CLINICAL CHARACTERISTICS PREDICTING RELAPSES FOLLOWING DISEASE MODIFYING THERAPIES DISCONTINUATION IN RELAPSING-REMITTING MULTIPLE SCLEROSIS: A MONOCENTRIC COHORT STUDY.

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OBJECTIVE
To report clinical and radiological disease activity in a cohort of RRMS patients who interrupted a DMT and to identify factors which can predict the occurrence of relapses after discontinuation.

BACKGROUND
The benefit of permanent discontinuation of DMTs in RRMS patients with a long period of absence of disease activity is not clear, and predictors of disease activity after discontinuation are not completely defined, and cases of MS relapses after interruption are reported in literature. Few studies showed that patients with a longer relapse-free period an older age are before DMTs discontinuation are not associated with an increased risk of relapse.

METHODS
Clinical and radiological data of 1107 patients treated with a disease modifying therapy (DMT) and followed in the Multiple Sclerosis Centre of Department of Neurology 2 AOU Careggi in Florence from 1994 to 2018.

INCLUSION CRITERIA
- patients who discontinued a DMT for at least 6 months
- age between 18 and 65
- Absence of pregnancy history

62 patients were included

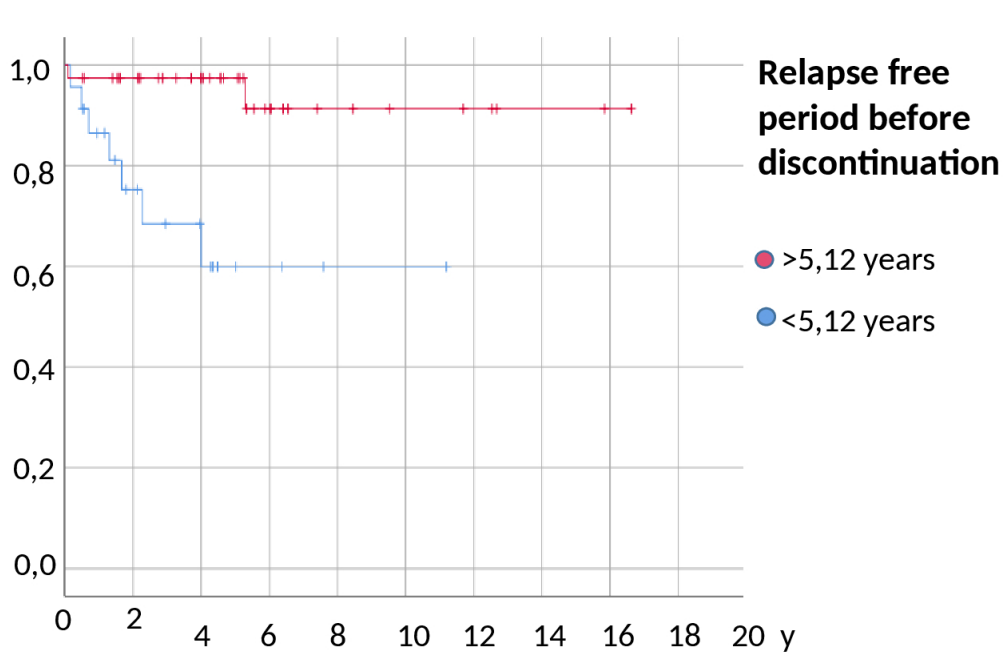
PRIMARY ENDPOINTS
- occurrence of a relapse after discontinuation of DMT
- determine any differences in demographic, clinical and MRI data between relapsing and non relapsing patients after discontinuation

SECONDARY ENDPOINT
- occurrence of a comfirmed disease progression after discontinuation of DMT

RESULTS
-A Mann-Whitney U test and a chi-square were conducted: Median relapse-free period before discontinuation was statistically significantly shorter in relapsing patients (table).
-Bivariate testing showed a correlation between absence of relapses after DMT discontinuation and a longer relapse-free period before discontinuation, $r_s(98) = -0.285$, $p = 0,025$.
-ROC analyses indicated the best possible cut-off values of 5,12 years of relapse free period before discontinuation (sensitivity: 70%, specificity: 78%). Using these cut-off value, only 2/39 (5,1%) patients with more than 5,12 years of stability of disease course before discontinuation reported a relapse after discontinuation of DMT compared to 7/23 (30,4%) patients with less than 5,12 years of stable disease course before discontinuation. This difference was confirmed as statistically significant with chi square test ($\chi2 = 7,47$, $p = 0,01$) and Kaplan-Meier survival analysis ($\chi2 = 9,63$, $p=0,002$).
-A multivariate survival analyses using Cox regression was performed to ascertain the effects of age at beginning and at discontinuation, relapse and radiological free period before discontinuation, DMTs duration and relapse-free period > 5,12 years before discontinuation on the occurrence of a relapse after discontinuation of therapy. Relapse-free period > 5,12 years before discontinuation was found to be independent predictor of absence of relapse after discontinuation of DMT (HR = 0,119, CI = 0,024-0,584, p = 0,009).

Demographic, clinical and radiological data	Relapsing patients (n=9)	Non relapsing patients (n=53)	p-value
gender (women)	6 (66,7%)	36 (67,9%)	0,609
Age at beginning of therapy (y)	31,38 (19,67 – 47,84)	38,59 (20,6 – 57,50)	0,374
Age at discontinuation (y)	37,27 (27,36 – 55,61)	48,35 (22,15 – 64,30)	0,108
MS pre treatment duration (y)	1,9 (0,08 – 16,59)	3,42 (0,06 – 34,32)	0,117
N° pre treatment relapses	2 (0 – 3)	2 (1 – 10)	0,225
Treatment duration (y)	5,39 (0,5 – 17,6)	7,36 (1,56 – 18,1)	0,610
Total disease duration(y)	9,74 (2,25 – 20,85)	12,38 (2,35 – 39,49)	0,407
EDSS at beginning of therapy	1 (0 – 3)	1 (0 -5)	0,610
EDSS at discontinuation	2 (0 – 3)	1 (0 -6)	0,272
Patients with a relapse on treatment	5 (55,6%)	26 (49,1%)	0,500
N° of relapse on treatment	1 (0 – 2)	0 (0 -6)	0,225
relapse-free period before discontinuation (y)	4,25 (0,33 – 9,22)	6,08 (0,09 – 14,73)	0,026
Patients with radiological activity on treatment	4 (44,4%)	26 (49,1%)	0,487
radiological activity - free period before discontinuation (y)	4,2 (0,1 – 11,1)	5,75 (0,08 – 14,63)	0,153
Follow-up post discontinuation (y)	4,83 (0,38 – 10,43)	4,28 (0,5 – 16,62)	0,928

- DMTs administered in this cohort were azathioprine (n= 36, 58,1%), any beta-interferon (n= 15, 24,2%), glatiramer acetate (n= 6, 9,7%); dimethyl-fumarate (n= 1, 1,6%) and azathioprine+ one beta-interferon (n= 4, 6,4%).
- Reasons for discontinuation were stable disease course (56,5%), adverse events (17,7%), patient's decision (17,7%) and occurrence of cancer during DMT (8,1%)



CONCLUSIONS
-14,5% of patients had a relapse after therapy discontinuation;
-only 3 patients (4,8%) switched to SP-MS after discontinuation;
-a shorter relapse free period at discontinuation was the only predictor of relapse after discontinuation;
-we identified that the absence of relapse for more than 5 years before discontinuation is associated with a lower risk of having relapses after discontinuation (HR 0,119).

BIBLIOGRAPHY
- Bsteh, G. *et al*. Discontinuation of disease-modifying therapies in multiple sclerosis - Clinical outcome and prognostic factors. *Mult. Scler. Houndmills Basingstoke Engl.* **23**, 1241–1248 (2017).
- Kister, I. *et al*. Predictors of relapse and disability progression in MS patients who discontinue disease-modifying therapy. *J. Neurol. Sci.* **391**, 72–76 (2018).