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Original Research Paper

Half-dose fingolimod for treating relapsing-remitting multiple sclerosis: Observational study

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Abstract

Objectives: To investigate the efficacy and safety of fingolimod (FTY) 0.5 mg administered every other day (FTY-EOD) compared to every day (FTY-ED) in multiple sclerosis patients.

Methods: Multicentre retrospective observational study. Clinical, laboratory and neuroimaging data were consecutively collected from 60 FTY-EOD and 63 FTY-ED patients. Baseline characteristics were compared using logistic regression. Efficacy in preventing occurrence of relapses and demyelinating lesions was tested using propensity score–adjusted Cox and linear regressions.

Results: Weight was inversely associated with risk of switch to FTY-EOD because of any reason (odds ratio (OR) = 0.94, 95% confidence interval (95% CI) = 0.89–0.99, $p = 0.026$), and female sex and lower baseline lymphocyte count were positively associated with switch because of lymphopenia. Compared to FTY-ED patients, FTY-EOD patients were at higher risk of developing relapses (hazard ratio (HR) = 2.98, 95% CI = 1.07–8.27, $p = 0.036$) and either relapses or new magnetic resonance imaging (MRI) demyelinating lesions (combined outcome, HR = 2.07, 95% CI = 1.06–4.08, $p = 0.034$). Within FTY-EOD, treatment with natalizumab before FTY and lower age were positively associated with risk of developing relapses and combined outcome, respectively (HR = 25.71, 95% CI = 3.03–217.57, $p = 0.002$ and HR = 0.85, 95% CI = 0.77–0.96, $p = 0.005$). FTY-EOD was overall well tolerated.

Conclusion: Disease reactivation was observed in a significant proportion of patients treated with FTY-EOD. Neurologists should be cautious when reducing FTY administration to every other day, especially in younger patients and those previously treated with natalizumab.

Keywords: Demyelination, fingolimod, lymphopenia, multiple sclerosis, relapsing-remitting, treatment response

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Introduction

Fingolimod (FTY) 0.5 mg is the first oral treatment approved for relapsing-remitting multiple sclerosis (RRMS). It is a sphingosine analogue that acts as a functional antagonist of sphingosine-1-phosphate receptors ($S1P_1$) and prevents the $S1P_1$-mediated egress of lymphocytes from secondary lymphoid tissues. This reduces their recirculation to the central nervous system and subsequent inflammatory damage.[1] FTY does not interact with food and its oral bioavailability is >90%. The prolonged half-life (6–9 days) and slow absorption of FTY contribute to its stable concentration over time.[2–4] Three different doses of FTY (0.5, 1.25 and 5 mg once daily) have been tested and showed superiority in reducing clinical and radiological activity of disease against placebo or intramuscular interferon beta-1a in phase III clinical trials.[1,5,6] No dose–response effect was observed and the FTY 0.5 mg every-day dose (FTY-ED) was therefore approved because of the favourable safety profile. Despite this, side effects such as persistent severe lympho-leucopenia or elevated liver enzymes can lead to FTY-ED discontinuation in a significant proportion of patients.[7,8] Given its

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long half-life and stable plasma concentration, reducing the frequency of FTY administration has been proposed as an alternative to drug discontinuation. Previous studies suggested that reduced FTY doses may not control disease activity effectively,[9,10] but these studies are hampered by their small sample size and heterogeneity of FTY reduction strategies. We therefore aimed at investigating the efficacy of FTY 0.5 mg administered every other day (FTY-EOD) in a multicentre study of larger simple size.

Methods

Study design

This was a multicentre retrospective observational study performed in one Swiss (Lugano) and four Italian (Milan, Gallarate, Legnano, Catania) multiple sclerosis (MS) centres.

Study aims

The aims of the study were to: (1) characterize MS patients who switched from FTY-ED to FTY-EOD for safety reasons, during real-world clinical practice; (2) compare the efficacy and safety of FTY-EOD versus FTY-ED; and (3) define potential factors predicting good therapeutic response to FTY-EOD.

Patient population

All RRMS patients treated with FTY-EOD were identified during routine follow-up visits at participating centres between June and November 2015. Their clinical, laboratory and magnetic resonance imaging (MRI) data were collected retrospectively from medical records and compared with those of a similar number of unselected FTY-ED patients ($N = 63$) who were consecutively seen at follow-up visits at the same centres and during the same period. All patients receiving FTY-EOD were originally treated with FTY-ED and switched to FTY-EOD after different time intervals according to local medical decision with a mean of 10.3 (9.2) months. No uniform criteria were applied for the FTY-EOD switch among centres. The reasons motivating the switch to FTY-EOD were based on local medical decisions and are summarized in the populations' baseline characterization.

Clinical assessment

Clinical follow-up of patients was homogeneous across centres. All patients received a complete neurological examination with Expanded Disability Status Scale (EDSS) assessment at FTY start and every 3 months thereafter. Relapses were defined as newly developing neurological symptoms or reactivation of pre-existing neurological deficits for a minimum of 24 hours in the absence of an increase in body temperature or infections occurring at least 30 days after the preceding episode and accompanied by new, objective neurological findings. In the case of a suspected relapse, patients received neurological assessment including EDSS assessment within 2 weeks of symptom onset as per clinical practice at all participating centres.

Laboratory assessment

Pretreatment screening was performed in all patients and included complete blood cell count with white blood cell differential, liver enzymes, creatinine, screening for varicella zoster virus, human immunodeficiency virus, B and C hepatitis, tuberculosis as well as a basal electrocardiogram. Complete blood cell count, white blood cell differential and liver function tests were repeated before switching to FTY-EOD, at month 1 and 3 of FTY-ED/EOD treatment, and every 3 months thereafter (according to medical practice).

Neuroimaging assessment

Brain MRIs were performed within 6 weeks prior to FTY-ED start and at least annually thereafter. Additional brain MRIs were performed based on individual neurologists' decision, clinical course and at the time of switch to FTY-EOD. Images were acquired using either a 3T MRI scanner (Lugano) or 1.5T scanners (Milan, Gallarate, Legnano, Catania), complying with the neuroimaging protocol guidelines suggested by Simon et al.[11] and Filippi et al.[12] All repeat follow-up examinations were performed on the same MRI scanner. Brain MRI examinations were reviewed at each corresponding Centre by a referring neuroradiologist, who was blind to patients' clinical data and treatment, on a Digital Imaging and Communications (DICOM)-compliant PC workstation. Images were inspected for relevant artefacts before lesion counting. The number of T2-hyperintense lesions was counted at the baseline scan. Then, new and/or enlarging T2-hyperintense lesions (NT2) were counted by comparing each follow-up scan with the previous one. Gadolinium-enhancing lesions (Gd+) were also recorded for each scan.

Statistics

Categorical and continuous variables were described by counts and percentages or mean and standard deviation (SD), respectively. Univariable and multivariable logistic regression models were used to identify

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Table 1. Characteristics of FTY-EOD and FTY-ED patients at FTY start.

	All (*N*=123)	FTY-EOD (*N*=60)	FTY-ED (*N*=63)
Age, mean (SD)	42.3 (10.6)	41.0 (10.0)	43.6 (11.2)
Gender (F), *n* (%)	86 (69.9)	51 (85.0)	35 (55.5)
Weight, mean (SD)	64.0 (11.8)	59.5 (9.0)	68.2 (12.6)
Disease duration, mean (SD)	12.5 (7.9)	11.8 (7.9)	13.1 (7.9)
EDSS, median (IQR)	2.5 (1.5–3.5)	2.0 (1.5–3.5)	2.0 (1.5–3.5)
Relapses in last year, mean (SD)	0.63 (0.80)	0.75 (0.89)	0.51 (0.69)
Number of T2 lesions			
1–9, *n* (%)	26 (21.1)	17 (28.3)	9 (14.3)
>9, *n* (%)	97 (78.9)	43 (71.7)	54 (85.7)
Lymphocyte count, mean (SD)	1.84 (0.75)	1.61 (0.75)	2.01 (0.71)

FTY: fingolimod; ED: each day; EOD: each other day; F: female; SD: standard deviation; IQR: interquartile range; EDSS: Expanded Disability Status Scale.

those variables associated with a higher risk of being switched to FTY-EOD (i.e. considering FTY-EOD vs FTY-ED status as the predicted dependent variable). A similar analysis was performed comparing those patients who were switched to FTY-EOD because of severe leucopenia and/or lymphopenia versus all remaining patients. Cox regression models were used to compare the time to the occurrence of first relapse, NT2, Gd+ lesions or combined outcome (either relapse, NT2 or Gd+ lesion) in FTY-EOD versus FTY-ED patients. We considered time of FTY start and time of FTY dose reduction as baseline in FTY-ED and FTY-EOD patients, respectively. Time to last follow-up and time to last MRI were calculated in months as the time between baseline ascertainment and the last one occurred before study inclusion (between June and November 2015). The assumption of proportional hazards was tested by including time-dependent covariates (interactions) in the model. The annualized relapse rate (ARR), NT2 and Gd+ lesion rates were calculated by dividing the number of these events by the length of follow-up expressed in years. These rates were compared between FTY-EOD and FTY-ED using linear regressions. To limit the potential bias due to imbalances in baseline covariate distributions between FTY-EOD and FTY-ED groups, both Cox and linear regression analyses were carried out with and without adjustment by propensity scores (PS) (i.e. the conditional probability of belonging to a treatment group given certain covariates).[13,14] The PS for this study were built based on age, sex, disease duration, EDSS scores, T2 lesion load (1–9 vs >9 T2 lesions), number of Gd+ lesions, number of relapses in the year before starting FTY and last treatment before FTY (natalizumab vs other treatments). All following variables were tested for association with time to first relapse, NT2 lesion, Gd+ lesion and combined outcome within the group of FTY-EOD patients using univariable and multivariable Cox regression models: sex, age, weight, EDSS, occurrence of relapses in the year prior to FTY, baseline T2 lesion load, last treatment before FTY (natalizumab vs other treatments), duration of FTY-ED treatment, last lymphocyte count before FTY-ED initiation, last lymphocyte count before FTY-ED discontinuation and mean lymphocyte count during FTY-EOD treatment. All analyses were performed using R (https://www.r-project.org/) and the R packages 'rms' and 'non-random'.

Standard protocol approvals, registrations, and patient consents

This research project was approved by the competent Ethics Committees. Patients' consent to re-use of clinical data was obtained.

Results

Baseline characteristics

The characteristics of FTY-EOD and FTY-ED patients at the time of starting FTY are presented in Table 1. This was a retrospective study and the reasons motivating the switch to FTY-EOD were based on local medical decisions. In all, 45 among 60 (75.0%) patients were switched to FTY-EOD because of lymphopenia, 13 (21.7%) because of persistent increased liver enzymes and 2 (3.3%) because of recurrent infections. No uniform criteria were used to define lymphopenia requiring FTY dose reduction. However, all patients who were switched to FTY-EOD because of lymphopenia had a reduction in lymphocyte count as compared to baseline of at least 75%. The mean lymphocyte count at FTY-ED interruption before dose reduction was 270/µL. Only four patients were treatment naïve before starting FTY (2 ED and

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Table 2. Univariable and multivariable logistic regression for FTY-EOD versus FTY-ED status.

Variable	Category	Univariable			Multivariable		
		OR	95% CI	*p* Value	OR	95% CI	*p* Value
Gender	F versus M	4.53	1.91–10.78	0.0006	2.30	0.70–7.52	0.165
Age		0.98	0.94–1.01	0.182	0.99	0.95–1.04	0.846
Weight		0.93	0.89–0.96	0.0001	0.94	0.89–0.99	0.026
Disease duration		0.99	0.99–1.00	0.355	1.00	0.99–1.01	0.781
Previous treatment	NTZ versus other	0.85	0.34–2.14	0.731	0.70	0.24–2.00	0.508
Relapses in last year		1.48	0.93–2.37	0.101	1.28	0.77–2.12	0.344
EDSS		0.82	0.63–1.07	0.138	0.83	0.60–1.15	0.263
T2 lesions	>9 versus <9	0.42	0.17–1.03	0.06	0.35	0.12–0.99	0.049

FTY: fingolimod; ED: each day; EOD: each other day; F: female; M: male; CI: confidence interval; OR: odds ratio; NTZ: natalizumab; EDSS: Expanded Disability Status Scale.
ORs for age and weight are estimated per 1 year and 1 kg increase, respectively.

2 EOD), and natalizumab was the last treatment before FTY in 10 (16.7%) FTY-EOD and 12 (19.0%) FTY-ED patients. The mean duration of FTY-ED treatment before switching to FTY–EOD was 10.3 (9.2) months. Female sex and low weight were both associated with FTY-EOD status in univariable logistic regression (Table 2). In multivariable analyses, only low weight remained clearly associated with the risk of being switched to FTY-EOD (odds ratio (OR) = 0.94, 95% confidence interval (95% CI) = 0.89–0.99, $p = 0.026$), while a marginal significance was detected for T2 lesion load (OR = 35, 95% CI = 0.12–0.99, $p = 0.049$) (Table 2).

We then restricted the analyses to those patients switching to FTY-EOD because of lymphopenia. In this group of patients, female sex was significantly associated with a higher risk of being switched to FTY-EOD in both univariable and multivariable analyses (OR = 20.44, 95% CI = 2.06–202.78, $p = 0.009$). Baseline lymphocyte count was also marginally and inversely associated with risk of being switched in the multivariable model (OR = 0.51, 95% CI = 0.24–1.03, $p = 0.059$).

Efficacy of FTY-EOD versus FTY-ED

Both FTY and FTY-EOD patients performed neurological assessment and blood examinations (including complete blood cell count and liver enzymes) every 3 months. Brain MRIs were performed within 6 weeks prior to FTY-ED start and at least annually thereafter. Additional brain MRIs were performed based on individual neurologists' decision, clinical course and at the time of switch to FTY-EOD. The mean follow-up was 12.4 (7.6) and 22.9 (12.2) months in FTY-EOD and FTY-ED patients, respectively. Patients experi-

7 (11.1%) in FTY-ED. The mean time to first relapse was 6.8 (5.2) and 12.0 (10.6) months in FTY-EOD and FTY-ED, respectively (Table 3).

FTY-EOD patients were at higher risk of developing relapses and fared worse at the combined outcome in survival analyses (hazard ratio (HR) = 3.27, 95% CI = 1.27–8.44, $p = 0.014$ and HR = 2.19, 95% CI = 1.17–4.09, $p = 0.014$, respectively). This association remained significant after adjusting by PS (HR = 2.98, 95% CI = 1.07–8.27, $p = 0.036$ and HR = 2.07, 95% CI = 1.06–4.08, $p = 0.034$, respectively) (Figure 1, Supplementary material Table 1). As an additional sensitivity analysis, we included both PS and time spent under treatment with FTY-ED before switching to FTY-EOD in the model and FTY-EOD patients were still at increased risk of relapses and combined outcome (HR = 3.58, 95% CI = 1. 14–11.20, $p = 0.028$ and HR = 2.39, 95% CI = 1.054–5.42, $p = 0.037$, respectively). Findings were independent from lymphopenia motivating the switch to FTY-EOD (data not shown). Similarly, when using linear regression, the ARR and NT2 rate were significantly higher in FTY-EOD than FTY-ED patients (regression coefficient = 0.45, $p = 0.003$ and regression coefficient = 1.36, $p = 0.001$, respectively). This difference remained significant after adjusting by PS (Figure 2).

Variables associated with response to FTY-EOD

In the univariable Cox regression analyses, weight (HR = 0.92, 95% CI = 0.87–0.98, $p = 0.017$) and treatment with natalizumab before FTY (HR = 3.02, 95% CI = 1.01–9.05, $p = 0.048$) were negatively and positively associated with a shorter time to first relapse in FTY-EOD patients, respectively. However, only treatment with natalizumab before FTY remained signifi-

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Table 3. Description of follow-up, occurrence of relapses, NT2 and Gd+ lesions.

	FTY-EOD	FTY-ED
Patients with MRI during FU, *n* (%)	45 (75.0)	52 (82.5)
Time to last MRI, mean (SD)	11.9 (7.0)	21.6 (11.0)
Time to last FU, mean (SD)	12.4 (7.6)	22.9 (12.2)
Patients with relapses, *n* (%)	14 (23.3)	7 (11.1)
Time to first relapse, mean (SD)	6.8 (5.2)	12.0 (10.6)
Total no. of relapses, mean (SD)	0.35 (0.7)	0.09 (0.3)
ARR, mean (SD)	0.49 (1.19)	0.04 (0.14)
Patients with NT2, *n* (%)	17 (37.8)	16 (30.8)
Time to first NT2, mean (SD)	8.1 (4.5)	15.0 (8.9)
Total no. of NT2, mean (SD)	1.0 (1.6)	0.4 (0.8)
NT2 rate, mean (SD)	1.64 (2.86)	0.28 (0.69)
Patients with Gd, *n* (%)	10 (22.2)	7 (13.5)
Time to first Gd, mean (SD)	10.8 (6.0)	11.6 (8.2)
Total no. of Gd, mean (SD)	0.4 (1.1)	0.2 (0.7)
Gd rate, mean (SD)	0.51 (1.23)	0.20 (0.78)

NT2: T2-hyperintense lesions; Gd+: gadolinium-enhancing lesions; FTY: fingolimod; ED: every day; EOD: every other day; MRI: magnetic resonance imaging; FU: follow-up; SD: standard deviation; ARR: annualized relapse rate.

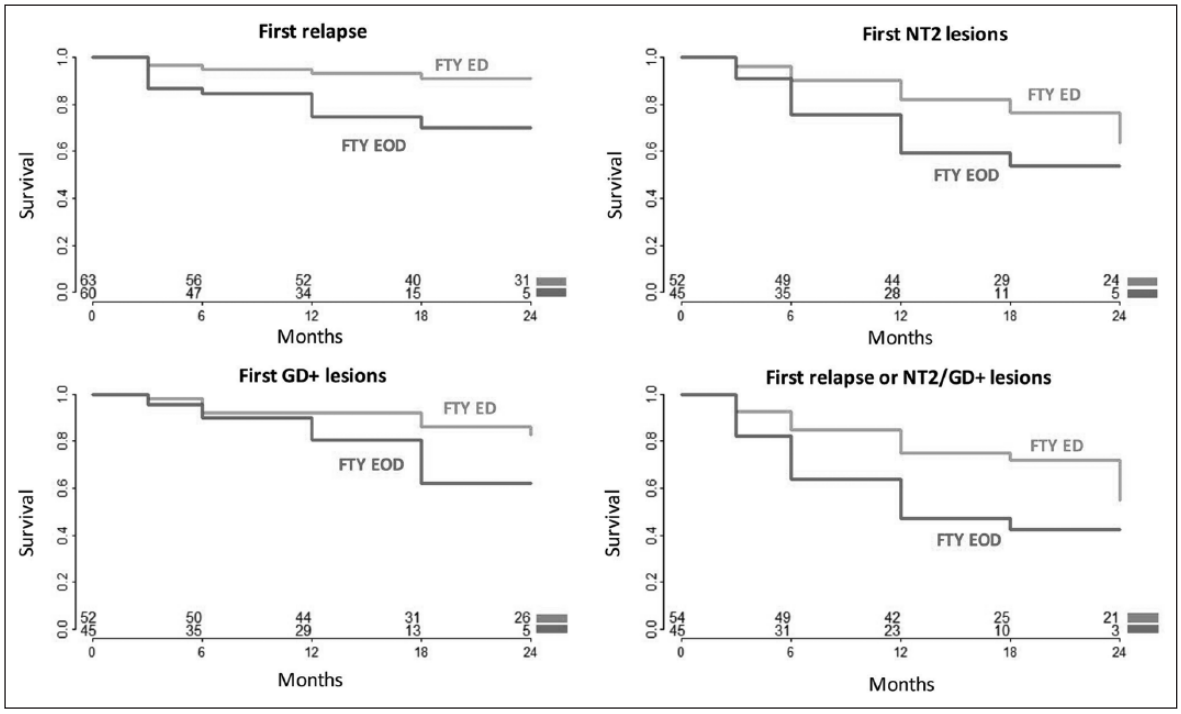

Figure 1. Survival curves with numbers at risk for time to first relapse, first NT2 lesion, first GD+ lesion and combined outcome in FTY-EOD (red) versus FTY-ED (green) patients.

CI = 3.03–217.57, $p = 0.002$). Sex, age, baseline EDSS, relapses in the year prior to FTY start, T2 lesion load, duration of FTY-ED treatment before FTY-EOD, lymphocyte count at FTY-ED start, FTY-ED stop as well as mean lymphocyte count during FTY-EOD treatment were not associated with the

When considering the combined outcome, only younger age was associated with a shorter time to first event in both univariable and multivariable analyses (HR = 0.93, 95% CI = 0.89–0.97, $p = 0.001$ and HR = 0.85, 95% CI = 0.77–0.96, $p = 0.005$, respectively), while the association of natalizumab treat-

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