Heart Rate Variability During Fingolimod Treatment in Patients With Relapsing-Remitting Multiple Sclerosis

S. Barone[1], M. Salsone[2], M. Trotta[1], T. Tallarico[1], A. Granata[1], E. Filippelli[1], B. Vescio[2], A. Quattrone[1-2], P. Valentino[1].

[1] Institute of Neurology, University "Magna Graecia", Catanzaro, Italy

[2] Neuroimaging Research Unit, UOS-IBFM, National Research Council, Catanzaro, Italy

Objective

Fingolimod is an immunomodulating agent used in the treatment of the relapsing-remitting Multiple Sclerosis (RRMS) eliciting transient and dose-dependent vagomimetic effect. Heart rate variability (HRV) is a quantitative tool for investigating cardiac autonomic balance. The primary aim of this study was to investigate in RRMS patients HRV parameters at baseline and during Fingolimod first-dose administration. The secondary aim was to evaluate whether parasympathetic activity, before Fingolimod treatment initiation, may influence vagomimetic effect of this drug.

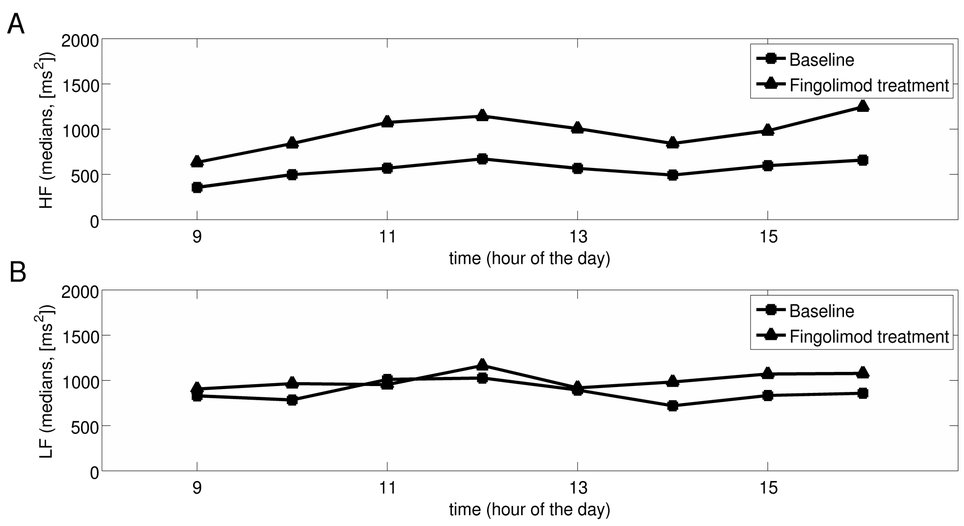
Materials and Methods

HRV parameters were calculated using spectral analysis in frequency domain in **25 RRMS patients** and 19 control subjects. The HRV protocol included: baseline evaluation performed 24 hours before Fingolimod treatment and evaluation during first oral therapeutic dose (0.5 mg orally) for six hours.

Results

At baseline evaluation, RRMS patients showed significantly lower values for all HRV variables low-frequency (LF), High-frequency (HF) and LF/HF ratio as compared to controls with a greater involvement of parasympathetic system activity. In RRMS patients during Fingolimod first-dose administration occurred a significant and selective increment of mean parasympathetic activity (HF=1225.5±649.9 ms^2) compared to baseline (HF=814.4±538.5 ms^2, p=**0.009**) whereas no significant increment of sympathetic activity was recorded during the treatment (Figure). When we divided our patients basing on initial parasympathetic system activity (HF≤1000 ms^2 and in HF>1000 ms^2) in two subgroups (A, B respectively) their clinical characteristics were statistically significantly different. The subgroup A showed a longer disease duration, more severe form of the disease and greater parasympathetic dysautonomia (HF=598.5 ms^2) as compared to subgroup B (HF=1717.3 ms^2). Five hours after Fingolimod treatment, HF value of subgroup A were lower (HF=770 ms^2) than those of subgroup B (HF=1910.3 ms^2). The mean increment of fingolimod-induced parasympathetic activity was comparable in both subgroups and ranged between 170-190 ms^2 (Table).

FIGURE: Autonomic fluctuations during fingolimod treatment.



Autonomic fluctuations during fingolimod treatment. The fluctuation of the high frequency (HF) (A) and low frequency (LF) (B) components of HRV (medians) in patients with RRMS at baseline (squares) and during fingolimod treatment (triangles).

TABLE: Demographic, clinical characteristics and HRV parameters of RRMS subgroups.

Variables	Subgroup A (N=15)	Subgroup B (N=10)	P-value
Age (y)	39.7±7.8	34.4±8.2	0.128[a]
Sex (f/m)	80%	80%	
Age at onset (months)	27.2±6.0	27.8±8.5	0.867[a]
Disease duration (months)	126.5±73.3	75.8±39.1	0.035[a]
EDSS	4.3±1.5	3.0±1.2	0.027[a]
HRV variables at T0			
HF(parasympathetic activity) ms^2	598.5±235.5	1717.3±506	0[a]
LF(sympathethic activity) ms^2	804.2±345.1	1579.9±715.6	0.013[a]
HF/LF	1.5±0.6	0.95±0.3	0.01[a]
HRV variables at T5			
HF(parasympathetic activity) ms^2	770.4±256.7	1910.3±457	0[a]
LF(sympathethic activity), ms^2	908.7±326.7	1623.8±678.8	0.009[a]
HF/LF	1.3±0.5	0.88±0.23	0.015[b]

Data are given as mean values (SD) or median range when appropriate. bpm, beats per minute; EDSS, Expanded Disability Status Scale; HF, high frequency; HRV, heart rate variability; LF, low frequency; ms, microsecond; RRMS, relapsing-remitting multiple sclerosis. [a]t-test ; [b]Wilcoxon signed rank test

Discussion & Conclusions

Our findings demonstrate and quantify, for the first time, the vagomimetic effect of Fingolimod in RRMS patients and provide to identify a phenotype whit a lower risk for developing cardiac autonomic effects. A longer disease duration, a more severe form of the disease and impaired parasympathetic activity could be protective factors reducing the risk for of developing cardiac adverse events in the first fingolimod dose administration. Further studies in larger cohorts of fingolimod-treated patients with RRMS are recommended.

References:

1. Vanoli E, Pentimalli F, Botto G. Vagomimetic effects of fingolimod: physiology and clinical implications. CNS Neurosci Ther. 2014;20(6):496-502.
2. Kale N, Magana S, Agaoglu J, Tanik O.T Assessment of autonomic nervous system dysfunction in multiple sclerosis and association with clinical disability. Neurol Int. 2009;1:e5.
3. McDougall AJ, McLeod JG. Autonomic nervous system function in multiple sclerosis. J Neuro Sci. 2003;215(1-2):79-85.

XLVI CONGRESSO NAZIONALE
10-13 OTTOBRE 2015 – GENOVA