

Disease reactivation after cessation of disease-modifying therapy in relapsing-remitting multiple sclerosis

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Background and Aim

Multiple sclerosis (MS) treatment interruptions are common, and leave patients vulnerable to breakthrough disease activity. The safe duration of the 'switchover time' for different therapies is not known.

We aimed to evaluate the rate of return of disease activity after cessation of disease-modifying therapy.

Methods

Retrospective cohort study from two large observational MS registries:

MSBase (international) and OFSEP (French national registry).

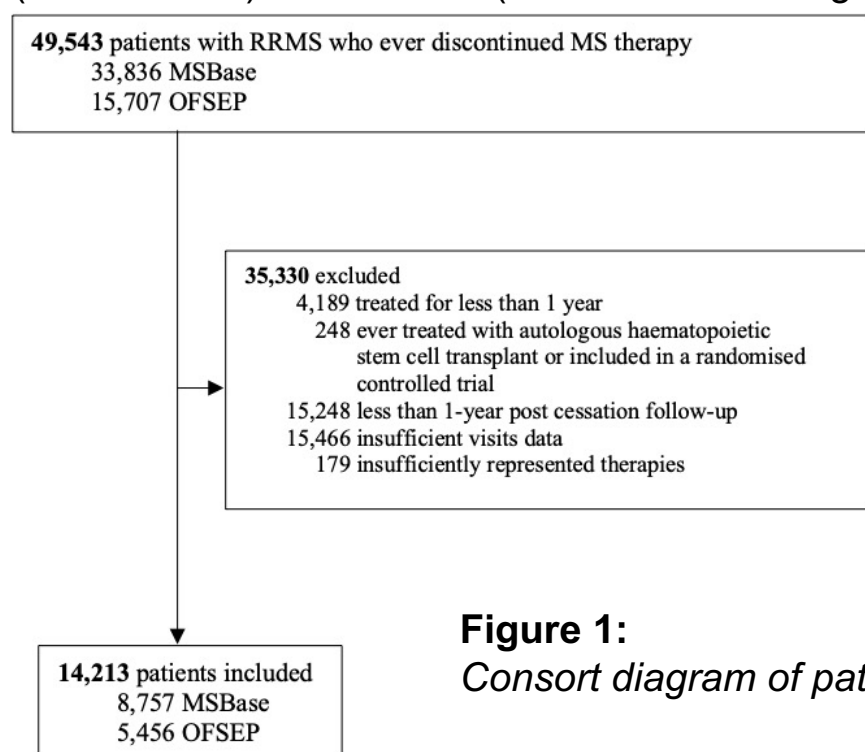


Figure 1:
Consort diagram of patient disposition

Primary Outcome: Annualised relapse rate in the 12 months after treatment discontinuation, stratified by subsequent treatment commencement

Secondary Outcome: Predictors of relapse and 6-month confirmed disability accumulation after treatment discontinuation (Cox proportional hazards models with treatment status as time-varying covariate)

Results

Table 1: Predictors of disease activity after cessation of therapy

	First Relapse	Disability Accumulation
	HR (95% CI)	
Therapy		
Interferon		Reference
Mitoxantrone	0.91 (0.74-1.13)	1.12 (0.81-1.55)
Natalizumab	1.87 (1.73-2.03)	2.06 (1.81-2.34)
Fingolimod	1.67 (1.49-1.87)	2.01 (1.67-2.43)
Dimethyl fumarate	1.08 (0.91-1.30)	1.33 (0.97-1.81)
Teriflunomide	0.89 (0.70-1.11)	1.08 (0.74-1.57)
Glatiramer acetate	1.01 (0.94-1.08)	1.17 (1.04-1.32)
Age at cessation	0.97 (0.97-0.98)	1.03 (1.02-1.03)
Sex (male)	0.81 (0.76-0.87)	1.32 (1.18-1.47)
MS duration at cessation	1.00 (0.99-1.00)	1.01 (1.00-1.02)
EDSS at cessation	1.05 (1.03-1.07)	0.95 (0.93-0.98)
Number of relapses in prior year	1.27 (1.24-1.31)	0.98 (0.93-1.03)
Commencement of next therapy	0.76 (0.72-0.81)	0.73 (0.65-0.80)
Year at cessation	0.93 (0.92-0.93)	0.98 (0.97-0.99)

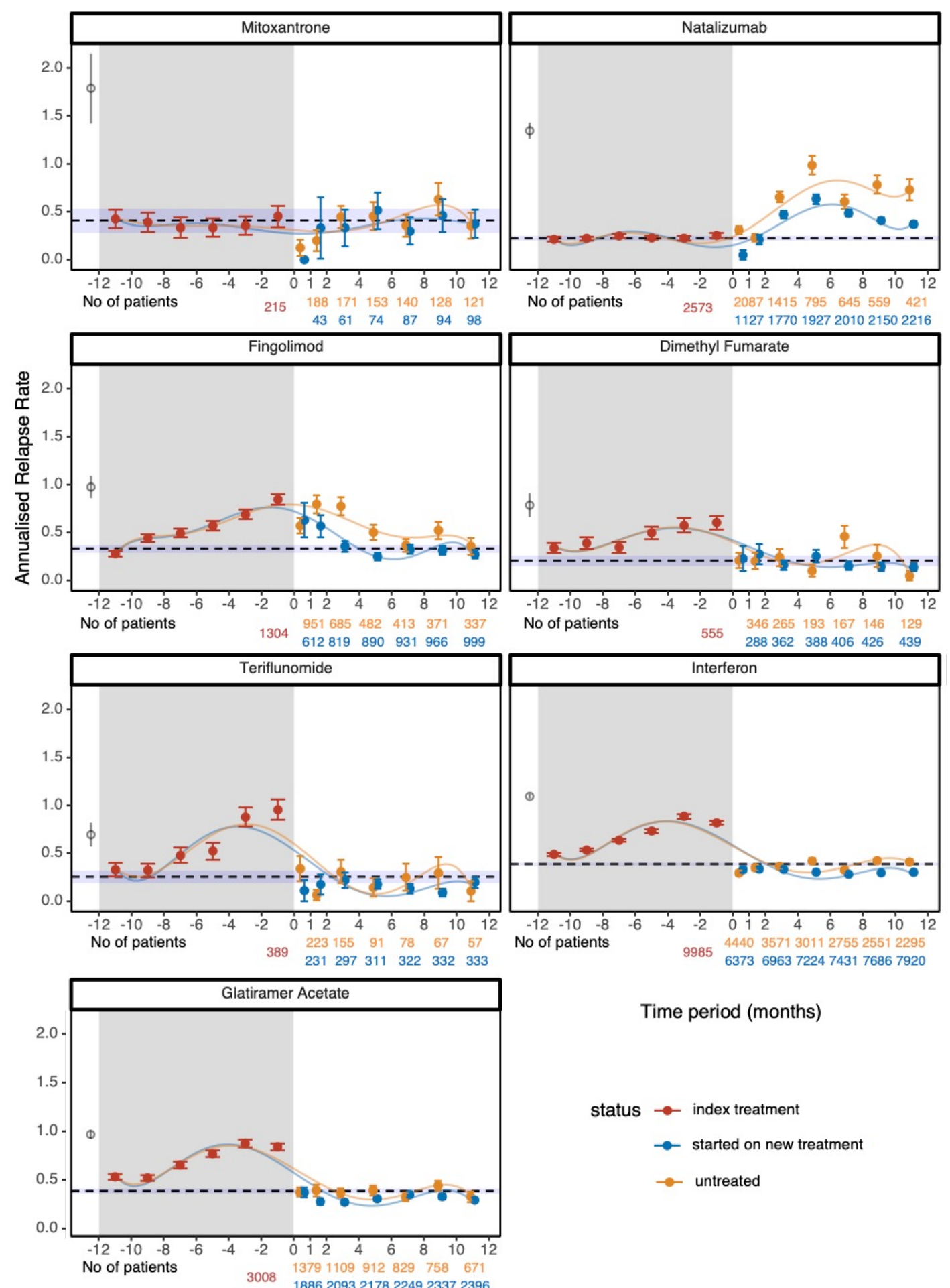


Figure 2: Annualised relapse rate in the year before baseline (during index treatment) and after treatment cessation.

Baseline (treatment cessation) is indicated by timepoint 0. The period after treatment cessation is stratified by patients who remained **untreated** or have **started a new treatment** (for each 1- or 2-month period). The **on-treatment period** is indicated by the grey shaded area. Point and whiskers show the relapse rates in each epoch. The pre-treatment relapse rate, and 95% confidence interval, is indicated by the open circle and line. The black dashed line is a visual reference of the mean relapse rate during the second year prior to treatment cessation, with the shaded area indicating 95% confidence intervals. Number of patients: patients that contribute some time to each period.

Results were consistent for all sensitivity analyses ((i)more stringent definition of relapses (severe/treated with steroids), (ii)excluding discontinuation for pregnancy planning, (iii) stratified by pre-baseline relapses. Results were consistent in an additional analysis where the post-baseline ARR was weighted for factors that may influence the decision to start a subsequent therapy.

Conclusion: For all studied therapies apart from mitoxantrone, disease reactivation is reduced by the commencement of a subsequent therapy within the first 10 months. Patients treated with natalizumab and fingolimod are at highest risk of clinical disease activity after treatment cessation and benefit from the earliest introduction of a subsequent therapy (**within 1 month for fingolimod and within 2 months for natalizumab**).

Importantly, any decisions regarding treatment switch after discontinuation of therapy should be individualised to patient's clinical profile, including prior on-treatment relapse activity, age, sex, and disability.