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Assessing the cumulative effects of disease-modifying therapies on the current risk of irreversible disability with relapsing-remitting multiple sclerosis

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Background: Long-term efficacy of disease-modifying therapies (DMT) remains a key question in Multiple Sclerosis (MS). Few real-world studies have confirmed the long-term efficacy of DMT on disability progression, especially when given early. Moreover, the possibility of cumulative effects of past DMT use has not been investigated so far.

Objective: To explore the relationship of mild disability risk, measured by irreversible DSS between 3 and 5 with current and prior DMT use in patients with relapsing-remitting MS (RRMS).

Method:

Study design

Multicenter observational study concerning four OFSEP centers providing comprehensive information on irreversible disability.

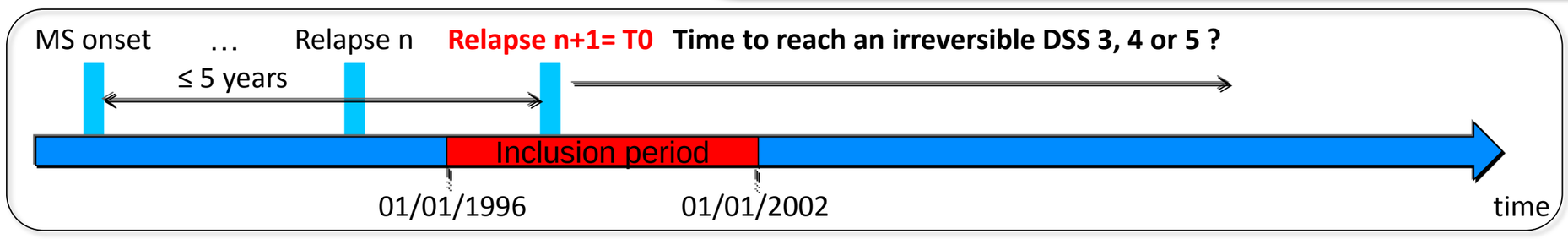
In order to limit bias related to treatment indications, patients had to be eligible for treatment with the criteria for marketing authorization prior to 2002.

Inclusion criteria:

- Patients with RRMS
- Patients with at least one relapse, beyond the first neurological episode, between 01/01/1996 and 01/01/2002
- Disease duration of less than 5 years at inclusion relapse
- Patients over 18 years old
- Irreversible DSS ≤ 2
- Naïve treatment patients

Statistical analysis

- To assess the impact of the use of DMT on irreversible DSS risk, we employed a novel analytical method[1,2] with **weighted cumulative exposure (WCE) model** correlating DMT exposure to the current risk of disability. That model assigns to each DMT use taken in the past a weight that represents the relative importance of this use. More specifically, **the WCE method takes into account the duration of the previous treatment up to the "current" time and the time of exposure to this treatment**. The regression spline-based method for modeling the WCE was considered as a time-dependent covariate in the Cox's PH regression analysis.
- Several baseline confounders were included: sex, duration of disease, time since last relapse, period, irreversible DSS (0, 1 or 2), semiology of relapse and centers. Age and cumulative number of relapses were considered as time-dependent covariates.



References

[1] *Abrahamowicz, Modeling cumulative dose and exposure duration provided insights regarding the associations between benzodiazepines and injuries. J Clin Epidemiol. 2006 Apr;59(4):393-403.*

[2] Sylvestre, Flexible modeling of the cumulative effects of time-dependent exposures on the hazard., Stat Med. 2009 Nov 30;28(27):3437-53. doi: 10.1002/sim.3701.

Results: Overall, **2,117 patients** were included in the study in Nancy, Rennes, Lyon and Nantes centers. The median follow-up was 14.9 years (IQR=[7.8-17.5]) and 878 patients (41.5%) reached the outcome.

- ***Patient's characteristics***

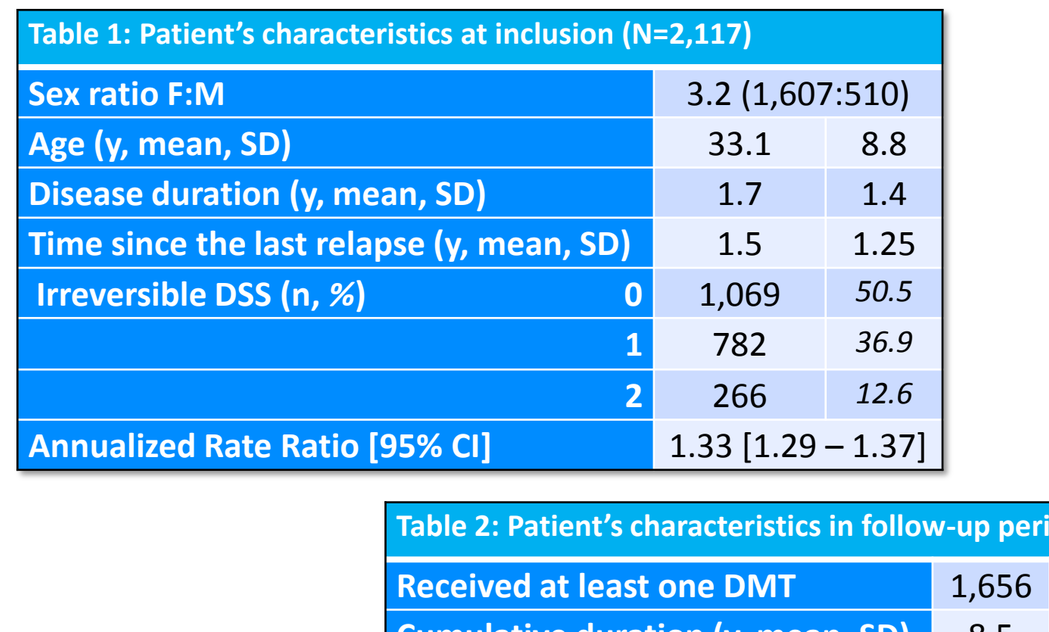
Table 1: Patient's characteristics at inclusion (N=2,117)

Sex ratio F:M		3.2 (1,607:510)	
Age (y, mean, SD)		33.1	8.8
Disease duration (y, mean, SD)		1.7	1.4
Time since the last relapse (y, mean, SD)		1.5	1.25
Irreversible DSS (n, *%*)	0	1,069	*50.5*
	1	782	*36.9*
	2	266	*12.6*
Annualized Rate Ratio [95% CI]		1.33 [1.29 – 1.37]	

Table 2: Patient's characteristics in follow-up period

Received at least one DMT	1,656	*78.2*
Cumulative duration (y, mean, SD)	8.5	5.3
% of follow-up duration	58.1	

Figure 1: Histogram of all therapeutic sequences of the follow-up (N=5,131)



- ***WCE method***

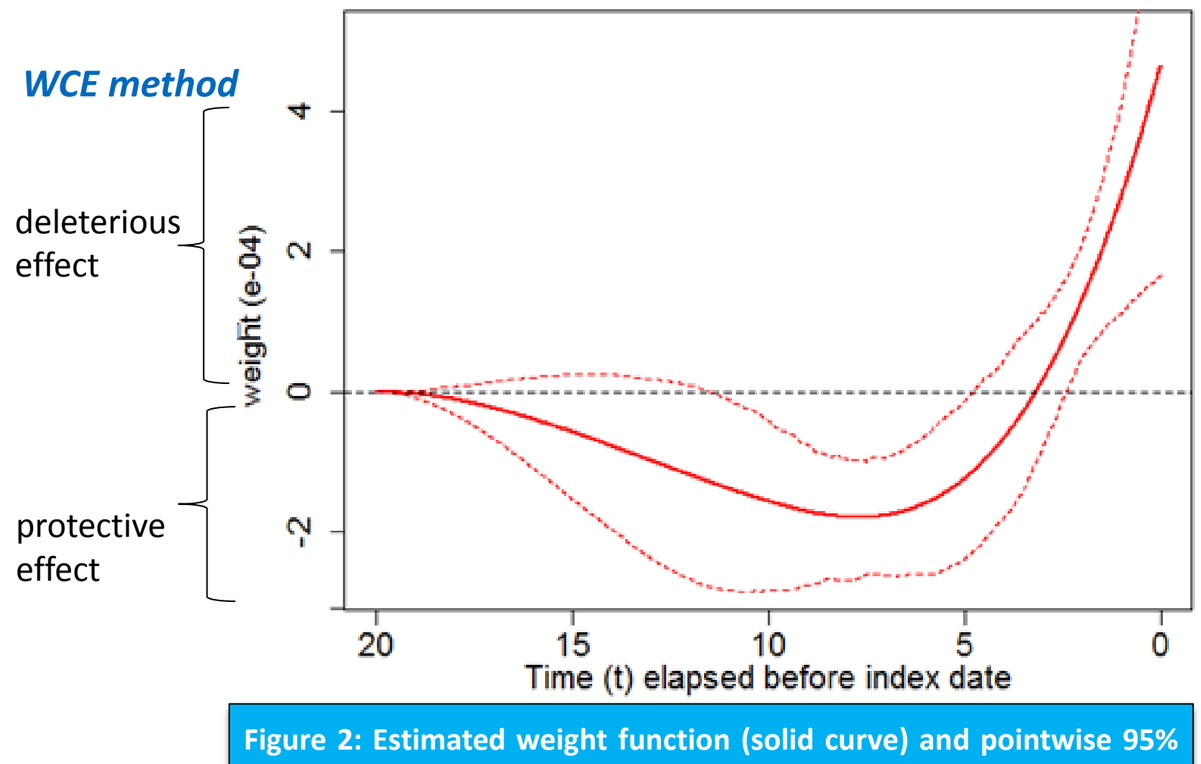


Figure 2: Estimated weight function (solid curve) and pointwise 95% bootstrap CI (dotted curves) for the weighted cumulative model of the association between previous DMT exposure and mild disability

The weights reflect the relative strength of the impact of DMT use taken *t* months ago on the current risk of mild disability. The current and recent use (near t=0) have the highest impact on current risk, and the effect of past DMT use decreases sharply with increasing time since exposure. The weight function suggests that past uses (more than 5 years ago) are associated with decreased current risk (weight < 0). These 'remote' uses can lead to an important cumulative effect if taken for a long time.

Table 3: Adjusted hazards ratio (HR) (with 95% CI) for the association between various patterns of DMT uses and risk of mild disability derived from the weight function

Pattern of use	Reference	HR	95% CI
Past user for 5 years, stopped 10 years ago	Current user for past 5 years	0.68	[0.51 – 0.90]
The earlier the patients were treated, the lower the risk			
Current user for past 15 years	Past user for 2 years, stopped 13 years ago	0.78	[0.60 – 0.96]
The longer the patients were treated, the lower the risk			
Current user for past 15 years	Current user for past 5 years	0.61	[0.44 – 0.80]
The longer and earlier the patients were treated, the lower the risk			

Conclusion: Mechanisms affecting the long-term risk of mild disability may include cumulative effects of DMT use in the previous years. Early use of DMT has a beneficial cumulative impact on the occurrence of mild disability.

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