**DOES INTERFERON THERAPY DELAY OR PREVENT THE DEVELOPMENT OF SECONDARY PROGRESSIVE DISEASE? – YES**

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Despite the inherent limitations of follow-up studies, most of the results from long-term extensions of the randomised controlled trials (RCTs) and from observational studies, published in the last years, support the evidence that currently available disease modifying drugs (DMDs) have, at least partially, impacted the long-term prognosis of relapsing remitting multiple sclerosis (RRMS) patients, especially when they are administered at an early stage and for a prolonged period of time. Moreover, while the extensions of RCTs demonstrated these effects on restricted and highly selected subgroups of RRMS patients originally enrolled in pivotal trials, observational studies extended the findings from RCTs by reporting these effects in large MS cohorts exposed to DMDs.

Methodological issues may hinder the analysis of observational studies, including the lack of randomization, variation in duration of treatment, incomplete data collection, dropouts, unaccounted drug switches, and inherent difficulty with historical comparators. In particular, the internal validity of observational studies may be undermined by previously either known or unknown confounding factors, which may not be evenly distributed between intervention groups and may influence the measured association between the exposure of interest and outcome. However, the introduction of the recently proposed propensity score-adjusted analysis, Bayesian approach and sensitivity analysis has allowed, in the last years, a step forward in reducing the bias in treatment comparisons in observational studies. The long-term impact (for up to 7 years) of IFN□ treatment on times from first visit and from date of birth to reach an irreversible clinical disability, corresponding to Expanded disability status (EDSS) scores 4.0 and 6.0, and to reach secondary progression (SP), was prospectively evaluated in a large cohort of untreated (n. 401) and IFN□-treated (n. 1103) RRMS patients, using an inverse weighting-PS-adjusted Cox proportional hazards regression **(1)**. The results of this observational study demonstrated that patients selected to receive IFN□ treatment have a better outcome than those who choose not to be treated or who are not selected for therapy. The IFN□-treated group showed a substantial reduction in the incidence of conversion to SP, and reaching EDSS scores 4.0 and 6.0 when compared with untreated patients. SP and EDSS scores of 4.0 and 6.0 were reached with significant delays estimated by time from first visit (3.8, 1.7, and 2.2 years, respectively) and time from date of birth (8.7, 4.6, and 11.7 years, respectively) in favour of treated patients. Similar conclusions were drawn from an observational, nonrandomized study **(2)**, using another approach for analyzing DMD, including IFN□, effectiveness on MS disability progression. A pre-post treatment analysis of change in EDSS was conducted in a cohort of 590 RRMS patients collected in a large database in Nova Scotia. Instead of an untreated control group, the investigators used DMD-treated patients as their own controls. DMD effectiveness was examined by comparing individuals' estimated annual changes on EDSS score during the treatment years with those in the years preceding and following the treatment. This study demonstrated an impact of DMDs on disability progression and, in particular, a more rapid EDSS increase during the years following drug switches and treatment stops.

In a more recent Italian study **(3)**, 1178 patients with RRMS and at least 10 years of disease duration, treated (59%) or untreated with DMDs, were stratified on the basis of the Bayesian Risk estimate for Multiple Sclerosis (BREMS) score, obtained from the Bayesian modelling of the natural history of MS **(4)** and predicting their propensity to reach SP. The results of Cox's proportional hazards models showed that the risk of SP was significantly lower in treated patients, regardless of the initial prognosis predicted by BREMS scores. Among the selected high risk patients, 4.1% and 25.4% of the treated patients reached SP versus 31.3% and 64.4% of the untreated patients after 10 and 20 years' disease duration, respectively. In the low risk group, 1.5 % and 7% of the treated patients reached SP versus 8.1% 26.5% of the untreated patients after 10 and 20 years' disease duration, respectively. Contrasting results derive from the recently published retrospective cohort study based on prospectively collected data from British Columbia, Canada **(5)**. In this study, patients with RRMS treated with interferon beta (n=868) were compared with untreated contemporary (n=829) and historical (n=959) cohorts. The main outcome measure was time from IFN□ treatment eligibility to a

confirmed and sustained score of 6. A multivariable Cox regression model with IFN□ treatment included as a time-varying covariate was used to assess the hazard of disease progression associated with IFN□ treatment. After adjustment for potential baseline confounders exposure to IFN□ was not associated with a statistically significant difference in the hazard of reaching an EDSS score of 6 when either the contemporary or historical control cohorts were considered. In this study, the contemporary untreated cohort had a lower annualized relapse rate and longer disease duration, but similar disability level, at baseline, compared with the treated cohort, indicating a more favourable course in the control group. Moreover the treated patients in this study were older at the start of IFN□ treatment in comparison to treated patients in previous observational studies **(1)**. The beneficial impact of early versus delayed IFN□ treatment on disability progression was indeed demonstrated in a large cohort of 2570 RRMS prospectively followed for up to 7 years in 15 Italian MS Centers **(6)**.The main objective of this study was to assess the optimal time to initiate IFN□ with regard to when the greatest benefit on clinical outcomes was observed. A Cox proportional hazards regression model adjusted for PS quintiles was used to assess differences between groups of patients with early versus delayed IFN□ treatment on risk of reaching 1-point progression on EDSS score, and the EDSS 4.0 and 6.0 milestones. A set of PS-adjusted Cox hazards regression models was calculated according to different times of treatment initiation (within 1 year up to within 5 years from disease onset). The lowest hazard ratios for the 3 PS quintiles adjusted models were obtained by a cut-off of treatment initiation within 1 year from disease onset. Early treatment significantly reduced the risk of reaching the EDSS 4.0 milestone and 1-pointprogression in EDSS score. Moreover, the results of this observational study confirmed, in a population with definite RRMS and a longer period of follow-up (7 years), those shown in the extension phase of the original BENEFIT study **(7)** in CIS patients (at 3 years). In conclusion the results from most of observational studies seem to suggest a positive long- term impact of IFN□ on the natural course of MS when compared with non treated patients over the same period, in a clinical practice setting, or when compared with historical cohorts, the only contrasting results derive from the Canadian study. Future methodological improvements to enhance the quality of observational studies are mandatory and future meta-analyses of similar observational data may be useful.

***References**:*


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