CLINICAL PREDICTORS OF FINGOLIMOD RESPONSE OVER 2-YEAR FOLLOW-UP IN AN ITALIAN COHORT OF RELAPSING REMITTING MULTIPLE SCLEROSIS PATIENTS

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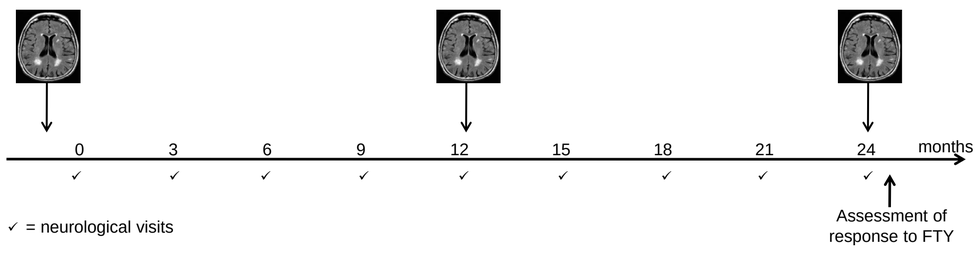
Introduction and Aim

Multiple sclerosis (MS) treatment options have dramatically increased in the recent years. Several drugs are now available for the treatment of MS, with high heterogeneity in terms of efficacy and side effects. The early identification of patients with a better response to specific approved MS drugs would be highly beneficial towards a more personalized management

The aim of the present study is to assess fingolimod (FTY – Gilenya®) effectiveness in a real life setting and to identify baseline clinical predictors of response in an Italian monocentric cohort of relapsing-remitting (RR) MS patients. These data could contribute to the identification of the patients who could benefit more from FTY treatment.

Patients and Methods

Study design



Inclusion criteria

- Subjects ≥ 18 years old
- Patients affected with RRMS according to McDonald criteria
- Patients who started FTY at OSR MS center by May 2014
- Patients treated with FTY for at least 6 months
- Patients who gave written informed consent to participate to the study (FINGO-MS internal protocol approved by IRB)

Exclusion criteria

- Patients with progressive MS (SPMS or PPMS)
- Patients who permanently discontinued FTY within the first 6 months from treatment start
- Patients lost to follow-up or who moved to another MS center in the first 6 months of treatment

Treatment response assessment

Treatment response was assessed using two different approaches:

1. *No evidence of disease activity (**NEDA** criterion) at 2-year follow-up*
   - No relapses
   - No new T2 or Gd-enhancing lesions at brain MRI scans
   - No EDSS progression confirmed at 6 months

   Patients with no evidence of any type of disease activity under FTY, but who discontinued the treatment before the 2 year-follow-up (n=20) were not included in this analysis, because we were not able to classify them according to the NEDA criterion.

2. ***Time to First Relapse***

   Patients who suspended the treatment or who were lost at follow-up within the 2-year follow-up were included in the analysis as long as they received the treatment.

Statistical analyses

- Candidate clinical baseline parameters were evaluated for their influence on response to FTY. We selected the following variables to be tested: gender, age at treatment start, age at disease onset, disease duration, EDSS, annualized relapse rate (ARR) in the 2 years before FTY, lymphocyte counts. Collinearity among variables with Variance Inflation Factor was evaluated, leading to removal of age as predictor.
- NEDA analyses were conducted with a logistic regression model. Time to First Relapse analyses were performed according to a Cox proportional hazard model.
- For both response outcomes, we conducted univariable and multi-variable analyses, selecting variables according to an Akaike Information Criterion). All analyses were performed within R statistical framework (https://www.R-project.org/). We evaluated the predictive performance of the AIC-based selected models for internal validation by means of a 10-fold cross-validation procedure.

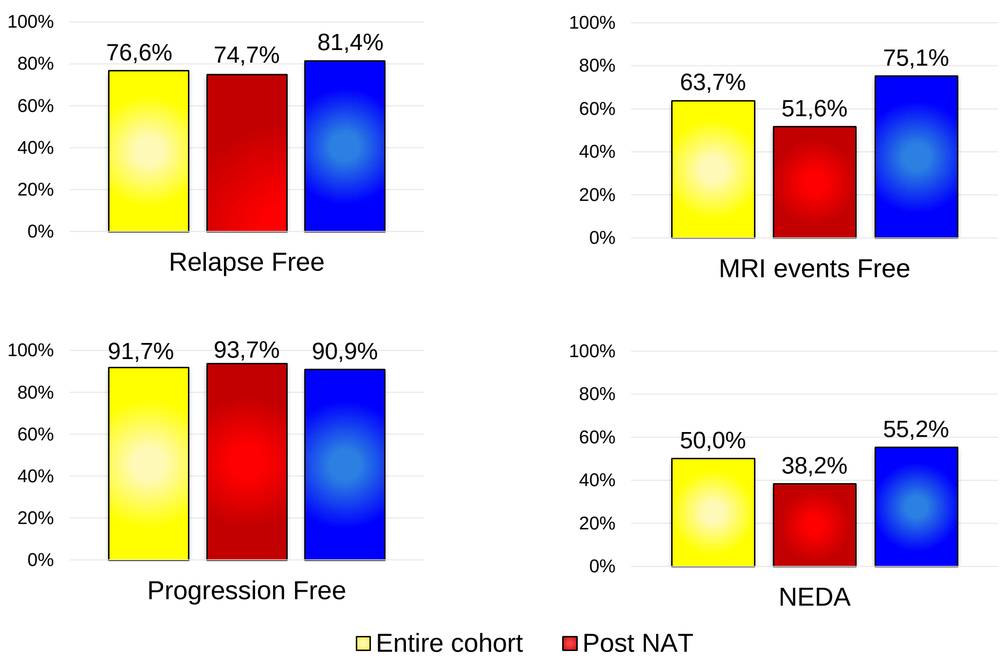
Results

Clinical characterization of the enrolled subjects

A total of 366 FTY-treated patients with at least 2 years of follow-up were available for clinical analyses. Given the known increase in disease activity after natalizumab (NAT) withdrawal, we stratified patients in two groups, according the the fact that they were treated with this drug in the year before FTY (post NAT) or not (No NAT).

Clinical and demographic features	Entire cohort (n=366)	Post NAT (n=86)	No NAT (n=280)
Female:Male ratio	254:112	57:29	197:83
Mean Age (± sd)	37.8 ± 9.4	35.3 ± 8.5	38.9 ± 9.5
Mean Age at Onset (± sd)	27.8 ± 8.8	25.8 ± 7.5	28.4 ± 8.9
Mean Disease Duration (± sd)	9.9 ± 6.9	9.5 ± 5.4	10.1 ± 7.3
Median EDSS (range)	2.0 (0.0 – 6.0)	2.0 (0.0 – 5.5)	2.0 (0.0 – 6.0)
ARR 2 years pre-FTY(± sd)	0.8 ± 0.9	0.4 ± 0.7	0.9 ± 0.6
Previous therapy	IFN (n=110) GA (n=82) NAT (n=114) Immunosuppressors (n=16) No Therapy (n=9) Naive (n=35)	NTZ <12 month pre (n=86)	IFN (n=110) GA (n=82) NTZ >12 months pre (n=28) Immunosuppressants (n=16) No Therapy (n=9) Naive (n=35)

Clinical, MRI activity and disease progression across subgroups



Predictors of response to FTY

We searched for the most influential baseline clinical and MRI parameters which impact on time to first relapse and disease activity (NEDA outcome).

Time to first relapse analysis – No NAT patients

Univariable model

Predictors	OR	SE	L95	U95	p-value
ARR 2 years pre	2.53	0.20	1.70	3.77	$5x10^{-6}$
EDSS at baseline	1.22	0.10	0.99	1.50	0.05

Multivariable model

Predictors	OR	SE	L95	U95	p-value
ARR 2 years pre	3.73	0.27	2.21	6.29	$1x10^{-6}$
Disease duration	1.06	0.02	1.02	1.11	0.003
Gd+ lesions at baseline MRI	1.17	0.08	0.99	1.37	0.05

Time to first relapse analysis – post NAT patients

Univariable model

Predictors	OR	SE	L95	U95	p-value
Age at disease onset	0.91	0.03	0.85	0.97	$2.9x10^{-3}$
New T2 lesions at baseline MRI	2.17	0.40	0.99	4.72	0.05

Multivariable model

Predictors	OR	SE	L95	U95	p-value
Age at disease onset	0.91	0.03	0.85	0.97	$6.5x10^{-3}$

NEDA analysis – No NAT patients

Univariable model

Predictors	OR	SE	L95	U95	p-value
Gd+ lesions at baseline MRI	1.38	0.12	1.12	1.78	0.006
ARR 2 years pre	1.52	0.20	1.02	2.28	0.04
Age at disease onset	0.97	0.01	0.95	0.99	0.04

Multivariable model

Predictors	OR	SE	L95	U95	p-value
Gd+ lesions at baseline MRI	1.40	0.14	1.09	1.86	0.01
Age at disease onset	0.96	0.017	0.93	0.99	0.01
ARR 2 years pre	1.62	0.24	1.02	2.60	0.04

Accuracy: 61.2%
Sensitivity: 45.5%
Specificity: 76.3%
PPV: 60.8%
NPV: 62.5%
AUC: 0.64
Nagelkerke R^2: 0.11

NEDA analysis – Post NAT patients

Univariable model

Predictors	OR	SE	L95	U95	p-value
Age at disease onset	0.93	0.04	0.86	0.99	0.03
New T2 lesions at baseline MRI	3.41	0.61	1.11	12.93	0.04
Gd+ lesions at baseline MRI	2.67	0.52	1.30	10.44	0.05

Multivariable model

Predictors	OR	SE	L95	U95	p-value
Gd+ lesions at baseline MRI	2.34	0.47	1.21	8.58	0.06

Accuracy: 64.5%
Sensitivity: 84.4%
Specificity: 46.6%
PPV: 72.1%
NPV: 47.1%
AUC: 0.70
Nagelkerke R^2: 0.21

Discussion

- FTY revealed to be effective in the studied population, with 50% of patients being NEDA at the 2-year follow-up in the entire cohort. This proportion increases up to 55.2% when considering the patients not previously treated with NAT.
- Higher ARR in the 2 years before FTY, longer disease duration and the presence of Gd+ lesions at baseline brain MRI were significantly associated with a shorter time to first relapse in patients not previously treated with NAT; in patients recently treated with NAT, a lower age at disease onset was the clinical parameter most significantly associated with time to first relapse.
- As regards the dichotomous outcome, the presence of Gd+ lesions at baseline brain MRI, a lower age at onset and a higher ARR in the 2 years before FTY were predictive of inflammatory disease activity in patients not previously treated with NAT. In patients with a recent treatment with NAT there was a trend towards an association between Gd+ lesions and an increased probability of disease activity.
- Further analyses are ongoing at the longitudinal level, assessing prospectively disease activity (relapses, new T2 lesions and Gd+ lesions) in the different subgroups.
- The predictors of response to FTY treatment will be integrated with the genetic data obtained from the enrolled patients, in the attempt of building a composite predictive model of response to FTY.

Disclosures

F. F. Esposito received honoraria from TEVA and Merck. L. Moiola received honoraria for speaking at meetings or for attending to advisory board from Sanofi-Genzyme, Biogen-Idec, Novartis and TEVA. B. Colombo received travel grant from Biogen-Idec, Merck, Bayer, Genzyme. V. Martinelli has received honoraria for consulting and speaking activities from Biogen-Idec, Merck, Bayer, TEVA, Novartis and Genzyme. M.A. Rocca received speakers honoraria from Biogen Idec, Novartis, Genzyme, Sanofi-Aventis and Excemed and receives research support from the Italian Ministry of Health and Fondazione Italiana Sclerosi Multipla. M. Filippi is Editor-in-Chief of the Journal of Neurology; serves on scientific advisory board for Teva Pharmaceutical Industries; has received compensation for consulting services and/or speaking activities from Biogen Idec, Excemed, Novartis, and Teva Pharmaceutical Industries; and receives research support from Biogen Idec, Teva Pharmaceutical Industries, Novartis, Italian Ministry of Health, Fondazione Italiana Sclerosi Multipla, Cure PSP, Alzheimer's Drug Discovery Foundation (ADDF), the Jacques and Gloria Gossweiler Foundation (Switzerland), and ARiSLA (Fondazione Italiana di Ricerca per la SLA). G. Comi has received compensation for consulting services with the following companies: Novartis, Teva, Sanofi, Genzyme, Merck, Biogen, Excemed, Roche, Almirall, Chugai, Receptos, Forward Pharma and compensation for speaking activities from Novartis, Teva, Sanofi, Genzyme, Merk, Biogen, Excemed, Roche. F. Martinelli Boneschi has received compensation for activities with Teva Neuroscienze as speaker and/or advisor. F. Clarelli, L. Ferre', G. Sferruzza, M. Radaelli, F. Sangalli, M. Rodegher have nothing to disclose.

This study is supported by the "Fondazione Italiana Sclerosi Multipla", project 2013/R/13