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Short Summary

Reactivation of Multiple Sclerosis (MS) activity has been described after fingolimod cessation. Because of its contra indication during pregnancy, switch towards lower efficacy treatments are frequent in MS patients with childbearing desire but expose them to a risk of disease reactivation.

In this retrospective study including 44 women with MS, a significant increase of the median annualized relapse rate was found in the year following fingolimod discontinuation compared to the period before ($p<0.0001$), and 57% of women experienced at least one relapse.

When considering to start fingolimod, particular attention should be paid to women with a short-term pregnancy desire.

Introduction:

Reactivation of Multiple Sclerosis (MS) activity has been extensively described after natalizumab cessation. Since 2012, several studies have also reported clinical and radiological activity after fingolimod (FTY) discontinuation, whatever the reasons for stopping [1–7]. Due to potential fetal toxicity, this treatment is contra indicated during pregnancy and a switch to injectable immunomodulatory drugs is frequent in this context but might be insufficient to preserve patients from the risk of disease reactivation. Thus, it is extremely important to properly evaluate the risk behind FTY discontinuation in this specific context of pregnancy planning, but specific data are very limited.

In this retrospective multicenter study, we aimed to describe the evolution of clinical activity in a cohort of women having stopped FTY for pregnancy desire.

Methods:

Cohort and data collection

This is a retrospective study using data prospectively collected in 6 MS centers in Western France. Inclusion criteria were: (1) Relapsing remitting MS (RRMS) women, (2) treated by FTY for at least 6 months and (3) having stopped FTY for pregnancy desire between 12/2010 and 12/2020 and with clinical follow up of at least one year after FTY cessation. Demographic and clinical data (relapse, EDSS, treatments) were systematically collected from one year before FTY start to one year after FTY withdrawal.

The study was approved by the local ethics committee.

Outcomes

The main outcome was to compare relapse activity (annualized relapse rate – ARR) between the FTY-treated period and the year following FTY cessation.

Secondary outcome was the time from FTY cessation to the first relapse.

Statistical analysis

Statistical analyses were performed using R version 4.0.2. Descriptive analysis of women/pregnancies was conducted as appropriate (number and percentage for qualitative variables; median, first and third quartiles for quantitative variables).

ARR were calculated and compared between periods (pre-FTY, during FTY, post FTY) with Wilcoxon signed rank tests. Time to first relapse after FTY stop was analyzed with Kaplan-Meier estimator. Women with disease reactivation after FTY stop were compared to women without relapse using Fisher exact tests or Mann-Whitney tests.

Results:

Forty-four MS patients were included. Three of them stopped twice FTY for pregnancy desire, so 47 FTY cessations were analyzed.

Median MS duration before FTY start was 5.2 years (Table 1). More than 70% of MS patients switched from a first line to FTY; 55.3 % of patients switched because of inefficacy of previous treatments and 17% for safety issues.

In the year after FTY cessation, we observed a significant increase of the median ARR compared to the ARR under FTY (1 vs 0, $p<0.0001$), getting similar to the ARR before FTY initiation (1) (Figure 1A). Overall, 57% (n=27/47) of MS patients presented at least one relapse during this period and 36% (n=17/47) 2 or more relapses. In this group of relapsing patients, 74% (20/27) had a relapse in the first 6 months after FTY stop. In addition, 38.3% (n=18/47) of patients presented a clinical rebound, i.e. a disease reactivation which surpasses the pretreatment activity level.

Median time from FTY withdrawal to first relapse was 10.5 months in the whole cohort (Figure 1B) and 3.4 months in the subgroup of relapsing patients.

After FTY cessation, 48.9% (n=23/47) started a DMT (injectables in 96%) after a median time of 14 days.

Among the 47 FTY withdrawals, 28 pregnancies occurred in the year after FTY stop. Patients with pregnancy (28/47) and patients with no pregnancy (18/47) were not significantly different concerning demographical and clinical baseline characteristics (not shown).

We found no significant difference between patients who relapsed and those who did not regarding (1) DMT start in the year after FTY stop (8/20 and 15/27 respectively, p=0.38, median delay=7.2 months, versus 3.6 months, p=0.89), (2) pregnancy occurrence (16/27 and 12/20 respectively, p=1), (3) median EDSS at FTY cessation (0.5 versus 1.5, p=0.11), and (4) median lymphocyte levels 3 to 6 months after FTY stop (1.7G/L and 1.7G/L, p=0.53). However, there was a trend to increased ARR before FTY start in the relapsing group versus the other (median 1 versus 1, mean 1.4 versus 0.8, p=0.086).

Table 1. Characteristics of the cohort

	N (%)	Median (Q1-Q3) * n (%)
Age at MS onset (years)	44	22.1 (14-35)
Age at FTY start (years)	47	26.9 (22.4-46.8)
Age at FTY stop (years)	47	29.3 (27.5-32.5)
MS duration at FTY start (years)	47	5.2 (0.2-14.3)
FTY treatment duration (years)	47	2.1 (0.6-7.6)
Previous treatment before FTY start *	47	
None		8 (17)
IFN beta-1		16 (34)
Glatiramer acetate		15 (31.9)
Dimethyl fumarate		1 (2.1)
Teriflunomide		1 (2.1)
Fingolimod		1 (2.1)
Natalizumab		3 (6.4)
Mitoxantrone		1 (2.1)
Mycophenolate mofetil		1 (2.1)
EDSS at FTY start	46	1.0 (0-2.0)
EDSS at FTY stop	45	1.0 (0-1.5)
ARR before FTY start	47	1.0 (0 – 2.0)
Patients with relapse in the year before FTY	31 (66)	
ARR under FTY	47	0.0 (0.0-0.0)
Patients with relapse during FTY	6 (12.8)	

MS = Multiple Sclerosis; FTY = fingolimod; ARR = Annualized Relapse Rate

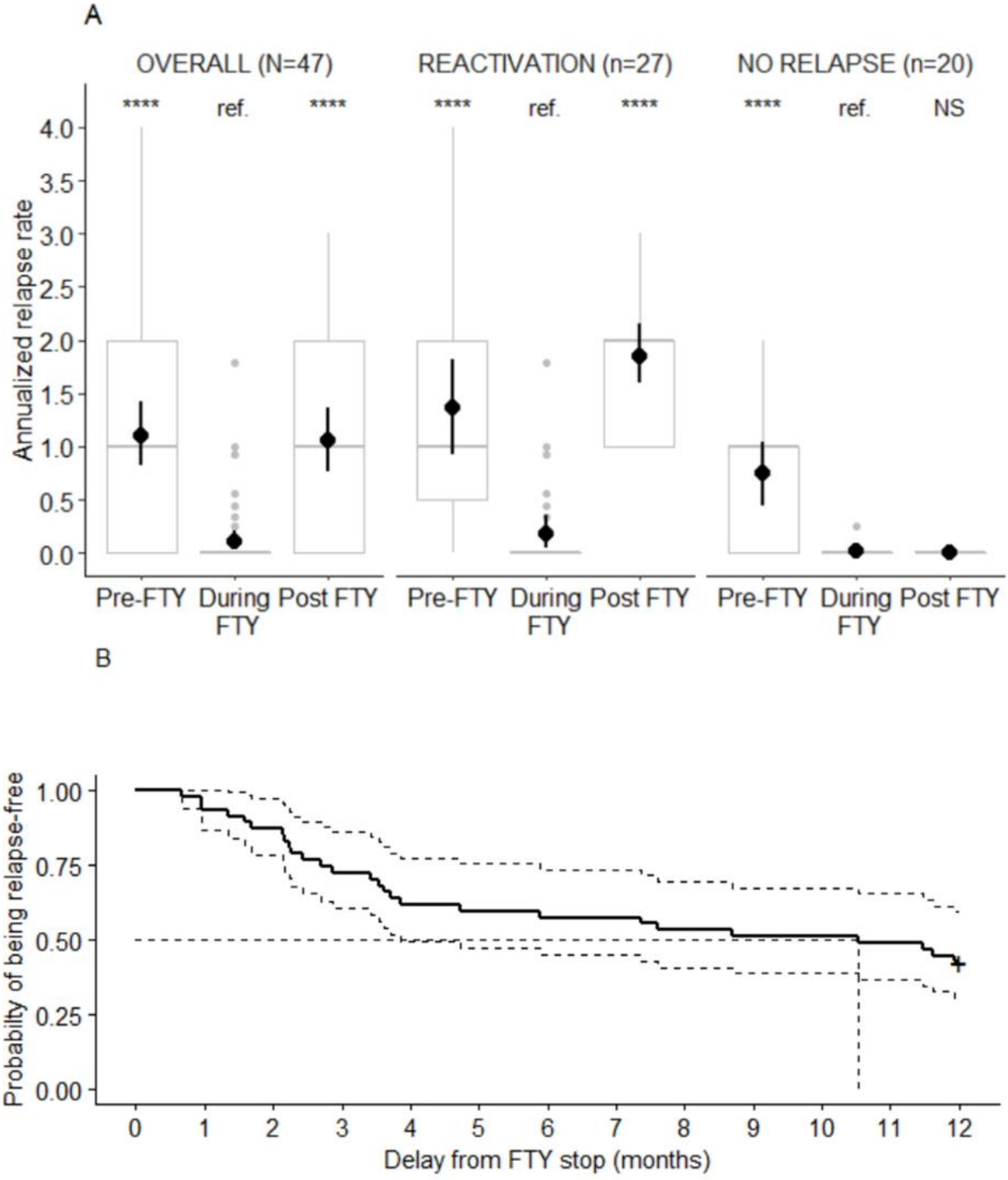

Figure 1: A- Annualized Relapse Rate during the year before FTY initiation, the period under FTY and the year after FTY cessation: in the whole cohort of patients (n=47 FTY cessations), in the group of MS patients with disease reactivation after FTY stop (n=27) and in the group of patients who did not relapse (n=20). Wilcoxon signed ranked tests. NS: not significant, * < 0.05, ** < 0.01, *** < 0.001, **** < 0.0001. B- Time to first relapse after FTY stop was analyzed with Kaplan-Meier estimator in the whole cohort.

Discussion:

Reactivation of disease activity after high-efficacy treatment discontinuation is a real issue in MS therapeutic management. MS patients with pregnancy desire are specifically exposed to this risk due to the limited number of drugs authorized during pregnancy. This risk of rebound has been extensively described using natalizumab, but with the possibility to continue the treatment during most of the pregnancy. As FTY must be stopped before conception, women can be exposed to a risk of clinical reactivation. In fact, in our study including 44 patients, we show that more than half of the women presented at least one relapse in the year after FTY cessation.

Several studies have reported MS reactivation after FTY withdrawal [1–8] with 4 to 26% of patients presenting severe disease reactivation or rebound. In the largest cohort (n=100) of FTY cessations for reasons unrelated to inefficacy, Frau et al. reported 26% of patients with relapse within 6 months after FTY discontinuation, and only 5% of rebound [1]. The reasons for withdrawal were mainly represented by side effects or patient's choice (67%) and most of their cohort (72%) started a new DMT within the months following FTY cessation. In our cohort, because of the specific context of pregnancy desire, less than 50% of patients started a new DMT.

In the situation of FTY discontinuation followed by a pregnancy within the year, disease reactivation has also been described with an increased ARR during pregnancy (from 0.49 to 0.7)[3,9,10] . In our cohort, the ARR in the year after FTY stop was higher (0.9), probably explained by the absence of the protective effect of pregnancy in more than 40% of our patients who did not get pregnant.

In conclusion, the rate of disease reactivation in the year following FTY discontinuation for pregnancy planning was estimated to be 57% in our cohort which is high compared to patients who stop FTY for other reasons (except for inefficacy). In this situation, a bridging therapy with a switch toward a highly active DMT should be preferred to avoid a risk of important disease reactivation.

Particular attention should be paid to women with a short-term pregnancy desire. We recommend to discuss treatment options with patients to avoid exposing them to a risk of MS reactivation after FTY cessation.

The authors declare that there is no conflict of interest.

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