Neurol Sci (2006) 27:S358–S361
DOI 10.1007/s10072-006-0694-8

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Italian Multiple Sclerosis Database Network

Abstract The Multiple Sclerosis Database Network (MSDN) is the first Italian multiple sclerosis (MS) registry. The preliminary results on the MSDN cohort demonstrated that the risk of disability progression, in a sample of 2090 MS patients, was reduced by about four- to five-fold in patients exposed to IFNβ for more than 4 years compared with patients exposed for up to 2 years. More recent results showed, in a subset of 1170 relapsing-remitting MS patients, of whom 918 were treated with IFNβ and 252 were untreated, that IFNβ-treated patients had a differential reduction in EDSS score change of –0.055 for each year of follow-up in comparison with the untreated group. These results provide significant information on the effectiveness of IFNβ treatment on long-term disability progression in MS.

Key words Multiple sclerosis • Databases • Databasing • MSDN

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Planning of the Multiple Sclerosis Database Network (MSDN)

MSDN is the first Italian multiple sclerosis (MS) registry, and one of the largest MS databases in Europe based on the iMed system. iMed [1] is a new electronic MS patient monitoring system recently developed by the Serono International Foundation. The programme is user-friendly with dynamic colour graphics (patient's course, relapses, EDSS, medication start/stop) and is currently freely available, in different languages, to the scientific community. The programme includes useful search features that may be useful in clinical research and selection of patients for clinical trials. Each Italian MS centre was provided with a computer, ISDN line, iMED software and a grant for data-entry personnel. One monitoring neurologist was responsible for reviewing quality and completeness of data collected at all study centres. Before the beginning of data collection, a training session of people in charge of data entry was performed to define clearly and agree on terminology, criteria and data recording on the iMED system. Participating neurologists may collect information using iMed and upload anonymised information to the iMed web-portal (www.imedweb.it) and enter it into a central database for the analysis. The central server is currently located at the Scientific Consortium Mario Negri in S. Maria Imbaro, Chieti, where substantial staffing and technical support was available for retrospective and prospective data analysis and biostatistics.

All patients with definite MS, or clinically isolated syndromes (CIS) suggestive of MS, treated or untreated, are eligible for inclusion in iMed-Web. Completion and uploading of a minimum dataset is mandatory for patient inclusion in the iMed-MS Registry. Medical history, patient demographic data and EDSS should be collected at entry visit. Evaluations of neurological status, relapses, paraclinical tests, treatments and disease course must be reported at least annually. Only members have access to the aggregate data. Anonymised aggregate data generated

from the iMed-MS Registry are reported to participating neurologists on a regular basis. Participating neurologists can benchmark their data against those of a national cohort or other subsets.

iMed-Web may also facilitate collaborative research by allowing the creation of online regional or national databases. An independent Scientific Advisory Board is responsible for the registry and data integrity and the overall scientific objectives of the database: study design, implementation, data analysis and publication policy.

After a preliminary pilot phase, in which a check of the quality of data entry on MS patient records was conducted [2], a second upload of data was performed on March 2005. By March 2006, 4987 MS patient records with complete data were available on the central server. Seventy-three percent of patients have relapsing-remitting (RR), 16.3% secondary progressive (SP), 7.3% primary progressive (PP) and 3.4% CIS courses. Eighty-one percent of the whole population is made up of patients treated with one or more disease-modifying drugs.

In this paper examples of analyses performed on subsets of the cohort collected up to now in the MSDN will be presented.

Most of these analyses focus specifically on the evaluation of the real effectiveness of IFNβ in slowing disability progression in MS in the context of the current clinical practice. Specifically we evaluated the risk of disability progression according to length of exposure to treatment and we compared EDSS progression in treated and untreated patients.

The risk of worsening according to IFNβ exposure in MS

The aim of this analysis [3] was to evaluate the risk of disability progression according to the length of exposure to IFNβ for a cohort of patients in the MSDN database.

A sample of 2090 patients (68% women and 32% men) exposed to IFNβ for at least 1 year, and who had sufficient prospective clinical information (1 visit at the start of treatment and at least 2 visits/year subsequently) for the assessment of clinical outcomes (i.e., disability progression) before and after IFNβ treatment was analysed. A total of 44,140 patient-visits were evaluated in a mean follow-up period of 10.1 years (SD=6.8; median=8.4; range 5.1–13.4 years) corresponding to 22,143 patient-years. Approximately 41% of patients (n=865) had been exposed to IFNβ for up to 2 years (mean±SD=1.29±0.5 years). A similar number (n=817; 39% of cohort) had received 2–4 years of IFNβ therapy (mean±SD=2.89±0.5 years) and 20% of patients (n=408) had been exposed to IFNβ for more than 4 years (5.39±0.9 years). Patients exposed to IFNβ for more than 4 years were younger at disease onset ($p<0.001$) and were less likely to have a SP disease course than patients with less than 4 years' exposure to IFNβ. Patients exposed to IFNβ for more than 4 years had suffered with MS for a longer time than patients exposed for up to 2 years ($p<0.001$) and for a shorter time in comparison with those exposed for 2–4 years, and they had lower EDSS scores and higher relapse rates, compared with patients exposed to IFNβ for 2–4 years. Patients exposed for 2–4 years had a longer disease duration ($p<0.001$), a higher EDSS score ($p<0.05$) and a lower relapse rate ($p<0.001$) than those exposed for up to 2 years. According to the assessment of clinical outcomes after IFNβ treatment, 422 patients (20.2%) were classified as having disability progression and 1668 patients were classified as censored. In the group of patients exposed to IFNβ for up to 2 years, 132 events (15.2%) were observed, while for patients exposed to IFNβ for 2–4 years and for those exposed to IFNβ for more than 4 years, 190 events (23.3%) and 100 events (24.5%) were observed, respectively.

Table 1 Risk of disability progression (confirmed 1 point EDSS increase) in patients exposed to IFNβ (n=2090) Cox regression analysis

Predictors	Hazard ratio	95% CI
Age	1.03*	1.02–1.04
Gender		
Males	1.00	
Females	1.01	0.82–1.24
Course		
RR	1.00	
SP	1.44#	1.03–2.0
Baseline EDSS	0.71*	0.66–0.77
Relapse rate/year	0.96	0.89–1.04
Disease duration before IFNβ start	1.01	0.99–1.03
IFNβ exposure		
≤2 years	1.00	
>2 years and ≤4 years	0.78#	0.62–0.98
>4 years	0.23*	0.17–0.30

*$p<0.001$; #$p<0.05$

A Cox regression analysis (Table 1) showed that the risk of disability progression was significantly higher in older patients ($p<0.001$), in those with a SP course ($p<0.05$) and with a lower EDSS before the treatment ($p<0.001$). After the adjustment for the other covariates, patients exposed to IFNβ for 2–4 years and those exposed to IFNβ for more than 4 years showed 22% and 77% reductions, respectively, in the risk of disability progression (95% CI: 38%, 2%, $p<0.05$ and 95% CI: 83%, 70%, $p<0.001$, respectively) compared with patients exposed to treatment for less than 2 years.

The direction of the effect on the risk of disability progression with the increase of IFNβ exposure did not change after the adjustment of the estimate of the hazard rate by propensity score. The propensity score is a common device to balance the different baseline covariates in treatment comparisons in observational studies [4].

In other words the results indicated a most favourable clinical outcome in patients exposed to IFNβ for the longest period of time.

Comparison of EDSS progression between IFNβ treated *vs.* untreated RRMS

A subset of 1170 RRMS patients (918 IFNβ treated and 252 untreated) followed for at least 1 year from the first visit up to 10 years was considered for this analyses. Overall 12,444 EDSS measures were collected according to a 6-months follow-up visit schedule. Mean follow-up time was 4.5 years.

Changes in EDSS score over time in treatment and control groups were assessed with a multivariate hierarchical linear model for repeated measurements [5]. Hierarchical linear models are particularly suited for longitudinal analysis with unbalanced designs. Baseline covariates tested in the model were: age at disease onset, sex, disease duration, number of bouts in the last year before first visit and treatment (IFNβ *vs.* control). The effects of the same baseline covariates over time were also evaluated as time-by-covariate interactions (slope differences).

IFNβ discontinuation (yes *vs.* no) was tested as a time-varying covariate and the mean difference in EDSS score between the overall period of IFNβ treatment *vs.* the overall period of suspension was assessed within patients who discontinued treatment. Continuous covariates are centred to their mean values to allow the interpretation of the intercept. During follow-up 127 out of 918 treated patients (12.7%) discontinued IFNβ. Significant results of EDSS longitudinal analysis are summarised in Table 2. The estimated baseline mean EDSS score for control group adjusted for mean-centred baseline covariates was 1.76. Mean EDSS score change in control group for each year of follow-up was 0.19. IFNβ group had a baseline mean EDSS score 0.69 higher than control group. A higher age at onset and a longer duration were significantly associated to higher EDSS score both at baseline and over time. Sex and number of bouts in the last year were not significantly associated to EDSS score (either at baseline or over time). In particular the IFNβ group had a differential reduction in EDSS score change of –0.055 for each year of follow-up (e.g., over 10 years of follow-up time, treatment would yield a 0.55 difference when compared to the control group). Moreover, IFNβ discontinuation within the treated group resulted in a significant mean increase in EDSS over time ($p=0.0444$).

Table 2 Change in EDSS score over time: IFNβ treated vs. untreated MS (multivariate hierarchical linear model for repeated measurements)

Effects	β	se β	*p*
Intercept*	1.67	0.066	<0.0001
IFNβ treatment (yes *vs.* no)	0.69	0.07	0.0009
Age at onset	0.03	0.003	<0.0001
Disease duration	0.05	0.005	0.001
No. of bouts	0.04	0.03	0.267
Time** (in years)	0.19	0.015	<0.0001
Time x IFNβ treatment	–0.055	0.017	0.0009
Time x disease duration	0.005	0.001	<0.0001
IFN β treatment discontinuation (yes/no)	0.045	0.02	0.044

*Intercept value represents the estimated baseline mean EDSS score for reference group (untreated) adjusted for continuous covariates (i.e., age and disease duration)

**Time value represents the estimated mean EDSS score change for reference group (untreated) for each year of follow-up

Conclusion

These preliminary results of the Italian MSDN project are an example of the validity of databasing in providing significant information on effectiveness of IFNβ treatment on long-term disability progression in MS patients at population level. We demonstrated that the magnitude of the effect of IFNβ in slowing disease progression increases with the exposure duration and that IFNβ treatment may decelerate EDSS progression in RRMS.

The advantages of longitudinal databasing in both MS clinical management and related research are obvious [6–8], especially considering that MS has a long and variable clinical course and there is no standardised treatment for the disease. Long-term prospective databasing of MS information provides a useful resource for natural history studies and is the most feasible way to address long-term safety in the general MS population and the question of whether early treatment eliminates or delays the inevitable and irreversible clinical worsening that is the hallmark of the late phase of illness. Future projects will continue to build on the results of clinical studies and will hopefully provide new insights into MS progression and management.

Italian MSDN group

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