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Is Gender Associated to Extended Cardiac Monitoring after First Dose of Fingolimod and Level of Satisfaction with the Monitoring Experience in Relapsing-Remitting Multiple Sclerosis Patients? A Post-hoc Analysis of the BEAT Study

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Abstract

Objective: Fingolimod, a second-line therapy for relapsing-remitting multiple sclerosis, may cause transitory effects on heart rate and atrioventricular conduction that may result in bradycardia and atrioventricular blocks, mainly following first administration; an ECG monitoring for at least 6 hours is therefore recommended, to be extended in case of bradycardia. The BEAT study showed that the dominance of cardiac vagal modulation, though not representing a risk factor for rhythm complications, can help identifying patients with higher probability to require extended monitoring.

Methods: This is a post-hoc analysis of the BEAT study, aimed at assessing the association between gender and need of extension of the ECG and gender differences in patients' satisfaction with drug administration and monitoring experience.

Results: Of the 625 patients evaluated in the BEAT study (67% were women), only 45 (7.2%; 95% CI: 5.3%; 9.5%) required an extended monitoring. Gender differences emerged in the assumption of drugs altering heart rate or atrioventricular conduction (6.4% of females *vs.* 0.5% of males, Chi-square test p-value=0.001) and in the sympathovagal balance status (median (interquartile range) RR LF/HF in women: 3.3 (1.3-7.4) respectively *vs.* 4.5 (2.1-10.2) in men, Wilcoxon test p-value=0.001). However, keeping constant the effect of these variables, no association emerged between sex and early ECG abnormalities requiring a prolongation of post-first dose monitoring. Our specifically developed satisfaction score showed a higher level of satisfaction with the overall care experience in women than in men (beta female *vs.* male=1.69 points) and women perceived a greater favorable impact of the drug on their daily living than man (median of 'impact of treatment' item in males and females 7.0 and 2.0, respectively, Wilcoxon test p-value=0.005).

Conclusion: No association emerged between sex and early ECG response to fingolimod administration requiring extended cardiac monitoring. More women than men reported a higher level of satisfaction with drug administration and monitoring procedures.

Keywords: Multiple sclerosis; Fingolimod; Heart rate variability; Cardiac monitoring; Gender-differences; Treatment satisfaction

Introduction

Sphingosine 1-phosphate (S1P) is a soluble signalling molecule deriving from the phosphorylation of sphingosine by sphingosine kinases that are ubiquitously expressed [1,2]. Through its interaction with the sphingosine 1-phosphate receptor (S1PR), S1P is involved in immunological, cardiovascular, and neurological processes. There are five S1PR subtypes (S1PR1-5), expressed in various cell types, such as lymphocytes, neurons, endothelial cells, myocytes and implicated in several immune-mediated disorders, such as rheumatoid arthritis, inflammatory bowel diseases, and multiple sclerosis (MS) [3-6]. Animal and human studies have suggested the presence of a disturbance in sphingolipid metabolism in MS patients [7,8].

Fingolimod has been the first S1PR modulator to receive regulatory approval as second-line treatment for the treatment of relapsing-remitting multiple sclerosis (RRMS). Fingolimod is a sphingosine 1-phosphate receptor modulator that inhibits the infiltration of potentially autoreactive lymphocytes from lymph nodes to the central nervous system (CNS). Fingolimod exerts its action by functionally antagonizing S1P-receptors (S1PRs) expressed on lymphocytes and reducing infiltration of autoreactive lymphocytes into the CNS, where they can induce inflammation and tissue damage [8,9]. These As these receptors are expressed in various tissues, including cardiac tissues, possibly causing transitory effects on heart rate (HR) and atrioventricular (AV) conduction, sometimes accompanied by a decrease in blood pressure (BP) [10,11]. These effects may result in bradycardia and AV blocks [12-16] and occur mainly following the first administration, as the fingolimod agonistic activity on S1P1

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produces then a rapid receptor internalization and degradation. Therefore, it is recommended that all patients have an ECG and blood pressure measurement performed before and 6 hours after the first administration of the drug and that, in case of bradycardia, monitoring is extended until abnormal ECG signs and related symptoms are resolved (Gilenya, Summary of Product Characteristics).

New agents selectively targeting subtype 1 of the S1PR, aimed at achieving better efficacy and reducing safety concerns, are currently in different stages of development, including ponesimod, siponimod, ozanimod, ceralifimod, and amiselimod, with promising phase II-III clinical trials results [17]. However, at the moment, no second-generation S1PR modulators have yet been approved.

The BEAT observational study [18] was aimed at characterizing the patients with RRMS for whom an extension of monitoring was required after routine first fingolimod dosing (FFD), in order to understand whether autonomic factors contribute to the heart rate (HR) effects. The study showed that the baseline autonomic profile, in particular the dominance of cardiac vagal modulation, does not represent a risk factor for rate or rhythm complications but can help identifying patients with higher probability to require monitoring beyond the first 6 hours after FFD.

It has been shown since several years that male and female patients exhibit differences regarding the pharmacology and toxicity of medications, and may differ in their response to drug treatment, not only as a result of physiological differences, such as body weight, surface area, extracellular and intracellular water, but also in terms of differences in pharmacokinetics and pharmacodynamics [19-22]. Sex and gender differences in the efficacy and tolerability of several types of pharmacological treatments have been extensively reported [23-30], however, this topic continues to draw limited attention. Since some years, Novartis has undertaken a wide gender-medicine project, called MetaGeM, with the purpose to evaluate gender differences that occur in therapeutic approaches, clinical outcomes, and safety parameters, by means of post-hoc analyses and meta-analyses of previously conducted observational trials. The MetaGeM project includes 12 Italian observational studies in different clinical areas, including immune-mediate disorders, organ transplants, and infectious, CNS, cardiovascular and respiratory diseases, performed between 2002 and 2016. Within the MetaGeM project, a post-hoc analysis of the BEAT study results has been performed with the following objectives: (i) assessing the association between gender and need of extension of the ECG monitoring, taking into consideration the effect of other variables having a statistically or clinically relevant impact on ECG monitoring prolongation; (ii) describing the gender-related differences in the degree of patients' satisfaction with FFD and monitoring experience, and assessing the association between gender and degree of satisfaction.

Methods

BEAT was an observational, prospective, multicentre study with duration limited to the observation period following FFD, i.e. 6 hours in the routine cases or up to 24 hours (or until resolution of the signs and symptoms) if an extension of the monitoring period was required. Before drug administration a continuous ECG recording of at least 15 minutes was performed, followed by clinical and ECG continuous monitoring over 6 hours after FFD. Adult outpatients of both sexes diagnosed with RRMS, for whom the decision to start treatment with fingolimod had already been taken, based on clinical judgment and regardless of the decision to recruit the patient into the study, were enrolled in the BEAT study. Early and permanent discontinuation of fingolimod in a previous fingolimod trial due to adverse event (AE) or serious adverse event (SAE) represented the main exclusion criterion. The study was performed in accordance with the Declaration of Helsinki and was approved by the local Ethic Committees of the centers involved in the study. All participants gave their written informed consent prior to their inclusion in the study. HR variability (HRV) data were obtained analyzing ECG registrations by means of dedicated software. Detailed study design, objectives, methods, and overall results have been reported elsewhere [18].

Patients' satisfaction with the FFD monitoring experience was assessed by means of an ad-hoc 13-item questionnaire, administered to each patient at the end of the ECG monitoring. Only 10 items were suitable for the gender analysis (items 1-8, 10, and 11) (Table 1), since they have numerically coded answers evaluating some attributes of the monitoring experience (e.g. ease, satisfaction, inconvenience) or patient feelings (e.g. nervousness); items range between 0 (not at all, none) and 10 (extremely, all) and the score of items #1, 4, 5, 7, 8, 10, 11 increases with treatment satisfaction, while the score of items #2, 3, 6 decreases while treatment satisfaction increases. The remaining three items (# 9, 12, 13) require open answers (about patient advice to other patients to improve the use of time during monitoring, on the advantages of oral therapy in allowing to carry out daily activities, and 5 words to describe the monitoring experience, respectively) and were thus not suitable for the patients' satisfaction total score calculation.

Statistical methods

All patients evaluated in the statistical analysis of the BEAT study were considered in this gender analysis, i.e. all patients fulfilling the study inclusion/exclusion criteria, having received the FFD, and for whom data about the decision to stop or extend the ECG monitoring beyond 6 hours were available. Missing values were not replaced and did not contribute to the analysis of the variable. The continuous, normally distributed variables were expressed as a mean and standard deviation (SD); in case of not normally distributed parameters, median and interquartile range (IQR) were provided; for qualitative data, absolute and relative frequencies were calculated.

First of all, some exploratory analyses were performed comparing, by means of statistical tests, the baseline demographic and clinical characteristics of patients needing *vs.* not needing extended monitoring. The considered patients' characteristics were: age, EDSS score, number of relapses in the year before enrolment, normalized spectral power in the LF band (RR LFnu), normalized spectral power in the HF band (RR HFnu), ratio between the absolute spectral power in LF and in HF band (RR LF/HF), assumption of drugs which can alter HR or AV conduction. These characteristics were also compared between male and female patients. The comparisons were performed with non-parametric Wilcoxon test, while differences between categorical variables were tested by Chi-square. The significance threshold was set at 0.05 (all p-values presented are exploratory, so no correction for multiple testing was applied) [31].

Then, in order to evaluate the association between gender and need of extension of the ECG monitoring, a multi-step approach was applied.

A univariate logistic regression model was applied where need of extension of the ECG monitoring (yes, no) and gender were the dependent and independent variables, respectively. Odds ratio (OR) and 95% Wald Confidence Intervals (CI) provided a raw measure of association, the effect of other covariates being not controlled.

Similarly, other seven logistic regression models were applied respectively considering as independent variables age (≤ 40, >40 years),

Item No.	Questions
1	On a scale from 0 to 10, how it was easy to take the first dose of Gilenya?
2	Thinking about to how you felt before going to the physician to take the first dose, on a scale from 0 to 10 how do you felt nervous?
3	Thinking about how do you felt during the 6-hour monitoring of the first dose, on a scale from 0 to 10 how stressful was this experience?
4	Overall, on a scale from 0 to 10, how satisfied are you about this experience?
5	On a scale from 0 to 10, how it is convenient to follow the instructions for drug-use?
6	If, during the first administration, you experienced some side effects, on a scale from 0 to 10, how much they were uncomfortable?
7	On a scale from 0 to 10, would you suggest the treatment to someone else?
8	On a scale from 0 to 10, how do you feel satisfied by the attention received at the center during the 6 hour of monitoring?
10	On a scale from 0 to 10, how much do you think the new method of administration can improve your daily activities?
11	On a scale from 0 to 10, how much do you think the new method of administration can affect your daily activities in terms of time?
Note: Items range between 0 (not at all, none) and 10 (extremely, all). The score of items #1, 4, 5, 7, 8, 10, 11 increases with treatment satisfaction, while the score of items #2, 3, 6 decreases while treatment satisfaction increases.	

Table 1: Questionnaire on patients' satisfaction with fingolimod first-dose monitoring experience (items involved in satisfaction score calculation)

EDSS score (<4, ≥ 4), N° of relapses in the last year (≥ 1, 0), use of drugs which can alter HR or AV conduction (yes, no), and RR LFnu, RR HFnu, RR LF/HF as continuous variables. These models provided raw measure of the association between extended monitoring and each independent variable.

Then, seven bivariate logistic regression models were run, where need of extension of the ECG monitoring (yes, no) was the dependent variable and gender was the independent one. In each model, another covariate was added in order to provide an estimate of association (OR and 95% CI) between the outcome and gender controlled by that covariate. As covariates, the same as in the previous step were chosen.

The last step involved the estimate of a multivariate logistic regression model; the dependent variable was the need of extension of the ECG monitoring and gender was the independent one. All previously mentioned covariates were added to the model and backward selection method was applied; the model provided a final estimate of the association between gender and need to prolong the ECG monitoring, keeping constant the effect of covariates.

The gender-related differences in the degree of patients' satisfaction were evaluated comparing (by means of non-parametric Wilcoxon tests) the answers to the 10 items of the questionnaire by males and females. In order to evaluate the association between gender and degree of satisfaction a multi-step approach was adopted again. First, a patients' satisfaction total score was created. The standardized Cronbach's alpha coefficient was calculated considering the 10 items of the patients' satisfaction questionnaire. Cronbach's alpha is known as an estimate of reliability of test scores; some professionals, as a rule of thumb, require a reliability of 0.70 or higher, with 0.60 as the lowest acceptable threshold [32]. Then, different Cronbach's alpha coefficients eliminating one at a time each item of the questionnaire were calculated, and the best solution was identified as the solution maximizing the number of items and the value of Cronbach's alpha in the meantime. Then an exploratory factor analysis (EFA) was performed to find independent latent constructs (factors), not directly measurable and influencing responses to the observed variables. Orthogonal VARIMAX rotation was applied; factors having an eigenvalue >1.0 [33,34] and individual variables with higher-than-0.4 loadings on retained factors were considered [35]. In the end, in order to evaluate the solution found, Cronbach's alpha coefficient was calculated considering the items retained after EFA. The patients' satisfaction total score was then calculated for each patient summing the responses to items retained after EFA.

The patients' satisfaction total score in males and females was compared by means of Wilcoxon test and a multivariate regression model was lastly estimated to evaluate the association between the patients' satisfaction score (dependent variable) and gender (independent variable). The model was adjusted for the following covariates: need of extending monitoring (yes, no), number of relapses in the year before enrolment (0, ≥ 1), age (≤ 40, >40 years) and EDSS score (<4, ≥ 4).

Statistical analysis was performed using SAS v9.2 and Enterprise Guide v4.3. Project management including data banking, quality control and statistical analysis, was performed by Medineos Observational Research (Modena, Italy).

Results

Overall 625 patients were evaluable in the BEAT study, with mean (SD) age of 38.26 (9.68) years and mean duration of MS of 7.63 (6.36) years; 67% were women. Demographic and baseline clinical characteristics are summarized in Table 2. Among evaluable patients, 580 (92.8%; 95% CI: 90.5%; 94.7%) were discharged at the sixth hour after FFD and only 45 (7.2%; 95% CI: 5.3%; 9.5%) required an extended monitoring, 11 (5.3%) among males and 34 (8.1%) among females. The following reasons for extended monitoring were provided (multiple response were admitted): 22 (46.8% of the total number of reasons provided) for low or decreasing HR, 13 (27.7%) for ECG abnormalities, 2 (4.3%) for other AEs, and 8 (17.0%) for other reasons. Overall, 27 (4.3%) patients experienced at least one AE and 6 (1.0%) had a serious AE (5 AV blocks and 1 sinus bradycardia); 25 (4.0%) patients had AEs considered possibly causally related to fingolimod and 4 (0.6%) patients had AEs causing fingolimod discontinuation.

Gender and prolongation of the ECG monitoring

Gender and extended monitoring *vs.* patient clinical characteristics (statistical tests): Statistical tests comparing patients who needed to extend the continuous ECG monitoring *vs.* those who did not showed statistically significant differences in the number of relapses in the year before enrolment, in the RR LFnu, RR HFnu and in RR LF/HF (Table 3). Moreover, statistical tests by gender showed that females assumed significantly more frequently drugs which can alter HR or AV conduction compared to men (6.4% of females *vs.* 0.5% of males) and that RR LFnu and RR LF/HF were lower in women (median (IQR): 72.0 (51.2-83.8) and 3.3 (1.3-7.4) respectively) than in men (79.0 (65.0-89.9) and 4.5 (2.1-10.2)), whereas RR HFnu was higher in females than in males (median (IQR): 21.3 (11.3-38.2) *vs.* 16.4 (7.3-28.2), respectively) (Table 3).

Association between gender and prolongation of the ECG monitoring: The univariate logistic regression models revealed no association between gender and need of extension of the ECG monitoring (OR (95% CI): 0.639 (0.317-1.288)). However, statistically significant ORs were found for number of relapses in the year before enrolment (OR of

Age at study entry (years) mean (SD)	38.26 (9.68)
Females, N (%)	419 (67.0)
Years from MS diagnosis, mean (SD)	7.63 (6.36)
Age at MS diagnosis, mean (SD)	30.65 (9.55)
EDSS score at study entry, mean (SD), n=616	2.84 (1.58)
N of relapses in the last year, mean (SD)	1.13 (0.70)

Note: SD: standard deviation; MS: multiple sclerosis; EDSS: Expanded Disability Status Scale. If not otherwise specified, descriptive statistics were computed on evaluable patients (n=625).

Table 2: Summary of study population demographic and baseline clinical characteristics.

	Patients who needed to extend the continuous ECG monitoring			Gender		
	Yes (n=45)	No (n=580)	p-value	Male (n=206)	Female (n=419)	p-value
Female (n, %)	34 (8.1)	385 (91.9)	0.207*	-	-	-
Age > 40 yrs (n, %)	23 (8.8)	239 (91.2)	0.195*	77 (37.4)	185 (44.2)	0.107*
EDSS score ≥4 (n, %)	14 (9.0)	142 (91.0)	0.258*	55 (27.1)	101 (24.5)	0.479*
N relapses in the year before enrollment ≥1 (n, %)	34 (6.3)	505 (93.7)	**0.031***	180 (87.4)	359 (85.7)	0.562*
RR LFnu^ (median (IQR))	63.4 (40.7-80.9)	75.6 (56.1-86.1)	**0.042****	79.0 (65.0-89.9)	72.0 (51.2-83.8)	**<0.0001****
RR HFnu^ (median (IQR))	24.9 (14.4-48.0)	19.0 (9.1-34.7)	**0.025****	16.4 (7.3-28.2)	21.3 (11.3-38.2)	**0.0001****
RR LF/HF ^^ (median (IQR))	2.7 (0.8-5.3)	3.9 (1.6-8.5)	**0.022****	4.5 (2.1-10.2)	3.3 (1.3-7.4)	**0.001****
Assumed drugs which can alter HR or AV conduction (n, %)	4 (14.3)	24 (85.7)	0.134*	1 (0.5)	27 (6.4)	**0.001***

Note: EDSS: Expanded Disability Status Scale; LF: low frequency; HF: high frequency; RR LFnu: Normalized spectral power in the LF band; RR HFnu: Normalized spectral power in the HF band; RR LF/HF: Ratio between the absolute spectral power in LF and in HF band; IQR: interquartile range; HR: Heart Rate; AV: Atrioventricular.
^value was available for 39 and 503 patients who needed and did not need extended monitoring, respectively.
^^ value was available for 38 and 493 patients who needed and did not need extended monitoring, respectively.
*Chi-square test p-values are showed.
**Non-parametric Wilcoxon Test p-values are showed.
Statistically significant tests (p-value <0.05) are in bold.

Table 3: Prolongation of the ECG monitoring and gender *vs.* patient clinical characteristics.

having extending monitoring patients with ≥ 1 *vs.* 0 previous relapses (95% CI): 0.459 (0.223; 0.945)), RR LFnu (as continuous value): 0.987 (0.975; 0.999), RR HFnu (as continuous value): 1.017 (1.003; 1.031).

The absence of association between gender and prolongation of the ECG monitoring was confirmed also by the results of bivariate logistic regression models (Table 4). The models confirmed the association between prolongation of the monitoring and number of relapses in the year before enrolment and RR HFnu.

The multivariate logistic regression model confirmed the absence of association between gender and need of extension of the ECG monitoring, and the association between number of relapses in the year before enrolment and prolongation of monitoring (Figure 1): keeping constant the effect of gender and of the other covariates included in the model, the patients with ≥ 1 relapse in the year before enrolment had about 60% less probability of needing extended monitoring compared to patients with no relapses (OR=0.366, 95% CI=0.166; 0.805). Moreover, patients assuming drugs which can alter HR/AV conduction had more than 3 times the probability of needing prolongation of ECG monitoring than patients not assuming them (OR=3.238, 95% CI=1.024; 10.239). Lastly, a one unit increase in RR HFnu increased of about 2% the probability of needing extended monitoring (OR=1.017, 95% CI=1.002; 1.032).

Gender and patients' satisfaction with FFD and monitoring experience

Gender *vs.* patients' satisfaction (statistical tests): Regarding treatment satisfaction, between-gender statistically significant differences emerged for the items 2, 5, 8, 10, and 11 of the questionnaire (Table 1, Figure 2) showing a higher level of satisfaction in women than men.

Association between gender and patients' satisfaction:

Patients' satisfaction total score: The standardized Cronbach's alpha coefficient calculated considering all the 10 items of the questionnaire was 0.66 indicating a questionable internal consistency. Then, different Cronbach's alpha coefficients eliminating one at a time each item of the questionnaire were calculated, and the best solution was the elimination of item 11 (How much do you think the new method of administration can affect your daily activities in terms of time?). The Cronbach's alpha considering items 1, 2, 3, 4, 5, 6, 7, 8 and 10 was acceptable (0.70). As results of the EFA on the items 1, 2, 3, 4, 5, 6, 7, 8 and 10 (ranging between 0 and 10), one factor was retained; its components were the items 1, 4, 5, 7, 8, and 10 (items 2, 3 and 6 were erased having lower-than-0.4 loadings on retained factor). Cronbach's alpha coefficient considering these 6 items increased to 0.75. Then, a patients' satisfaction total score summing the value of these 6 items was calculated, ranging between 0 (not at all satisfied) and 60 (extremely satisfied).

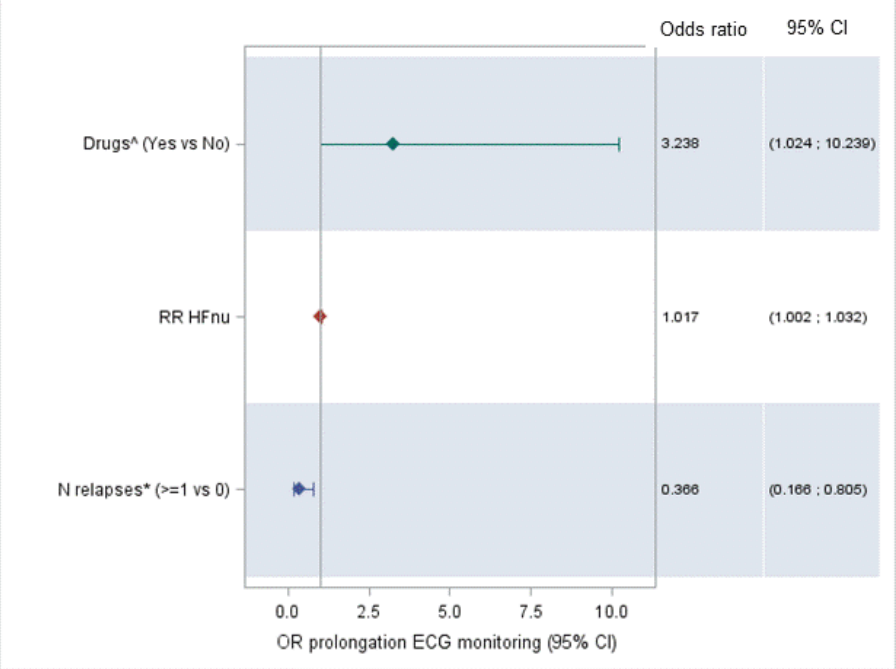
Gender *vs.* patients' satisfaction total score (statistical test): The patients' satisfaction total score (calculated at the previous step) was higher in women (median (IQR)): 54.0 (49.0-58.0)) than in men (median (IQR): 53.0 (46.0-57.0); Wilcoxon test p-value=0.024).

Association between gender and patients' satisfaction total score (multivariate regression model): Analyzing the association between satisfaction, gender, and other covariates in a multivariate model (Table 5), gender resulted significantly associated to treatment satisfaction: female patients had a score 1.7 points higher than man taking constant the effect of age, EDSS score, number of previous relapses and need of extended monitoring.

Model	Variable	OR (95% CI)
1)	Gender (females vs. males)	1.527 (0.756; 3.084)
	Age classes (≤ 40 *vs.* > 40 years)	0.686 (0.373-1.262)
2)	Gender (females vs males)	1.484 (0.731; 3.011)
	EDSS score (< 4 *vs.* ≥ 4)	0.674 (0.346-1.313)
3)	Gender (females *vs.* males)	1.545 (0.764; 3.122)
	N° of relapses in the last year (>=1 *vs.* 0)	**0.464 (0.225-0.956)**
4)	Gender (females *vs.* males)	1.447 (0.665; 3.153)
	RR LFnu (continuous variable)	0.988 (0.976-1.000)
5)	Gender (females *vs.* males)	1.451 (0.667; 3.154)
	RR HFnu (continuous variable)	**1.016 (1.002-1.030)**
6)	Gender (females *vs.* males)	1.635 (0.729; 3.670)
	RR LF/HF (continuous variable)	0.944 (0.881-1.011)
7)	Gender (females *vs.* males)	1.482 (0.728; 3.014)
	Use of drugs which can alter HR or AV conduction (yes *vs.* no)	2.029 (0.663-6.211)

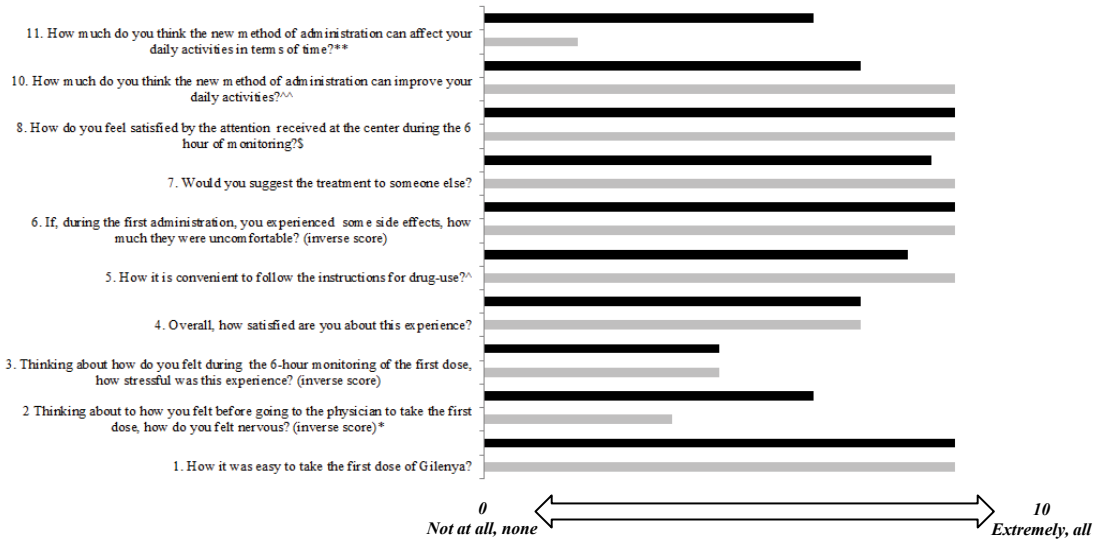
Note: OR: odds ratio; CI: Confidence interval; EDSS: Expanded Disability Status Scale; LF: low frequency; HF: high frequency; RR LFnu: Normalized spectral power in the LF band; RR HFnu: Normalized spectral power in the HF band; RR LF/HF: Ratio between the absolute spectral power in LF and in HF band; HR: Heart Rate; AV: Atrioventricular.
OR and 95% Confidence Limits of needing extended monitoring are showed.
Statistically significant associations are in bold.

Table 4: Association between gender and prolongation of the ECG monitoring (bivariate logistic regression models).



OR: odds ratio; HF: high frequency; RR HFnu: Normalized spectral power in the HF band.
OR and 95% Confidence Limits of needing extended monitoring are showed.
RR HFnu was included as continuous variables in the model.
*in the year before enrollment.
^which can alter HR/AV conduction

Figure 1: Association between gender and prolongation of ECG monitoring (multivariate logistic regression model).



	Median (IQR)	
	Female	Male
Item #1	10.0 (8.0-10.0)	10.0 (8.0-10.0)
Item #2	4.0 (2.0-8.0)	7.0 (3.0-10.0)
Item #3	5.0 (4.0-9.0)	5.0 (3.0-8.0)
Item #4	8.0 (7.0-10.0)	8.0 (6.0-10.0)
Item #5	10.0 (8.0-10.0)	9.0 (8.0-10.0)
Item #6	10.0 (8.0-10.0)	10.0 (9.0-10.0)
Item #7	10.0 (8.0-10.0)	9.5 (7.0-10.0)
Item #8	10.0 (9.0-10.0)	10.0 (9.0-10.0)
Item #10	10.0 (8.0-10.0)	8.0 (7.0-10.0)
Item #11	2.0 (0.0-9.0)	7.0 (1.0-9.0)

* Non-parametric Wilcoxon Test p-value <0.0001

^ Non-parametric Wilcoxon Test p-value =0.037

Non-parametric Wilcoxon Test p-value =0.011

^ ^ Non-parametric Wilcoxon Test p-value =0.0002

** Non-parametric Wilcoxon Test p-value =0.005

Items range between 0 (not at all, none) and 10 (extremely, all). The score of items #1, 4, 5, 7, 8, 10, 11 increases with treatment satisfaction, while the score of items #2, 3, 6 decreases while treatment satisfaction increases.

Figure 2: Satisfaction questionnaire: descriptive statistics of numerical items by gender (median).

Parameter		Estimate	p-value
Intercept		49.696	<0.0001
Gender	**Female *vs.* Male**	**1.687**	**0.013**
Extended monitoring	No *vs.* Yes	0.433	0.727
N of relapses in the year before enrollment	0 *vs.* ≥ 1	-0.934	0.31
Age	≤ 40 *vs.* > 40 years	-0.257	0.702
EDSS score	< 4 *vs.* ≥ 4	1.324	0.079

Note: EDSS: Expanded Disability Status Scale.
P-value of Wald Chi-square test testing the significance of the contrast is showed.

Table 5: Association between satisfaction, gender, and other covariates (multivariate model).

Discussion

For many years, clinical and drug therapy research has mainly focused on male sex, assuming that studying females would give similar results. However, several diseases - including MS - affect males and females differently and medications were shown to obtain different efficacy and safety outcomes in men and women [36-40]. In addition, optimal dosing of medications, in terms of efficacy and side effects, has been studied for long time in patient populations mainly composed of men, whereas they may significantly differ between the two sexes. In recent years, sex differences in disease susceptibility and response to pharmacological therapy have deserved greater attention, and it has been progressively accepted that medical research should increase women presence in clinical trials in order to be equal and correct [41]. Gender differences concerning fingolimod treatment have been previously reported in terms of treatment understanding - with women reporting significantly more knowledge on fingolimod therapy than men [42] – and of AEs – with women developing more infections and men more liver function test alterations during long-term fingolimod treatment [43]. Our post-hoc gender analysis of the multicenter observational BEAT study – focused on FFD and the requirement of prolonged ECG monitoring – while confirming in both

sexes the reassuring cardiac safety profile of fingolimod, whose first administration had no significant cardiac consequences in both males and females, showed that gender was not associated with the occurrence of early ECG alterations requiring the extension of monitoring beyond the first 6 hours.

The mechanism of action of fingolimod on S1PRs is known to be responsible of its effects on HR and AV conduction at therapy initiation and for the mild but possibly persistent effects on blood pressure observed in some patients on long-term treatment, and it may be useful for physicians to know more about the epidemiology of the risk factors for such cardiac effects. The BEAT study has explored some factors potentially predicting ECG alterations following the first administration of the drug, highlighting that the background autonomic profile and specifically the dominance of cardiac vagal modulation could help identifying patients with higher probability to require ECG monitoring beyond the first 6 hours. We wanted to assess whether sex could be in some way associated to the need for extensive cardiac monitoring, but it seems from our results that there is no association between sex and early ECG abnormalities requiring a prolongation of the routine 6-hour post-FFD monitoring.

Statistically significant between-gender differences emerged in the assumption of drugs altering HR or AV conduction, and in the sympathovagal balance status (RRLFnu, RR HFnu, and relative ratio, Table 3) but, as confirmed by our stepwise analysis, taking constant the effect of these variables, gender was not associated to the probability of requiring an extended monitoring, while the use of drugs which can alter HR/AV conduction had the highest association with the need for prolonging ECG monitoring, having experienced relapses during the year preceding FFD was negatively associated to the probability of requiring extended ECG monitoring and RR HFnu was modestly positively associated to it.

There is a growing emphasis on patient satisfaction about pharmacologic treatments and medical or surgical procedures, in the attempt to improve patient's adherence to the physician's recommendations and also in the light of "paying for performance". In the United States, for example, hospitals are financially rewarded or penalized based on the patient experience scores they obtain [44]. The Institute for Health Care Improvement defines the patient's "experience of care" as composed by both the quality of care and the degree of patient's satisfaction [45]. Few data are available about gender differences in satisfaction with medical treatments. Women rated their satisfaction with hospital stay significantly lower than men, requiring more gender-sensitive care [46]. Women were shown to be more prone than men to stop or switch statin treatment due to AEs [47]. On the other hand, women showed higher adherence to other medications in different settings [27,48]. To our knowledge, nothing has been reported about gender differences in satisfaction with fingolimod treatment. Though limited to FFD and its monitoring experience, our evaluation showed significantly higher overall satisfaction among women compared to men. In particular, women reported significantly less anticipatory nervousness about taking FFD and more easiness in taking the medication according to the given instructions. Furthermore, they were significantly more satisfied with the experience of care and perceived a greater favorable impact of the drug on their daily living (Figure 2). Considering that in addition to literature data [27,48], clinical experience have taught us that women generally have a greater attention to care and a more favorable compliance to treatments, we think these results can perhaps be better interpreted in this sense, than as a specific greater satisfaction with the fingolimod treatment and monitoring experience.

This study has the obvious limitation of being a post-hoc analysis of a study that had not originally been designed with the aim of detecting gender differences. Another limitation is that the number of patients undergone prolonged ECG monitoring was small, limiting the power of gender comparison. A variety of patient satisfaction survey instruments to measure patient experience/satisfaction in both the hospital and outpatient clinic settings have been developed for different clinical conditions [27,49-52]. It may be objected that our satisfaction questionnaire is not a known and validated one. However, it is recognized that patient satisfaction has a complex construct and is highly context dependent. Therefore, we made the effort to develop a specific satisfaction score, which showed to be satisfactory for the internal consistency assessment (Crohnbach alpha 0.75) and whose 6 considered items proved to address a single latent dimension.

Conclusion

Overall, this post-hoc gender analysis suggests that, even if gender differences emerged in the assumption of drugs altering heart rate or AV conduction and in the sympathovagal balance status, keeping constant the effect of these variables, there is no association between sex and early ECG response to FFD administration. Our specifically developed satisfaction score shows that women report a higher level of satisfaction with drug administration and monitoring procedures, adding another piece to the knowledge on gender differences in the response to drug therapies.

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Declaration of Conflicting Interests

Colombo Delia is a part-time employee of Novartis Farma Italy and received grants from Allergan and Aventis.

Zagni Emanuela is an employee of Novartis Farma, Italy.

Alessandra Ori is an employee of Medineos Observational Research.

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Giuseppe De Angelis received consulting fees from Novartis.

Emilio Vanoli received consulting and advisory board fees from Novartis. He is consultant to LIVANOVA for vagal stimulation, Molteni, CVRx, Sanofi, STm.

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