Prognostic parameters of medium-term response to fingolimod treatment in Relapsing Remitting Multiple Sclerosis patients

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INTRODUCTION

Fingolimod (FTY) is an oral second-line drug approved for the treatment of Relapsing Remitting MS. Its efficacy has been demonstrated in both randomized controlled trials and post-marketing studies, with ~50% patients showing no evidence of disease activity (NEDA) at 2-year follow-up. Nonetheless, despite therapy a proportion of patients continue to show ongoing inflammatory activity that could benefit from more aggressive drugs; for this reason, the identification of non-responders (NR) patients early during FTY treatment is essential, in order to reduce the risk of disease progression and diability accuumulation.

In the present study we investigated the persistence of response to FTY up to 4 years after treatment start and we investigated the existence of prognostic markers of treatment failure, with a specific focus on the influence of early disease activity during the first year of FTY treatment on later disease course

PATIENTS AND METHODS

We enrolled 339 patients that started FTY treatment at the MS center of Ospedale San Raffaele (OSR) in Milan, Italy, between January 2012 and May 2014, that were treated for at least one year. Patients were prospectively followed-up with periodic neurological examination every 3 months and brain MRI scan at least once a year.

Response to treatment was defined at 4 years according to the Non Evidence of Disease Activity (NEDA) criterion, time to first relapse (TFR) and time to confirmed disease progression (TCDP). In order to identify prognostic markers of response, a logistic regression model was applied when analyzing binary outcomes, while a Cox proportional hazard model was used for TFR and TCDP. Specifically we investigated the influence of on-treatment parameters on the occurrence of disease activity in the subsequent 3 years of follow-up. Clinico-demographic features such as gender, age at onset and age at FTY start were also considered in the analysis.

All the analyses were performed using R software, version 3.4.2.

RESULTS

Three-hundred thirty-nine subjects were enrolled and clinico-demographic characteristics of included patients are reported in Table 1.

Included patients (n = 339)		Included patients (n = 339)	
Gender (Females:Males)	231:108	MRI with Gd+ lesions at FTY start, %	28.2%
Age at onset, mean±SD	27.92 ± 8.57	Nb. of Gd+ lesions at FTY start, mean±SD	0.66 ± 1.6
Age at FTY start, mean±SD	38 ± 9.27	MRI with new T2 lesions at FTY start, %	44.1%
Disease duration, mean±SD	10.07 ± 7.04	Nb. of new T2-lesions at FTY start, mean±SD	1.49 ± 3.15
EDSS at FTY start, mean±SD	2.41 ± 1.16	Previous therapy, n (%)	INF-b: 106 (31.3%) NTZ: 105 (31%) GA: 75 (22.1%) Naìve: 34 (10%) IS: 10 (2.9%) NO therapy: 7 (2.1%) Other DMT: 2 (0.6%)
ARR 2y pre, mean±SD	0.78 ± 0.9		

Table 1: Baseline clinico-demographic characteristics of included patients.
EDSS: Expanded Disability Status Scale; ARR: annualized relapse rate; FTY: fingolimod; Gd+: gadolinium-enhancing lesions. IFN-b: interferon beta; GA: glatiramer acetate; IS: immunosuppressant.

RESULTS

Overall, at 4 years 317 patients were classified according to the NEDA-3 criterion, among who 104 (33%) showed NEDA while 213 (67%) experienced disease reactivation: Besides, 117 (37%) patients had at least one clinical relapse and 43 (13.5%) patients experienced disease progression confirmed at 6-months.

A) NEDA-3 status at 4 years			
Predictors	**OR**	**95% CI**	**P-value**
Gender (male)	2.95	1.74-5.12	7.90E-05
Relapses during 1st year	0.37	0.18-0.72	0.005
New /enlargign T2 lesions at 1st year MRI scan	0.42	0.22-0.78	0.006
Disease duration	1.06	1.01-1.1	0.008
Age at disease onset	1.04	1.01-1.07	0.009
EDSS at the 1st year visit (≥3.0)	0.55	0.3-0.98	0.044

B)TFR			
Predictors	**HR**	**95% CI**	**P-value**
Relapses during 1st year	2.81	1.76-4.5	1.65E-05
Age at disease onset	0.96	0.93-0.99	0.01
Gender (male)	0.56	0.34-0.92	0.02
New/enlarging T2 lesions at 1st year MRI scan	1.78	1.09-2.91	0.02

C) TCDP			
Predictors	**HR**	**95% CI**	**P-value**
EDSS at the 1st year visit (≥ 3.0)	2.76	1.37-5.54	0.004
Age at disease onset	1.04	1-1.08	0.076

Table 2: Predictors of response to FTY treatment at 4 years.
A) predictors of NEDA-3 status; B) predictors of time to first relapse; C) predictors of time to confirmed disease progression. Expanded Disability Status Scale

As shown in Table 2, A and B, the occurrence of clinical relapses and/or MRI activity during the first year of FTY treatment are the parameters most strongly associated to persistent inflammatory activity in the subsequent 3 years.

Specifically, experiencing at least 1 relapse in the first year has a positive predictive value (PPV) of 75.9% for non response at 4 years. Similarly, showing MRI activity at the 1° year brain scan has a PPV of 75.9% while having both clinical and MRI activity has a PPV of 86.4%.

On the contrary, being male is linked to a lower risk of drug failure, as is a later age at disease onset, even if the effect is slight.

Finally, we found that an EDSS higher than 3.0 at the 1° year visit is predictive of an increase in disability level during follow-up.

DISCUSSION

The proportion of NEDA patients decreases during longer follow-up and is 33% after 4 years from treatment start. Nonetheless, most of patients were clinically stable 4 years after FTY start thus confirming the good efficacy profile of the drug.

An early reactivation during FTY treatment is highly predictive of occurrence of disease activity during follow-up, thus stressing the the need for a close monitoring during the first year of therapy in order to identify NR patients that require treatment optimization.

LITERATURE:.

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