INRODUCTION & METHODS

Rationale:
- Interferon (IFN) widely prescribed in patients with relapsing onset multiple sclerosis (MS) since 1996
- Efficacy on reduction of relapses shown through randomised clinical trials and observational studies
- Long-term effect on disability progression assessed through several real-life studies
- Seems that IFN can reduce it (Signori, 2016), but some non-significant results (Shirani, 2012)
- Methodological issues in the assessment of treatments in real-life settings (Sormani, 2014) such as indication bias (lack of ambivalence), immortal bias, choice of the control group, period effect...
- Need to use sophisticated statistical methods to address those problems
- Additional well-designed observational studies are still needed

Design: Retrospective cohort study comparing two groups (IFN-treated versus control) no DMD

Outcome: Time to reach irreversible EDSS score of 6 (a cane required to walk 100 meters)

Follow-up duration starts at eligibility to interferon treatment (based on market authorization criteria) in the 1996-2007 period and ends at the earliest of: irreversible EDSS score of 6 or start of another disease-modifying drug or last clinical information date.

Data: Gender, age, disease duration, relapse rate in the two previous years and calendar year were considered as potential baseline confounders.

Statistical analysis: Analysis was « on-treatment » (data were censored at start of any other DMD). Multivariate Cox regression model with interferon treatment as a time-varying covariate to address immortal time bias, and sIPITW propensity score (stabilized Inverse Probability of Treatment Weighing) to address confounding by indication.

RESULTS

The number of patients reaching irreversible EDSS score of 6 was higher in the IFN-treated group than in controls (19 vs 8, p=0.12). But, as often in observational studies, the IFN group was not similar to the control group on baseline characteristics. As shown in Table 1, use of a propensity score has permitted to make the two groups comparable with very small differences.

Table 1: Characteristics of the treated patients compared with the control group before and after propensity score weighting

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Treat N=717</th>
<th>Controls N=591</th>
<th>p</th>
<th>Treat N=717</th>
<th>Controls N=591</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Women</td>
<td>75.8</td>
<td>76.0</td>
<td>0.90</td>
<td>76.6</td>
<td>76.5</td>
<td>0.99</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>32.8±9.1</td>
<td>34.0±9.8</td>
<td>0.02</td>
<td>33.3±9.2</td>
<td>33.4±9.7</td>
<td>0.86</td>
</tr>
<tr>
<td>Mean MS duration (yrs)</td>
<td>2.8±4.7</td>
<td>2.9±4.7</td>
<td>0.70</td>
<td>2.8±4.9</td>
<td>2.8±4.6</td>
<td>0.77</td>
</tr>
<tr>
<td>Annual Relapse Rate the 3 previous years</td>
<td>3.1±4.8</td>
<td>3.4±4.5</td>
<td>0.22</td>
<td>3.3±4.9</td>
<td>3.2±4.8</td>
<td>0.70</td>
</tr>
</tbody>
</table>

Mean follow-up duration from baseline was 4.5 years (± 3.9) and 3.4 years (± 4.7) in the IFN-treated and in the control group, respectively.

In the IFN-treated group, treatment was initiated after a mean duration of 4.1 years (± 5.3) after MS clinical onset and 1.3 year (± 2.6) after study baseline. In the control group, the total number of person-years of follow-up was 2154, and in the IFN-treated group, it was 4491, respectively 2829 on-treatment and 1662 off-treatment.

The final Cox multivariate analysis gave the following results: HR= 0.58 (0.25-1.33).showing a probability of IFN compared to absence of treatment on the time to reach an irreversible EDSS score of 6 in relapsing-remitting patients.

DISCUSSION

The present study gave results in accordance with the meta-analysis recently published (Signori, 2016) and it incredibly led to the exact results of the study from Trojano in 2009. The result failed to reach statistical significance probably due to a lack of power (number of patients/events need to be increased).

The strengths of the study is the selection of a study population at IFN arrival (1996-2007), a rigorous exposure assessment (time-varying variable) and a high control of the indication bias at baseline (clause of ambivalence), with groups comparable aside treatment group (as demonstrated in the Table and on the propensity scores distributions). Controls are not benign MS who did not need of being treated.

Our main limitation is the lack of MRI parameters in the analysis.

Our perspectives for further analyses are per protocol analysis (no censoring), extension of the inclusion period (>2007), and assessment of the effects of early treatment (based on disease duration, number of relapses or baseline EDSS) on the delay to reach irreversible EDSS score of 3.

LITERATURE