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

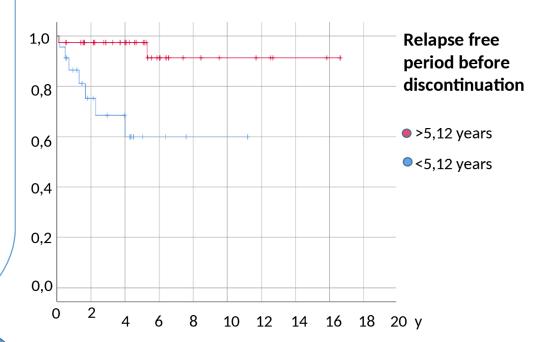
occurrence of a comfirmed disease progression after discontinuation of DMT

<u>RESULTS</u>

- A Mann-Whitney U test and a chi-square were conducted: Median relapsefree 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 (χ 2 = 7,47, p = 0,01) and Kaplan-Meier survival analysis (χ 2 = 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).

| gender (women) 6 (66,7%) 36 (67,9%) 0,609 Age at beginning of therapy (y) 47,84) 57,50) Age at discontinuation (y) 55,61) 64,30) MS pre treatment 1,9 (0,08 - 34,22) 0,06 - 0,117 | Demographic, clinical and radiological data | Relapsing patients (n=9) | Non relapsing patients (n=53) | p-value |
|---|---|-----------------------------|-------------------------------------|--------------|
| therapy (y) Age at discontinuation (y) Age at discontinuation (y) MS pre treatment duration (y) N° pre treatment relapses Treatment duration Patients with a relapse-free period before discontinuation (y) Pollow-up post Age at 37,27 (27,36 - 48,35 (22,15 - 0,108 - 44,28 (0,5 - 0,610 - 0,117 - 0 | gender (women) | 6 (66,7%) | 36 (67,9%) | 0,609 |
| discontinuation (y) 55,61) 64,30) MS pre treatment duration (y) 1,9 (0,08 - 3,42 (0,06 - 0,117 34,32) N° pre treatment relapses 2 (0 - 3) 2 (1 - 10) 0,225 7,36 (1,56 - 0,610 18,1) Treatment duration (y) 5,39 (0,5 - 7,36 (1,56 - 0,610 18,1) 0,610 18,1) Total disease duration(y) 9,74 (2,25 - 20,85) 12,38 (2,35 - 0,407 39,49) EDSS at beginning of therapy 1 (0 - 3) 1 (0 - 5) 0,610 10 EDSS at discontinuation 2 (0 - 3) 1 (0 - 6) 0,272 10 Boss at elapse on treatment 5 (55,6%) 26 (49,1%) 0,500 10 Patients with a relapse on treatment 5 (55,6%) 26 (49,1%) 0,500 10 Patients with a relapse-free period before discontinuation (y) 4,25 (0,33 - 9,22) 6,08 (0,09 - 14,73) 0,026 14,73 Patients with radiological activity on treatment 4 (44,4%) 26 (49,1%) 0,487 14,63 Patients with radiological activity on treatment 4,2 (0,1 - 5,75 (0,08 - 14,63) 0,153 14,63 Pollow-up post 4,83 (0,38 - 4,28 (0,5 - 0,928) | | | | 0,374 |
| duration (y) 16,59) 34,32) N° pre treatment relapses 2 (0 - 3) 2 (1 - 10) 0,225 Treatment duration (y) 5,39 (0,5 - 18,1) 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 EDSS at discontinuation 5 (55,6%) 26 (49,1%) 0,500 Patients with a relapse on treatment 1 (0 - 2) 0 (0 - 6) 0,225 N° of relapse on treatment 4,25 (0,33 - 9,22) 6.08 (0,09 - 9,22) 0,026 Defore discontinuation (y) 4 (44,4%) 26 (49,1%) 0,487 Patients with radiological activity on treatment 4 (44,4%) 26 (49,1%) 0,487 Patients with radiological activity on treatment 4,2 (0,1 - 14,63) 5,75 (0,08 - 14,63) 0,153 Follow-up post 4,83 (0,38 - 4,28 (0,5 - 0,928) 0,928 | • | | | 0,108 |
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| (y) 17,6) 18,1) Total disease duration(y) 9,74 (2,25 - 20,85) 12,38 (2,35 - 39,49) 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 treatment 4.25 (0,33 - 9,22) 6,08 (0.09 - 14,73) 0,026 before discontinuation (y) 4 (44,4%) 26 (49,1%) 0,487 Patients with radiological activity on treatment 4 (44,4%) 26 (49,1%) 0,487 radiological activity on treatment 4,2 (0,1 - 11,1) 5,75 (0,08 - 14,63) 0,153 Follow-up post 4,83 (0,38 - 4,28 (0,5 - 0,928) | • | 2 (0 - 3) | 2 (1 – 10) | 0,225 |
| duration(y) 20,85) 39,49) 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 treatment 4.25 (0,33 - 9.22) 6.08 (0,09 - 14,73) 0.026 before discontinuation (y) 4 (44,4%) 26 (49,1%) 0,487 Patients with radiological activity on treatment 4,2 (0,1 - 5,75 (0,08 - 14,63) 0,153 free period before discontinuation (y) 4,83 (0,38 - 4,28 (0,5 - 0,928) | | | | 0,610 |
| EDSS at discontinuation Patients with a relapse on treatment N° of relapse on treatment relapse-free period before discontinuation (y) Patients with 4 (44,4%) 26 (49,1%) 0,500 A (49,1%) 0,500 O(0 - 6) 0,225 O(0 - 6) | | | | 0,407 |
| discontinuation 5 (55,6%) 26 (49,1%) 0,500 Patients with a relapse on treatment 1 (0 - 2) 0 (0 - 6) 0,225 N° of relapse on treatment 1 (0 - 2) 0 (0 - 6) 0,225 treatment 4,25 (0,33 - 9,22) 6,08 (0,09 - 14,73) 0,026 before discontinuation (y) 4 (44,4%) 26 (49,1%) 0,487 Patients with radiological activity on treatment 4,2 (0,1 - 11,1) 5,75 (0,08 - 14,63) 0,153 free period before discontinuation (y) 4,83 (0,38 - 4,28 (0,5 - 0,928) | | 1 (0 - 3) | 1 (0 -5) | 0,610 |
| relapse on treatment N° of relapse on treatment $\frac{1 (0-2)}{1 (0-2)} = \frac{0 (0-6)}{0.225} = \frac{0.025}{0.025} = \frac{0.08 (0.09-0.026)}{0.025} = \frac{0.026}{0.025} = \frac{0.026}{0.025$ | | 2 (0 - 3) | 1 (0 -6) | 0,272 |
| treatment 4.25 (0.33 - 9.22) 6.08 (0.09 - 14.73) 0.026 before discontinuation (y) 4 (44.4%) 26 (49.1%) 0,487 Patients with radiological activity on treatment radiological activity - free period before discontinuation (y) 4,2 (0.1 - 11.1) 5,75 (0.08 - 14.63) 0,153 Follow-up post 4,83 (0.38 - 4.28 (0.5 - 0.928) | | 5 (55,6%) | 26 (49,1%) | 0,500 |
| before discontinuation (y) 9,22) 14,73) Patients with radiological activity on treatment 4 (44,4%) 26 (49,1%) 0,487 radiological activity on treatment 4,2 (0,1 - 5,75 (0,08 - 14,63) 0,153 14,63) free period before discontinuation (y) 11,1) 14,63) 0,928 | • | 1 (0 - 2) | 0 (0 -6) | 0,225 |
| radiological activity on treatment radiological activity - 4,2 (0,1 - 5,75 (0,08 - 0,153 free period before discontinuation (y) Follow-up post 4,83 (0,38 - 4,28 (0,5 - 0,928 | <u>before</u> | | | <u>0,026</u> |
| free period before 11,1) 14,63) discontinuation (y) Follow-up post 4,83 (0,38 - 4,28 (0,5 - 0,928) | radiological activity | 4 (44,4%) | 26 (49,1%) | 0,487 |
| | free period before | | | 0,153 |
| | | | | 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).

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