Long-term effect of interferon-β and glatiramer acetate in real-world settings on disability progression: input of time-dependent propensity score

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Introduction

- **Beta interferon (β-IFN) and Glatiramer Acetate (GA)**, are the most widely prescribed disease-modifying therapies in patients with relapsing-remitting multiple sclerosis (RRMS). Both treatments present the same indication. **Their long-term effect on disability progression** has been studied but remains **unclear** maybe due to **lack of appropriate control of indication bias**[1].
- Indication bias occurs when treated and untreated are **not comparable**. **Propensity score (PS)** is a method to handle this bias. Indeed, using this balance score taking into account patients **characteristics at the time of therapeutic decision** could allow to **mimic a randomized clinical trial**[2].
- Nevertheless, in observational studies, the time of therapeutic decision is **difficult to define when controls are untreated**. The use of time-dependent PS can handle this issue, but this method was never used in RRMS.

Objective: To better assess the long-term effect of β-IFN and GA on disability progression in RRMS patients by considering time-dependent confounders.

Patients & methods

Study population

- **Retrospective observational study** including **1300 patients** according to the following inclusion and exclusion criteria on the period from 30/11/1995 to 31/12/2005:
  - Inclusion: **treatment naive, RRMS patients who did not reach an irreversible EDSS score of 3 or involve as secondary progressive MS** before treatment availability
  - Exclusion: patients followed during **less than 2 years** since MS onset and **with less than 3 visits** in the MS expert center

Variables

- **Sex, age at MS onset** and as time dependent covariates: **punctual disability progression** (improvement, stable, worsening according punctual EDSS score) and **recent relapse activity** according the annualized relapses rate since last visit.

Time-dependent PS matching

- Time dependent PS[3] = **the probability to be treated** estimated with a **Cox model** adjusted on preceding variables

↳ **2 groups: treated *vs* not yet treated**

Long-term effect of β-IFN and GA assessment

- The times to reach an irreversible EDSS score of 3 and 6 have been estimated using Kaplan-Meier estimator.
- The mean times before reaching an irreversible EDSS score of 3 and 6 have been compared between the two groups in an intention-to-treat analysis.

Results

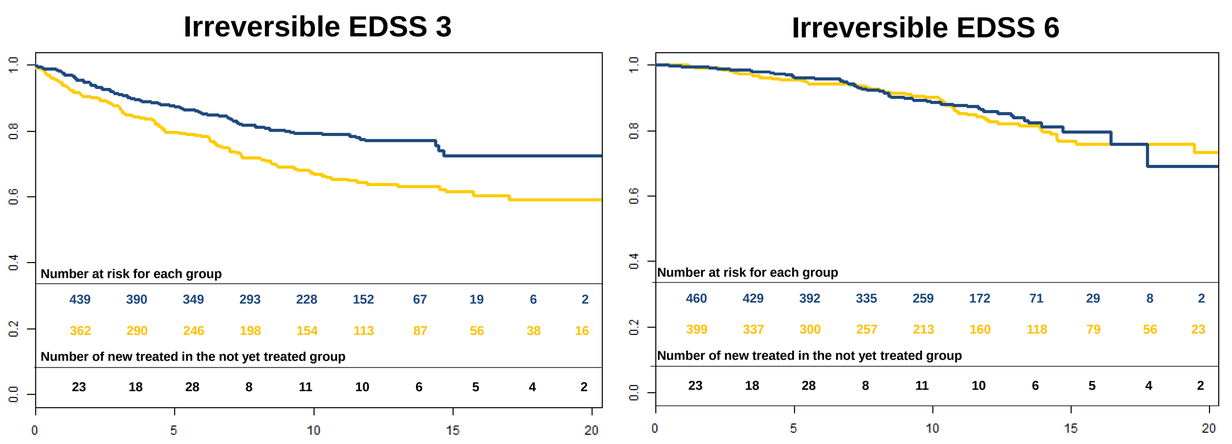
Descriptive analysis

- Our study included 1300 patients, 627 of whom were treated. Among them, 479 patients were matched as treated.

	Treated N=479	Not yet treated N=479
Gender	77%	76%
Age at MS onset	28 ± 8.4	29 ± 6.7
Recent relapse activity at matching		
[0; 1[	70%	72%
[1; 2[	14%	12%
2 and more	16%	16%
Punctual disability progression at matching		
Improvement	9%	10%
Stable	78%	75%
Worsening	13%	15%

- Treated patients initiated their treatment at 34 ± 9.3 years old (mean ± sd) and after a MS durationof 5.0 ± 5.1 years. The mean duration of treatment was 4.1 ± 3.8 years.

Long-term effect of β-IFN and GA assessment



- The mean time before reaching an irreversible EDSS 3 was 12.7 years for treated and 11.4 years for not yet treated. Thus, the time to reach an **irreversible EDSS 3 was delayed by 1.3 year (95%CI: [0.49; 2.02])** in the IFN/GA-treated group, over 15 years.
- The time to reach an irreversible **EDSS 6 was delayed by 0.87 year ([95%CI: [0.34; 1.38])** in the IFN/GA-treated group, over 15 years.

Discussion

- Our results tended to show that early β-IFN and GA treatment delayed the time to reach EDSS 3 and EDSS 6 over 15 years. Although beneficial, this effect remains moderate. The period of the study (1996-2006) could explain this result since patients could have been treated later than it is now recommended.
- We used for the1st time in MS, the time-dependent PS that seems relevant to well balance the two groups over time while conventional PS ignores the temporal features of the treatment. In a context of long term outcome and largely prescribed treatment, this ignorance may lead to inappropriate design, often comparing two not comparable groups (treated *vs* never treated).
- Our main limitation is the lack of MRI parameters in the analysis.
- Further analyses will be performed to study the benefit of β-IFN and GA on a more recent period (2006-2011).

Literature

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