PREDICTORS OF RESPONSE TO FINGOLIMOD TREATMENT IN AN ITALIAN MONOCENTRIC COHORT OF MULTIPLE SCLEROSIS PATIENTS

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Introduction and Aim

✓Individual patients responses to MS therapies are highly heterogeneous, highlighting the need for a more personalized therapeutic choice aimed at optimizing the risk-benefit profile of treatments.

✓MS is a typical condition where a more personalized intervention would be highly beneficial, favorably impacting long-term clinical outcomes and optimizing treatment costs.

The aim of this project is to assess fingolimod (FTY) efficacy and to identify predictors of response at 2-year follow-up in an Italian monocentric cohort of relapsing-remitting (RR) MS patients.

Patients

Inclusion criteria

- RRM patients treated for at least 6 months with FTY.
- Patients who started the treatment before 28/02/2013 at San Raffaele Hospital (Milan).
- Patients with at least 2 years of follow-up clinical data.

Exclusion criteria

- Patients with SPMS or progressive MS.
- RRMS patients previously treated with FTY (clinical trials).

Material and Methods

Study design

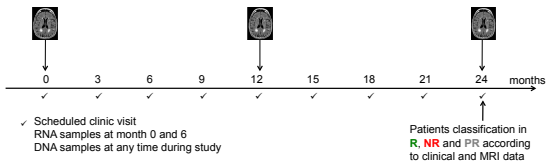
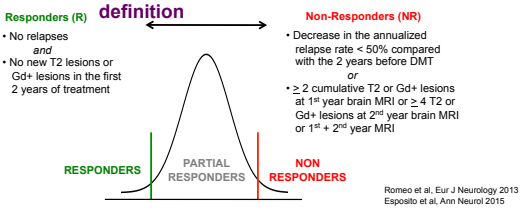


Figure 1 – Study design aimed to collect clinical, MRI and genomic data for future studies

Treatment response definition



Romeo et al, Eur J Neurology 2013
Esposito et al, Ann Neurol 2015

Figure 2 – Definition of response used to classify patients

Results

Eligible patients

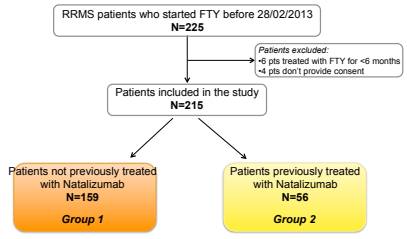


Figure 3 – Flow chart of the cohort of MS patients included in the study

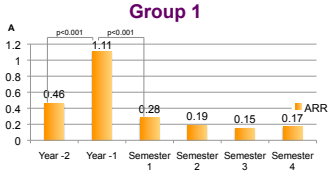
Clinical and demographic features	Entire cohort (N=215)	Group 1 (N=159)	Group 2 (N=56)
Gender (F:M)	2.02	2.11	1.8
Mean age at disease onset (±SD)	26.7 ± 8.7	27.0 ± 8.9	25.8 ± 8.1
Mean age at FTY start (±SD)	37.3 ± 9.2	38.3 ± 9.1	34.6 ± 8.9
Mean disease duration (±SD)	10.6 ± 6.9	11.3 ± 7.4	8.7 ± 4.7
ARR in the 2 previous years (±SD)	0.7 ± 0.6	0.8 ± 0.6	0.5 ± 0.6
Mean EDSS at baseline (±SD)	2.1 ± 2.1	2.2 ± 1.2	1.9 ± 1.0
Mean EDSS 2 years before FTY (±SD)	2.2 ± 2.1	2.2 ± 1.2	2.3 ± 1.1
Gd+ lesions at baseline (±SD)	1.0 ± 1.7	0.19 ± 1.6	0.95 ± 1.7

Figure 4 – Demographic and clinical characteristics

Patients were divided according to the treatment received before FTY. Specifically, given the known presence of disease activity (~50%) and the reported cases of rebound (~10%) after Natalizumab discontinuation, we distinguished patients previously treated with Natalizumab (Group 2) from the remaining patients (Group 1).

As expected, the two cohorts differ especially in terms of parameters of disease activity in the years before FTY start.

Group 1



Group 2

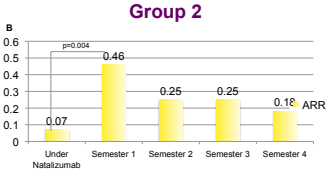


Figure 5 – Annualized relapse rate (ARR) at the different timepoints in the two groups of treatment: patients not previously treated with Natalizumab (A) and previously treated with Natalizumab (B)

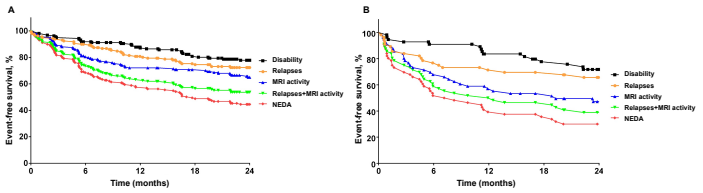


Figure 6 – Assessment of the clinical and MRI activity and disease progression in the two groups of treatment: patients not previously treated with Natalizumab (A) and previously treated with Natalizumab (B)

Clinical predictors of response

	Responders (N = 74)	Non-responders (N = 49)	p-value
Gender (F:M)	1.4	3.5	0.026
Mean age at onset (±SD)	28.9 ± 9.7	24.9 ± 8.3	0.022
Mean age at FTY start (±SD)	40.3 ± 9.4	37.1 ± 8.9	0.066
Mean disease duration (±SD)	11.3 ± 8.2	12.1 ± 6.9	0.602
ARR in the 2 previous years (±SD)	2.2 ± 1.1	2.3 ± 1.1	0.439
Mean EDSS 2 years before FTY (±SD)	2.3 ± 1.1	2.4 ± 1.2	0.387
Mean EDSS at baseline (±SD)	0.8 ± 0.6	0.8 ± 0.6	0.386
Mean Gd+ lesions at baseline (±SD)	0.5 ± 1.0	1.2 ± 1.7	0.009

Figure 7 – Demographic and clinical characteristics according to response status

- The classification in Responders and Non-responders was applied only in the Group 1, in order to avoid treatment response misclassification due to disease reactivation/rebound after Natalizumab discontinuation.
- After applying a multivariate analysis, female gender and earlier disease onset were associated with a worse response.

Discussion

✓Among the patients not previously treated with Natalizumab (Group 1) the 40% of patients is free from any evidence of disease activity/progression (NEDA criteria) at 2-year follow-up, whereas in patients belonging to Group 2 less than one third of subjects satisfies this definition.

✓The main differences between the two groups are observed especially during the first year of treatment.

✓Our data are in line with what reported in clinical trials and provide the opportunity to assess FTY efficacy profile in the medium-long term follow-up, in a real-life setting.

✓As regards the search for clinical predictors of response, female gender and younger age at disease onset seem to be associated with a poor response to the drug.

✓Additional patients need to be included in the study, in order to confirm the reported data.

✓The clinical and MRI data will be integrated into a predictive model of response, that will include also genome-wide genetic data, in the context of the so-called "personalized medicine" .

Disclosures

L. Ferre', I. Keller Sarmiento, M.J. Messina, M. Radaelli, M. Rodegher, B. Colombo, F. Sangalli report no competing financial interests. F. Esposito received honoraria from Serono Symposia International Foundation. M. A. Rocca received speaker honoraria from Biogen Idec, Novartis, Genzyme, Sanofi-Aventis and Merk Serono and receives research support from the Italian Ministry of Health and Fondazione Italiana Sclerosi Multipla. L. Moiola received speaker honoraria from Biogen and Sanofi-Aventis. V. Martinelli received speaker honoraria or funding for participation to congresses from Biogen-Idec, Merck Serono, Bayer Schering, Teva Pharmaceutical Industries, Novartis and Sanofi-Aventis. M. Filippi serves on scientific advisory board for Teva Pharmaceutical Industries; has received compensation for consulting services and/or speaking activities from Bayer Schering Pharma, Biogen Idec, Merck Serono, and Teva Pharmaceutical Industries; and receives research support from Bayer Schering Pharma, Biogen Idec, Merck Serono, Teva Pharmaceutical Industries, Italian Ministry of Health, Fondazione Italiana Sclerosi Multipla, Cure PSP, and the Jacques and Gloria Gossweiler Foundation. F. Martinelli Boneschi received honoraria for consulting, research grant and travel expenses from TEVA neuroscience, Biogen IDEC, Merck Serono. VM received honoraria for speaking, consultancy or support for participation to National and International Congresses from Bayer-Schering, Biogen-Dompè, Merck-Serono, Novartis, Sanofi-Aventis and TEVA Pharmaceutical. G. Comi received honorarium for consultancy and/or speaking activities in the past 12 months from Biogen, Novartis, Teva, Sanofi, Genzyme, Merck Serono, Bayer, Serono Symposia International Foundation, Roche, Almirall, Chugai, Receptos

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