients (25), there are a lack of early predictors of long-term disability in the former group. A study that examined the prognosis of pooled patients (2 doses and placebo combined) included in the pivotal trial of IFNβ-1b showed that changes in EDSS ($p<0.0001$) and relapse rate ($p<0.025$) during the study (0-2 years) were associated with a worse prognosis, defined as reaching an EDSS score of 6 or transitioning to SPMS after 16 years (26). Another recent study evaluating the 15-year prognosis in patients treated with IFNβ demonstrated that patients with at least two relapses during the first two years of therapy had a higher of severe

disability at 15 years (OR 4.44, CI 1.43-13.85, p<0.01) (15). Similarly, in our study, we observed that the presence of relapses or EDSS worsening during the first 2 years of therapy had a very negative impact on the long-term prognosis.

Although new T2 lesions during the first 12 months of IFNβ has been associated with a poor clinical outcome over 2 years (27) the degree of MRI activity that confers a significant risk of EDSS worsening in the long-term has not been determined. In a recent systematic review, the presence of one new T2 lesion did not show statistical significance in the prediction of treatment failure (28). Our data, with a much longer follow-up period, confirmed these findings. The presence of 1 or 2 new T2 lesions does not pose a significant risk of long-term disability (HR 0.8, 95% IC 0.2-2.7). However, significant MRI activity (≥3 new T2 or ≥2 Gd-enhancing lesions) at 12 months clearly predicts a poor long-term outcome.

The main relevance of the scoring systems is to facilitate evidence-based and quantitative decision-making to determine the best therapeutic approach for a given patient (29). In our work, the scores studied show that the combination of relapses, sustained disability and new T2/gadolinium lesions (RS ≥2) allow for better identification of patients with a worse prognosis (HR 3.3, 95% CI 1.7-6.4). Similarly, the MAGNIMS study group, demonstrates that a high increase in the risk of progression is present when, after 1 year of IFN-β treatment, there is 1 relapse and a substantial MRI activity (i.e., ≥3 new T2 lesions) (20).

NEDA has garnered increasing attention as a measure that may allow for earlier and more accurate prognostication and has become a secondary outcome

measure in clinical trials for new therapies in MS (18). However, in our study NEDA did not reach a ststistical significance for predicting outcomes in individual patients (HR 1.7; 95% CI 0.8-3.6), although we cannot rule out a lack of statistical power due to the sample size.

Overall, the predictive value of all the studied scores was limited, as the observed PPVs did not exceed 50% and the NPVs were lower than 90%. The criterion with the best-balanced accuracy was a RS≥2. As has been recently described (30), the MRS had the highest specificity (88%) but with a lower sensitivity than RS≥2 (19% vs. 40%). However, MRS (a pure activity based measure) does not perform as well as the RS – a combination of activity and worsening / progression, in predicting future EDSS deterioration (17).

New drugs are not free of toxicity, nor do they always have complete efficacy, thus, their use must be reserved for patients at risk for long-term disability. However, we lack data to assure that switching or escalating therapy in this group of patients will improve their long-term prognosis. On the other hand, the degree of early disease activity that confers a potential risk of a poor long-term prognosis is currently unknown. Our results reveal that MEDA (one relapse without an impact on disability, the presence of minimal isolated radiological activity (one or 2 new T2 lesions or a single Gd-enhancing lesions), or even the presence of minimal clinical and radiological activity (1 isolated relapse and 1 new T2 lesion)), did not confer a significant risk of EDSS worsening during the study follow-up. Data with a longer follow-up (i.e. 15 or 20 years) and larger sample are needed in order to clarify this observation.

Disease duration at treatment initiation in our cohorts are longer than expected today, thus, predictions may not be fully useful for patients with CIS or early MS.

Despite this and other limitations, such as: different treatment strategies during follow-up, adherence, presence of neutralizing antibodies, lack of information about spinal cord MRI, lack of a control untreated group or the appearance of new T2 lesions that could develop in the period between the baseline MRI scan and the beginning of the treatment, potentially reducing the predictive power of MRI; our study has several strengths. First, because long-term data are so critical for obtaining valid and accurate information on a therapeutic effect, we used very strict long-term outcomes. Second, the study has been developed in a real-life setting and finally, the study had a low rate of patients lost to follow-up.

In summary, the data reported in this study reinforce the idea that early significant clinical and MRI activity during IFNβ treatment is associated with a poor long-term prognosis. In contrast, in patients with MEDA, a watchful waiting period is reasonable before implementing treatment changes. However, these findings should be interpreted with caution and need to be confirmed in other cohorts and with drugs other than IFNβ.

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Figure Legends

Figure 1. Cohorts and study design.

Figure 2. Flowchart of the patients included in the study.
a. As per Rio et al. Ann Neurol 2006 (16)
b. As per Rio et al. Mult Scler 2009 (12)

Figure 3. Effect of early clinical activity on the development of long-term disability.
CI: Confidence interval
HR: Hazard ratio
OR: Odds ratio
a. No relapses as the reference category
b. No relapses and <1 EDSS point as the reference category

Figure 4. Effect of early clinical and radiological activity on the development of long-term disability.
CI: Confidence interval
a. No relapses as the reference category
b. No new T2 or Gd lesions as the reference category
c. No relapses and no new T2 or Gd lesions as the reference category
d. RS or MRS <2 as the reference category
e. NEDA as the reference category

Figure 5. Kaplan-Meier curves showing the cumulative probability of EDSS worsening ≥2 points according to the different scoring systems during the follow-up period.
a. Rio score
b. Modified Rio score
c. Evidence of disease activity