Cardiovascular profile improvement during Natalizumab treatment

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KEYWORDS

Multiple sclerosis; cardiovascular; cholesterol; uric; Natalizumab

ABSTRACT

BACKGROUND. Cardiovascular comorbidities are associated with the risk of MS progression. Thus, we aim to measure variations of cardiovascular risk factors during Natalizumab treatment and their possible clinical associations.

METHODS. Seventy-one relapsing-remitting MS patients treated with Natalizumab were followed-up during a 12.9±6.2 months. Cardiovascular risk factors were recorded on first and last study visits: systolic blood pressure, uric acid, total cholesterol, LDL, HDL, and triglycerides. EDSS progression and relapse occurrence were recorded.

RESULTS. At multilevel mixed-effects linear regression models, the population presented with a significant reduction of total cholesterol (Coeff=-7.340; 95%CI=-13.152--1.527; p=0.013), and of HDL cholesterol (Coeff=-3.473; 95%CI=-6.333--0.613; p=0.017), and a non-significant reduction of LDL cholesterol (Coeff=-1.872; 95%CI=-8.481-0.736; p=0.053), and of triglycerides (Coeff=-8.815; 95%CI=-34.011-5.380; p=0.094). Uric acid levels increased during the study period (Coeff=0.159; 95%CI=0.212-0.340; p=0.038). No significant associations were found with clinical outcomes.

CONCLUSION. Serum lipids decreased and anti-oxidant uric acid increased during Natalizumab treatment. These biomarkers need to be further explored in relation to clinical outcomes on larger cohorts with longer follow-ups.

INTRODUCTION

Cardiovascular comorbidities are associated with the risk of multiple sclerosis (MS) progression (Hon et al. 2009; Weinstock-Guttman et al. 2013; Tettey et al. 2014, 2017; Marrie et al. 2015; Moccia et al. 2015b; Kappus et al. 2016; Uher et al. 2017). In keep with this, an improvement in the cardiovascular profile can affect MS evolution positively (Lanzillo et al. 2010; Chataway et al. 2014). Cholesterol lowering agents (statins) showed possible efficacy on both clinical and

radiological progression (Lanzillo et al. 2010; Chataway et al. 2014). Besides, disease-modifying treatments (DMTs) can improve the cardiovascular profile. Interferon beta has been associated with sustained decrease in cholesterol levels in a longitudinal cohort (Brescia Morra et al. 2004), and 37 MS patients treated with Natalizumab presented with a more anti-atherogenic lipid profile, when compared with no treatment (Sternberg et al. 2014).

The present study aims to: 1) measure variations of cardiovascular comorbidities (blood pressure, obesity, uric acid, diabetes, cholesterol and triglycerides) in a longitudinal cohort of relapsing-remitting (RR) MS patients treated with Natalizumab; 2) evaluate associations between variations of cardiovascular risk factors and clinical relapses, 3) and disease progression.

METHODS

STUDY DESIGN

The present observational prospective cohort study has been conducted at the MS Clinical Care and Research Centre of the Federico II University Hospital of Naples, Italy, between January 2015 and June 2016. In compliance with current Italian applicable laws and regulations, considering that all data was publicly available and that the analyses included anonymized data, specific ethics approval was not required. The study was performed in accordance with Declaration of Helsinki.

POPULATION

Inclusion criteria were: 1) diagnosis of RRMS (Polman et al. 2011); 2) treatment with Natalizumab, in agreement with regulatory indications (Italian and European Medicines Agencies).

Exclusion criteria were: 1) age <18 years; 2) pregnancy; 3) concomitant diseases (i.e. cancer, or hepatitis) or treatments (i.e. anti-hypertensive, statins) affecting cardiovascular risk factors.

CARDIOVASCULAR VARIABLES

Following cardiovascular variables were recorded: systolic blood pressure, body mass index (BMI),

uric acid, diabetes, total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides. Standard methods for data collection have been fully described elsewhere (Moccia et al. 2015a, 2015b). Patients were asked whether they had major changes in their diet during the study period.

The simplified 10-year Framingham General Cardiovascular Disease Risk Score (FR) was calculated, in order to stratify the population for their overall cardiovascular risk (Moccia et al. 2015b).

CLINICAL VARIABLES

MS patients attended the MS Centre monthly for Natalizumab infusions.

Relapses were recorded and reported on an annual basis (annualized relapse rate -ARR-). Relapsing patients met commonly used standards for relapse as determined by clinical neurologists (Polman et al. 2011).

Disability was scored with the Expanded Disability Status Scale (EDSS) by certified clinicians. The difference between follow-up and baseline EDSS was calculated.

STATISTICS

In order to evaluate variations of cardiovascular risk factors during Natalizumab treatment (aim 1), each cardiovascular risk factor was included in a different multilevel mixed-effects linear regression model. Results are presented as coefficients (Coeff), and 95% confidence intervals (95%CI). Variables included in the model were tested for multicollinearity and values of the variance inflation factor were all smaller than 2.5, indicating that the assumption of reasonable independence among predictor variables was met. Covariates included in these models were: age, gender, disease duration at baseline, EDSS at baseline, duration of Natalizumab treatment before study entry, and study duration. Baseline creatinine was included when studying uric acid. Baseline BMI was included when studying systolic pressure, uric acid, total cholesterol, LDL, HDL, and triglycerides.

With regard to clinical correlates, mixed effect logistic regression models were employed to assess the association between variations in each cardiovascular risk factor and the occurrence of relapse (aim 2) (results are presented as Odds Ratio -OR-, and 95%CI). Mixed effect linear regression models were employed to assess the association between variations in each cardiovascular risk factor and EDSS progression (aim 3) (results are presented as Coeff, and 95%CI). The population was categorized on the median FR in order to identify patients with higher cardiovascular risk, and this was used to fit an interaction term. Covariates included in these models were age, gender, disease duration at baseline, EDSS at baseline, duration of Natalizumab treatment before study entry, and study duration.

Statistical and graphical methods have been applied to test normal distribution of variables and residuals, when appropriate. Stata 12.0 has been used for data processing and analysis. Results were considered statistically significant if $p<0.05$.

RESULTS

Seventy-one patients were included in the present study and were followed-up during a 12.9±6.2 month period. Demographic and clinical characteristics are reported in Table 1. No patients presented with diabetes. Patients did not report major changes in their diet during the study period.

VARIATIONS OF CARDIOVASCULAR RISK FACTORS

The population presented with a significant reduction of total cholesterol (Coeff=-7.340; 95%CI=-13.152--1.527), and of HDL (Coeff=-3.473; 95%CI=-6.333--0.613), and a non-significant reduction of LDL (Coeff=-1.872; 95%CI=-8.481-0.736), and of triglycerides (Coeff=-8.815; 95%CI=-34.011-5.380) (Table 1; Figure 1). Uric acid levels increased during the study period (Coeff=0.159; 95%CI=0.212-0.340). No variations were found when considering systolic blood pressure (Table 1; Figure 1).

CLINICAL VARIABLES

No associations were found between relapse occurrence and systolic blood pressure (OR=0.849; 95%CI=0.708-1.017; p=0.076), BMI (OR=0.007; 95%CI=-0.001-0.798; p=0.053), uric acid (OR=1.031; 95%CI=0.133-7.985; p=0.976), total cholesterol (OR=0.973; 95%CI=0.898-1.054; p=0.509), LDL (OR=0.787; 95%CI=0.598-1.037; p=0.089), HDL (OR=1.072; 95%CI=0.941-1.222; p=0.293), and triglycerides (OR=1.001; 95%CI=0.982-1.019; p=0.929).

No associations were found between EDSS progression and variations of systolic blood pressure (Coeff=0.001; 95%CI=-0.013-0.017; p=0.820), BMI (Coeff=-0.016; 95%CI=-0.174-0.141; p=0.836), uric acid (Coeff=0.030; 95%CI=-0.239-0.300; p=0.823), total cholesterol (Coeff=0.004; 95%CI=-0.004-0.013; p=0.310), LDL (Coeff=0.001; 95%CI=-0.008-0.009; p=0.296), HDL (Coeff=0.010; 95%CI=-0.005-0.027; p=0.187), and triglycerides (Coeff=0.001; 95%CI=-0.001-0.001; p=0.840).

DISCUSSION

The present longitudinal cohort study found a reduction of lipids and an increase of uric acid levels in RRMS patients during 12-month treatment with Natalizumab.

Reduction of circulating lipids during DMTs has been described for Interferon beta previously (Brescia Morra et al. 2004; Uher et al. 2017), whereas this is the first report for Natalizumab. Changes in lipid metabolism might result as a consequence of both disease evolution and treatment (Zhornitsky et al. 2016). On the one hand, higher cholesterol levels have been associated with worse clinical and radiological outcomes and, so, improvement of lipid profile in our population might be driven by more metabolically active neurons during clinical stability (Novakova et al. 2015; Zhornitsky et al. 2016). On the other hand, we cannot exclude a direct role of Natalizumab in cholesterol metabolism. Indeed, Natalizumab exerts its clinical activity through the blocking of the very late activation antigen-4 (VLA-4) adhesion molecule at the level of the blood-brain barrier. However, VLA-4 integrin is expressed in different compartments and its activity in the peripheral

blood has been associated with cholesterol levels (Cerda et al. 2015). Also, VLA-4 blocking within atherosclerotic plaques can be responsible for changes in cholesterol metabolism (Sternberg et al. 2014).

In the present cohort, HDL decreased, along with total cholesterol and LDL. HDL can affect the cardiovascular risk positively, but their properties are influenced by maturation and structure, which can be impaired in RRMS (Jorissen et al. 2017). Thus, a detailed characterisation of HDL might have provided a better perspective (Weinstock-Guttman et al. 2013).

The increase of uric acid levels after 12-month Natalizumab treatment can be considered a sign of improved oxidative balance, rather than a worsening of the cardiovascular profile. Of note, increased uric acid levels have been previously associated with reduced risk of relapse and of disability progression (Moccia et al. 2015a).

We did not find any association between cardiovascular factors and clinical variables. Considering the relatively short follow-up, the sample size and the use of a highly active medication, the number of patients with relapses or disability progression was limited, reducing the possibility to detect significant results. However, associations between cardiovascular risk factors and MS evolution have been widely reported (Hon et al. 2009; Weinstock-Guttman et al. 2013; Tettey et al. 2014, 2017; Marrie et al. 2015; Moccia et al. 2015b; Kappus et al. 2016; Uher et al. 2017), and this study was specifically designed to measure changes in the cardiovascular profile during Natalizumab treatment. Of note, we previously reported on clinical outcomes of Natalizumab in a study with adequate design (Lanzillo et al. 2017).

Possible limitations include the lack of a control population, although placebo-controlled studies are nowadays considered unethical in RRMS (Polman et al. 2008; Solomon and Bernat 2016); in the future a re-analysis of already existing datasets from registration trials might be considered. We also did not have specific data on dietary and lifestyle habits. More sensitive tests might have been used to assess glucose tolerance (Penesova et al. 2015).

In conclusion, our findings suggest that Natalizumab treatment has a beneficial effect on the lipid

profile and on the oxidative balance. Possible subsequent associations with disease outcomes deserve to be investigated in larger cohorts with longer follow-ups and with more detailed clinical and neuroradiological outcomes.

COMPLIANCE WITH ETHICAL STANDARDS

The authors declare that they have no conflict of interest.

In compliance with current Italian applicable laws and regulations, considering that all data was publicly available and that the analyses included anonymized data, specific ethics approval was not required. The study was performed in accordance with Declaration of Helsinki.

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FIGURE 1. Cardiovascular risk factors at baseline and follow-up.

Box-and-whisker plots show values of systolic blood pressure (A), body mass index (B), uric acid (C), total cholesterol (D), LDL cholesterol (E), HDL cholesterol (F), and triglycerides (G) at baseline and after 12.9±6.2 months. P-values and coefficients are shown from adjusted multilevel mixed-effects linear regression models. Asterisks indicate statistically significant results ($p<0.05$).

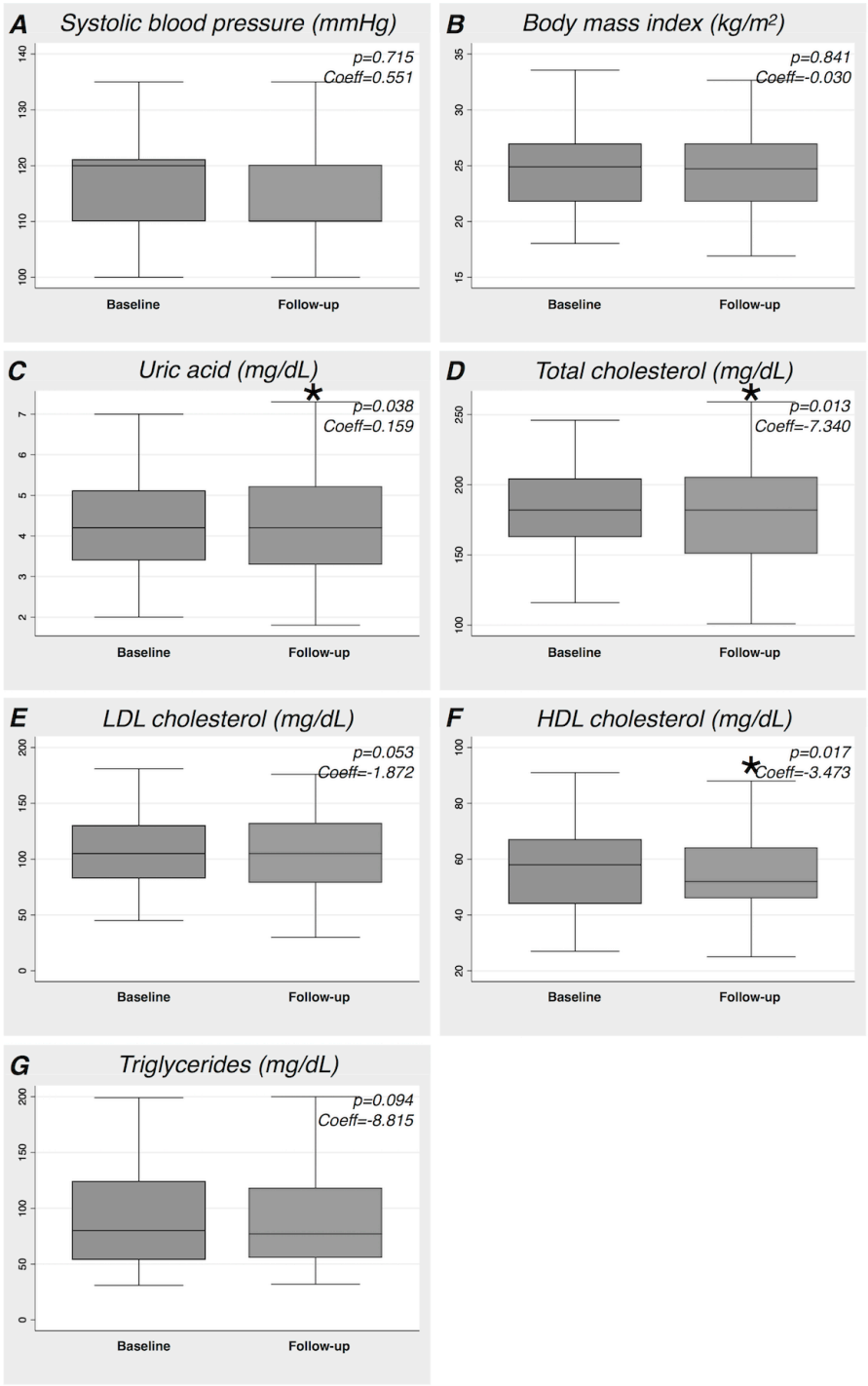

TABLE 1. Demographic, clinical and cardiovascular features.

Table shows demographic, clinical and cardiovascular features of the population at baseline and follow-up. Data are presented as mean±standard deviation, number (percentage), or median (minimum and maximum value), as appropriate. P-values are shown from adjusted multilevel mixed-effects linear regression models (*: p<0.05).

	Baseline *(n=71)*	***Follow-up*** *(n=71)*	*p-values*
Age, *years*	35.7±10.7		
Gender, *female (%)*	50 (70.4%)		
Disease duration, *years*	8.8±14.4		
Duration of Natalizumab treatment at study entry, *months*	11.7±14.1		
Study duration, *months*		12.9±6.2	
Patients with relapse, *number (%)*		8 (11.3%)	
Annualised relapse rate		0.18±0.57	
EDSS, *median (min-max)*	3.0 (2.0-5.0)	3.0 (2.0-5.5)	
Systolic blood pressure, *mmHg*	115.7±11.0	115.9±13.2	0.715
BMI, kg/m^2	24.9±3.9	24.3±4.0	0.841
Uric acid, *mg/dL*	4.1±1.1	4.4±1.3	0.038*
Total Cholesterol, *mg/dL*	189.3±40.5	181.0±39.6	0.013*
LDL Cholesterol, *mg/dL*	111.1±38.3	106.4±36.6	0.053
HDL Cholesterol, *mg/dL*	58.4±16.4	53.2±14.0	0.017*
Triglycerides, *mg/dL*	108.3±100.6	97.3±66.9	0.094

EDSS: expanded disability status scale; BMI: body mass index; LDL: low-density lipoprotein; HDL: high-density lipoprotein.