Recurrence of multiple sclerosis activity after fingolimod discontinuation is not rare in older patients previously stable on treatment.

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Objective: To study the incidence of recurrence and rebound disease activity after fingolimod (FTY) discontinuation, especially in older MS patients without evidence of disease activity.

Methods: Retrospective analysis of 101 patients from the Lausanne prospective MS registry.

Inclusion criteria: (i) Relapsing Remitting or Secondary Progressive MS (McDonald 2010 criteria), (ii) on FTY > 6 m, (iii) follow-up duration after discontinuation > 6 m.

Data collected. (i) total n. of relapses (ii) EDSS (iii) n. of T2 and T1 Gd+ lesions, prior to FTY initiation, during FTY, and 6 months post FTY discontinuation. Reason for discontinuation and type of relay disease modifying treatment (DMD) was assessed. We specifically focused on a **subgroup** of **patients with high estimated progressive multifocal leukoencephalopathy (PML) risk** (positive JCV status, older >45y, on FTY >2y) .

Definitions : Recurrence of disease activity (RDA) either clinical and/or MRI activity after FTY discontinuation. **Rebound** much higher disease activity after discontinuation than before FTY onset.

Results

Prior to FTY initiation : median number of relapse 1 (0-4), mean EDSS score 2.0. Active MRI in the majority of patients (71.1 % new or enlarged T2 lesions, 38 % GD enhancing lesions.

On FTY : **NEDA 3 status in 60 % of patients.**

Reasons for FTY discontinuation : **estimated high risk of PML** (n=31, 30.7 %), **lack of efficacy** (n=28, 27.7 %), **pregnancy planning** (n=18, 17.8 %), **patients' convenience** (n=10, 9.9 %), **side effects** (n=8, 7.9 %) and **physician's decision** (because of transition to SPMS or comorbidities) (n=6, 5.9 %).

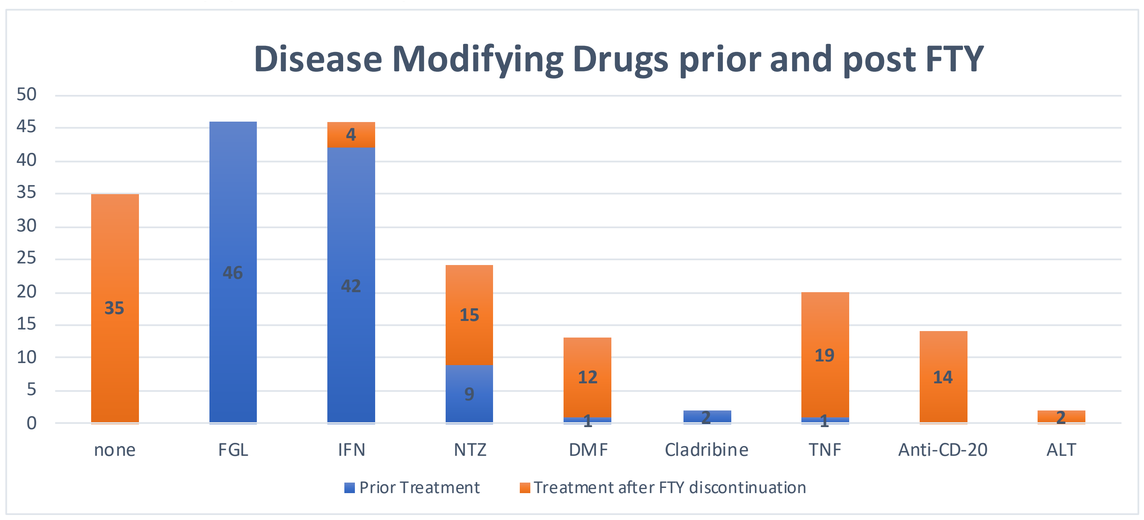
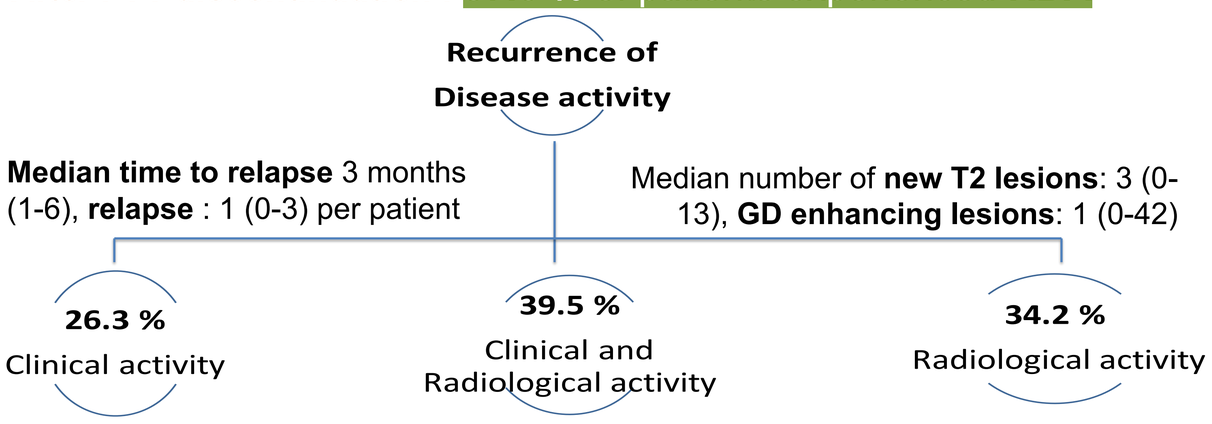


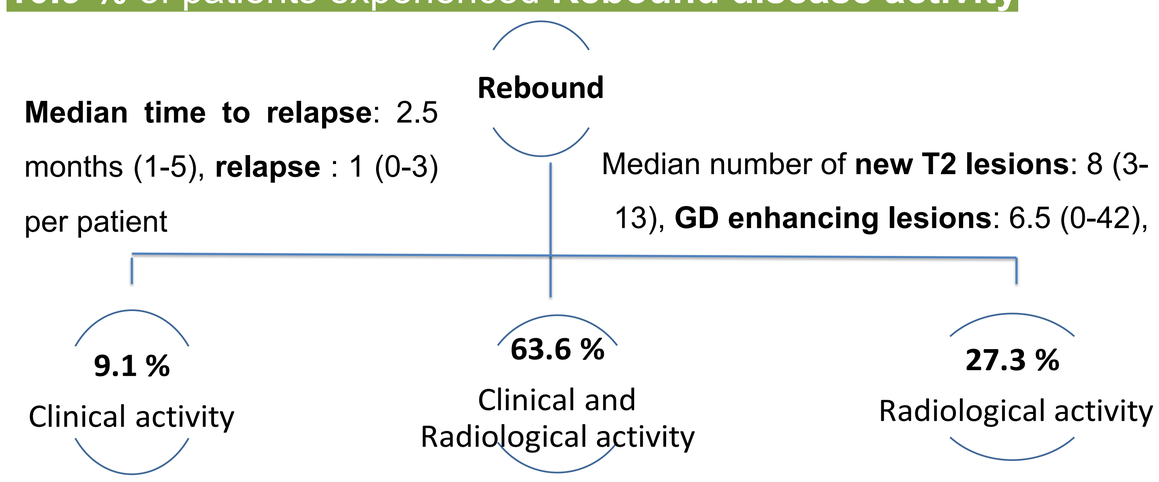
Figure 1: *Disease modifying drugs (DMD) used prior to FTY initiation (blue) and after FTY discontinuation (orange).*

After FTY discontinuation : **37.6 %** of patients experienced **RDA**



WHICH PATIENTS experience RDA? More common in patients who discontinued treatment for **disease activity** (34.2%). **Higher pre-FTY disease activity** in RDA patients (OR 4.479, 95% CI 1.41–14.14, p= 0.01).

10.9 % of patients experienced **Rebound disease activity**



WHICH PATIENTS experience **rebound?**

- 81.82% of patients previously **stable on treatment**.
- 63.6% of patients : no DMD at rebound.
- **MRI activity** (p=0.058) rather than clinical relapses (p=0.774) pre-FTY correlated with rebound.

32.3 % of older and stable on treatment patients experienced **RDA** and **10% rebound**

Table 1: *Demographic, clinical and MRI characteristics of the 31 patients with high estimated PML risk.*

	Total (N=31)	RDA (N=10)	Rebound (N=3)
Age (y) at disease onset (median, range)	38, 17-60	34, 27-40	**30**, 27-40
Sex, F/M (n)	19/12	5/5	3/0
Disease activity prior to FTY (median, range)			
- **Relapses (median, range)**	1, 1-2	1, 0-2	1, 1-2
- **New T2 lesions (median, range)**	1, 0-30	1, 0-30	0, 0-30
- **Gd + lesions (median, range)**	0, 0-6.0	**0**	**0**
- **EDSS (mean, SD)**	2.13, 1.0	1.8, 0.48	**2.76**, 0.76
NEDA 3 status on FTY	80.6 %	n.a	n.a
NEDA 3 status after FTY	67.7%	n.a	n.a

In older and stable patients, RDA and rebound occurrence rates were similar to the whole cohort. No correlation between clinical (p=0.370) or MRI activity (p=0.657) pre-FTY and type of DMD pre-FTY treatment (p=0.513) and RDA/rebound.

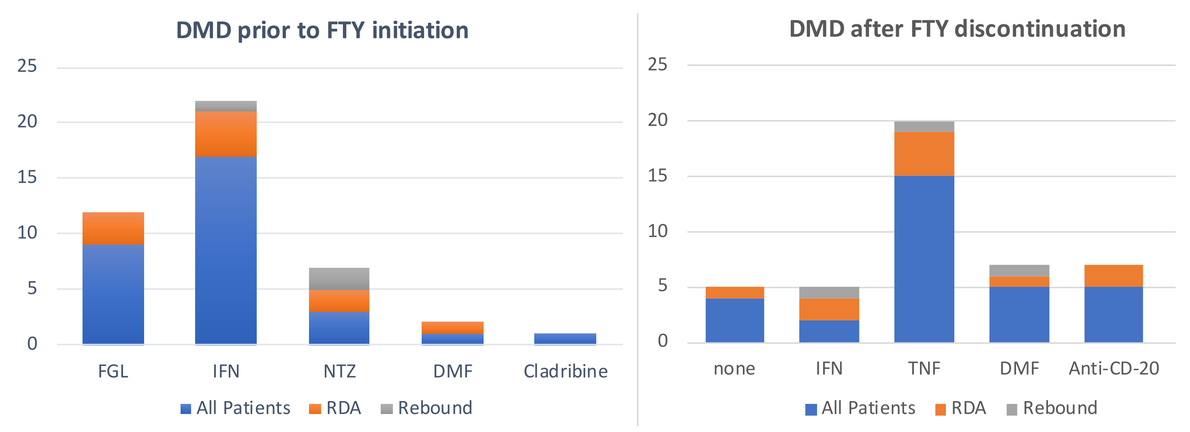


Figure 3: *DMD use prior to and after FTY treatment in the high estimated PML risk subgroup (blue) and at RDA (orange) / rebound (grey). NTZ prior to FTY and IFN/TNF after FTY were mostly associated with reactivation of disease activity after FTY discontinuation.*

Conclusion : RDA in almost 40 % of our patients and severe rebound in 10 %. Main risk factor for rebound : absence of treatment after FTY discontinuation. 30 % of the older patients, expected to have a less active disease given their age and the absence of disease activity for several years on FTY experienced RDA, and 3 a rebound, despite they were all (but one) on a relay DMD.