A Metabolomic study of MS patients treated with fingolimod by high resolution NMR

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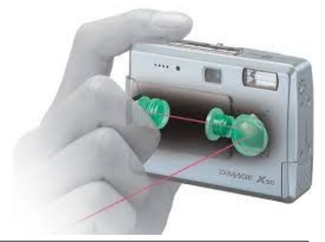
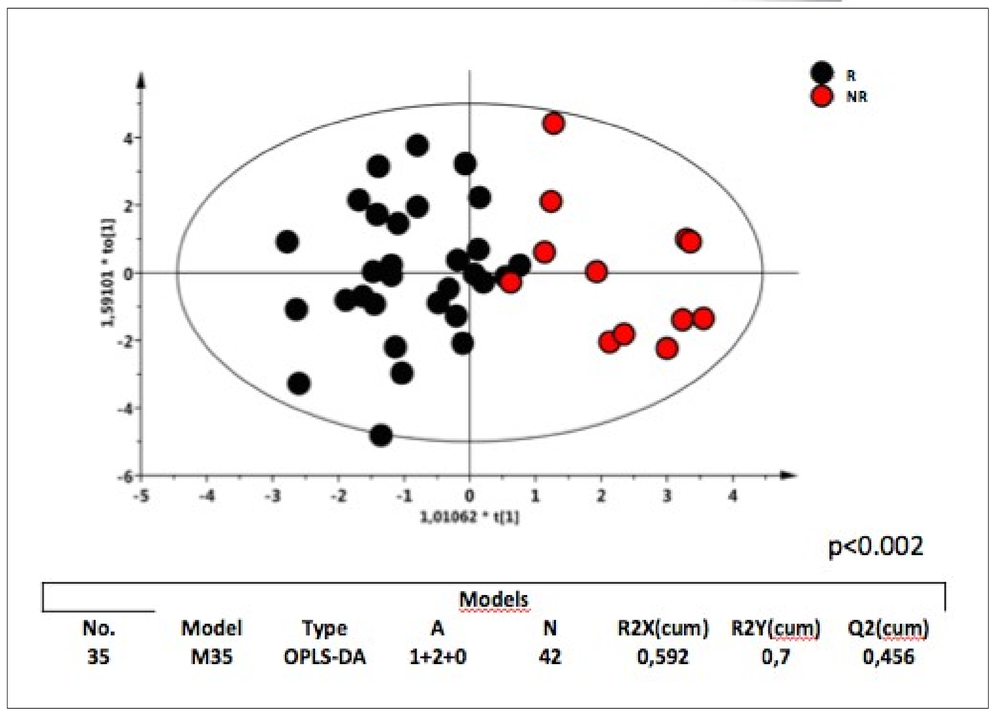
Background. Fingolimod (F) is the first oral disease-modifying agent approved for relapsing remitting multiple sclerosis (MS). Its efficacy and safety profile has increasingly become defined through postmarketing studies and real-world clinical experience (La Mantia L,.2016). However, no biological markers to predict treatment efficacy and safety are available today. In the last years, metabolomics, a new science "omics" based on detailed analysis of metabolites, has been considered as important tool for biomarker discovery (Del Boccio P,.2016; Cocco E., 2015). Therefore, in this study we investigated, by using the metabolomic approach, whether patients who started treatment with F had a basal metabolic profile able to predict the subsequent response to treatment and cardiac complication at first dose (CC).

Methods. Blood samples, obtained before starting F, were analysed by ^{1}H-NMR spectroscopy. Patients were divided in two groups based on the treatment efficacy after one year, according to NEDA 3 definition (Banwell B, 2013) (absence of relapses, no EDSS progression and no new/enlarging T2 or T1 Gd-enhancing lesions on MRI), and samples analyzed to find possible metabolic differences.
The same dataset were used to assess whether metabolic differences exist between CC and NCC patients. Multivariate analysis was conducted with a supervised analysis (OPLS-DA). The metabolites were identified and metabolic pathways characterization was performed.

Results. The study included 54 patients (23; 42.5% male), of which 41 (75.9%) R after one year of treatment.
Three patients (female) presented CC following first-dose administration.

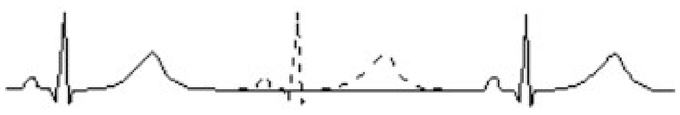


The basal metabolic profile allowed differentiating **R and NR patients** (R vs NR, R2X=0.592, R2Y=0.7, Q2=0.492, p=0.002).
The following metabolites, involved principally in the energetic metabolism and protein biosynthesis, were found to be responsible of the difference between groups: lactate, lysine, branched-chain aminoacids, 2-OH-isovalerate (increased in R patients) and sugars, threonine, aspartate, hydrocinnamic acid, 2-OH-butyrate (increased in NR patients).

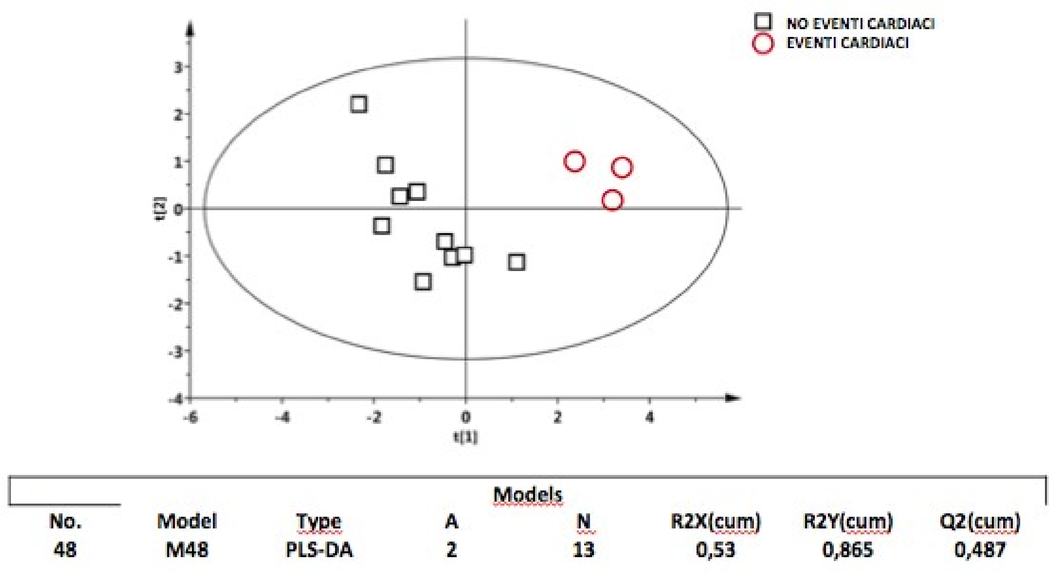


Models

No.	Model	Type	A	N	R2X(cum)	R2Y(cum)	Q2(cum)
35	M35	OPLS-DA	1+2+0	42	0,592	0,7	0,456



The second model (CC vs NCC, R^2X=0.530, R^2Y=0.865, Q^2=487, P=NS) showed differences of following metabolites: lysine, alanine, ketone bodies (increased in CC), glucose and lactate (increased in NCC). These are ≤predominantly involved in synthesis and degradation of ketone bodies, glycolisis and gluconeogenesis and propanoate metabolism.



Models

No.	Model	Type	A	N	R2X(cum)	R2Y(cum)	Q2(cum)
48	M48	PLS-DA	2	13	0,53	0,865	0,487

Conclusions. 1H NMR-based metabolomic analysis of blood appears to be a promising, non-invasive approach to predict the efficacy and safety of MS therapies. However, our results are only preliminary and need to be replicate in larger samples.