Characteristics of MS Patients Treated With PR-Fampridine in a Real-world Setting Based on the NeuroTransData Network in Germany

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Introduction

- In controlled clinical trials, treatment with prolonged-release fampridine (PR-FAM) resulted in clinically meaningful improvements in self-reported walking ability vs. placebo in patients with all subtypes of multiple sclerosis (MS).[1-4]
- During the past 7 years, real-world data of PR-FAM have accrued and may inform on patient characteristics, treatment persistence and effectiveness in the in-label (Expanded Disability Status Scale [EDSS] score 4–7)[5] post-approval setting.
- NeuroTransData (NTD) is a German network of office-based neurologists documenting in-depth practice-based data for patients with MS and constitutes the first analysis of a multicentre real-world data cohort for PR-FAM.

Objectives

- The primary objectives of this observational study were to characterise patients with MS exposed to PR-FAM and investigate persistence with PR-FAM, including predictors, in a descriptive manner.
- The secondary objective was to compare change in EDSS ambulation score over time between propensity score–matched responders and non-responders in a descriptive manner.

Methods

- Patient data were captured prospectively by NTD centres during out-patients visits.
- Patients were included in this analysis based on the availability of baseline data (e.g., MS subtype, background disease-modifying therapy, EDSS score, use of physiotherapy and PR-FAM exposure).

Populations Analysed

- All PR-FAM–treated patients with data as of 1 July 2018 (N=1163).
- A subset of patients with an EDSS score of 4–7 and systematic capturing of total EDSS and EDSS ambulation at baseline and Month 6 was selected for the propensity score–matched analysis of responders vs. non-responders (N=495).
  - Responders were defined as patients who persisted on PR-FAM treatment for ≥3 months (3 months is the most prevalent frequency of assessment in the NTD network database and the earliest potential documentation of such status);
  - Non-responders were defined as patients stopping PR-FAM within 3 months due to any reason.

Outcomes

- A univariate Cox regression was performed in the cohort of PR-FAM–treated patients with no missing data for candidate predictors (n=1104) to assess the influence of potential baseline predictors on PR-FAM discontinuation due to lack of effectiveness. A similar analysis was performed examining discontinuation due to adverse events (data not shown).
- Propensity score matching was conducted to compare PR-FAM responders and non-responders.
  - All baseline characteristics shown in Table 2, including EDSS and EDSS ambulation scores, were used in the derivation of the propensity score analysis.
- Longitudinal analyses were conducted to describe the clinical course, including EDSS ambulation scores.
  - For the analysis, EDSS assessments have been assigned to baseline (defined as PR-FAM initiation), Month 6 and Month 12.
  - Change in EDSS ambulation score was assessed from baseline (from PR-FAM initiation) and a roving baseline (as adapted from Kappos *et al*.[6]).
- Proportions of patients with at least a 1-point score improvement (from baseline) vs. patients who did not improve (were stable or progressed) in EDSS ambulation score (not confirmed) were analysed using a generalised estimating equations logistic regression model.
  - Odds ratios (ORs) were used as a measure of treatment effect.

Results

- As of 1 July 2018, 1163 patients were exposed to PR-FAM in 63 NTD centres.
- Baseline characteristics are described for the whole cohort and by responder status (Table 1).
  - In all PR-FAM–treated patients, 70.7% (822/1163) were responders and 29.3% (341/1163) were non-responders. The median (interquartile range [IQR]) exposure to PR-FAM was 17.4 (2.0–48.2) months for all PR-FAM–treated patients, 32.9 (14.6–59.2) months for responders and 0.6 (0.5–1.4) months for non-responders.
  - The demographics of the different groups are representative of the overall population initially treated with PR-FAM.
- Based on 1104 patients with available data for all candidate predictors, a univariate prediction model for FAM discontinuation due to lack of effectiveness found that response to PR-FAM was independent of baseline disease characteristics (Figure 1).
  - A sensitivity analysis based on a multivariable Cox regression was performed and revealed consistent results (data not shown).
- Four hundred ninety-five patients (responders, n=335 [68%]; non-responders, n=160 [32%]) had EDSS and EDSS ambulation scores fitting the inclusion criteria. Propensity score matching resulted in 160 responder and non-responder pairs with similar post-matched baseline characteristics and treatment history (Table 2, Figure 2).
  - The C-statistic was 0.569.
  - Median (IQR) follow-up time was greater in responders vs. non-responders (21.6 [9.7–55.1] months vs. 11.5 [2.2–36.6] months).
- A greater percentage of PR-FAM responders demonstrated improvement in EDSS ambulation score compared with non-responders at Months 6 and 12 (Figure 3).
  - All included patients had a Month 6 EDSS ambulation measurement but there were patients with missing values at Month 12.
  - Reasons for missing patients at Month 12 included: insufficient follow-up time (responders 6.9% [11/160]; non-responders, 21.9% [35/160]) and DMT/physiotherapy change (responders 17.5% [28/160]; non-responders, 22.5% [36/160]).
  - Responders were more likely than non-responders to show improvement vs. no improvement (stable or progressed) from baseline on EDSS ambulation score at Month 6 (OR [95% CI], 1.69 [0.81–3.52]) and Month 12 (OR [95% CI], 2.55 [1.19–5.46]; Figure 3A).
- The percentage of patients with progression in EDSS ambulation score (not confirmed) at Month 6 was similar between responders and non-responders. At Month 12, a slightly greater percentage of non-responders progressed; however, these results should be interpreted with caution due to the observed imbalance of missing data.

Limitations

- The degree to which changes in EDSS ambulation score reflect changes in conventional measures of walking speed used in the randomised clinical trial setting (e.g., Timed 25-Foot Walk) is not yet known.
- The impact of the decrease in available patients at Month 12 may limit the interpretation of these analyses.
- Future analyses will investigate confirmed measures of ambulation improvement, stability and progression.

Table 1. Baseline characteristics

Characteristic[a]	All PR-FAM–treated patients N=1163	By PR-FAM responder status: Non-responder N=341	By PR-FAM responder status: Responder N=822
Mean (SD) age, y	50.9 (10.9)	52.2 (11.8)	50.3 (10.4)
Female, %	66.2	66.3	66.2
Mean (SD) time since first symptoms, mo	190.4 (120.1)	189.9 (129.4)	190.7 (116.1)
Mean (SD) no. of relapses in prior 12 months	0.34 (0.66)	0.35 (0.66)	0.33 (0.67)
No. of relapses in 12 months before fampridine, %			
0	74.3	72.4	75.1
1	19.9	21.7	19.2
2	4.3	4.7	4.1
3	1.0	0.6	1.2
4+	0.4	0.6	0.4
MS subtype, %			
PPMS	9.5	9.7	9.5
RRMS	59.1	60.7	58.4
SPMS	31.4	29.6	32.1
Prior DMT, %			
0	49.3	49.6	49.1
1	26.5	25.2	27.0
2	14.1	14.4	14.0
3	6.7	7.9	6.2
4+	3.4	2.9	3.6
Background DMT, %			
Interferon/GA	29.3	29.0	29.4
Oral	13.9	14.1	13.9
High efficacy	7.7	7.0	8.0
No DMT	49.0	49.9	48.7
Physiotherapy, yes, %	66.0	67.2	65.5
Sustained 12-week EDSS progression in 24 months before PR-FAM, yes, %	23.6	25.2	23.0
Mean (SD) EDSS score (within ±12 weeks)	4.8 (1.4)	4.8 (1.5)	4.9 (1.4)
Mean (SD) MSSS score since first MS symptoms	1.0 (11.8)	1.8 (20.3)	0.7 (4.9)

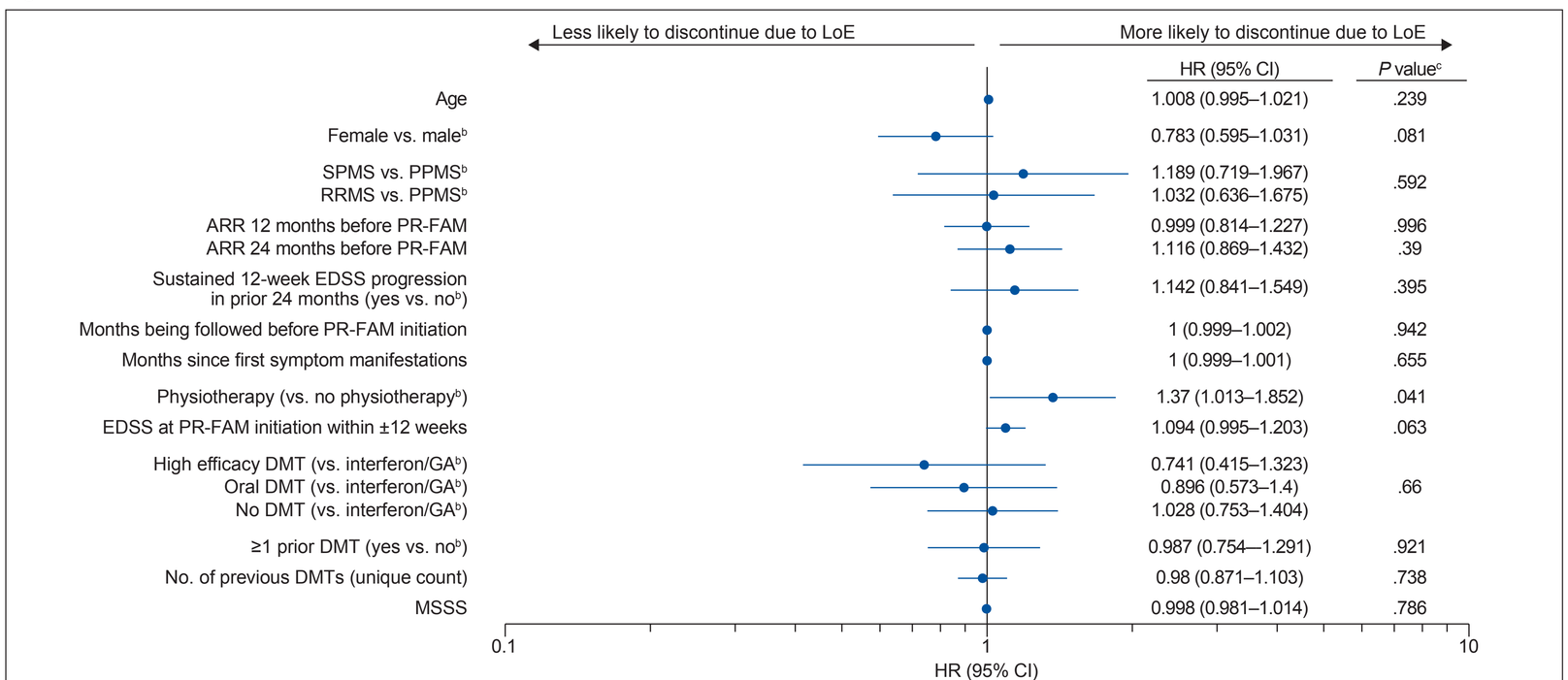
DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale; GA = glatiramer acetate; MS = multiple sclerosis; MSSS = Multiple Sclerosis Severity Score; PPMS = primary progressive multiple sclerosis; PR-FAM = prolonged-release fampridine; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis
[a]At PR-FAM initiation unless otherwise specified

Table 2. Baseline characteristics used to generate propensity scores in the matching process of PR-FAM responders and non-responders (post-matching characteristics)

Characteristic[a]	PR-FAM non-responder N=160	PR-FAM responder N=160	Standardised difference	*P* value
Mean (SD) age, y	53.4 (12.5)	51.8 (10.4)	0.139	.337
Sex, %			0.026	.907
Male	34.4	35.6		
Female	65.6	64.4		
Mean (SD) time since first symptoms, mo	202.8 (128.9)	186.7 (113.3)	0.133	.399
Relapse in prior 3 months, %			0.062	.713
0	90.6	88.8		
1	9.4	11.2		
Sustained 12-week EDSS progression in prior 24 months, %			0.028	.9
No	73.8	72.5		
Yes	26.2	27.5		
MS subtype, %			0.102	.662
PPMS	12.5	9.4		
RRMS	56.9	58.1		
SPMS	30.6	32.5		
Mean (SD) no. of prior DMTs			–0.01	.764
Mean (SD)	0.93 (1.14)	0.94 (1.27)		
Median (range)	1 (0–6)	1 (0–7)		
Prior DMT type, %			0.114	.793
Interferon/GA	31.2	34.4		
Oral	12.5	13.8		
High efficacy	8.1	9.4		
No DMT	48.1	42.5		
Physiotherapy, %			0.109	.404
No	22.5	18.1		
Yes	77.5	81.9		
Mean (SD) EDSS score (within ±12 weeks)	5.21 (1.00)	5.27 (1.01)	–0.059	.611
EDSS ambulation score, %			0.102	.843
0	11.9	13.8		
1–4	58.1	53.1		
5–6	23.8	26.2		
7	6.2	6.9		
C-statistic[b]	0.569			
Median (IQR) follow-up time, mo	11.5 (2.2–36.6)	21.6 (9.7–55.1)		

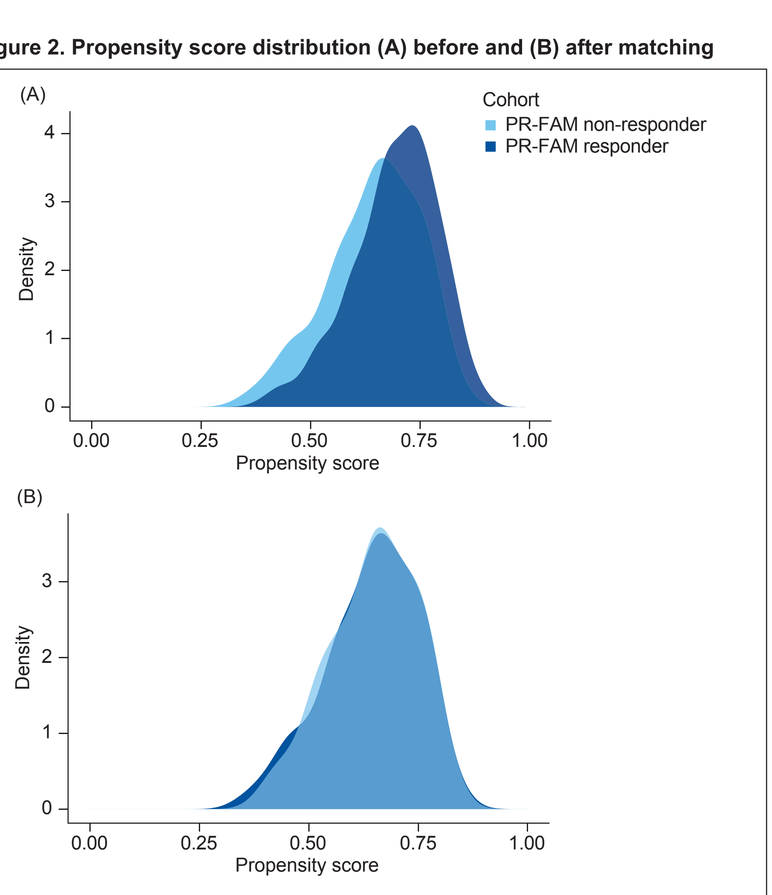
DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale; GA = glatiramer acetate; IQR = interquartile range; MS = multiple sclerosis; PPMS = primary progressive multiple sclerosis; PR-FAM = prolonged-release fampridine; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis; standardised difference = Cohen's d (effect size)
[a]At PR-FAM initiation unless otherwise specified
[b]C-statistic is a measure of balance in matched data and ranges from 0.5–1.0, with the minimum value indicating that the propensity score model is perfectly balanced and has no ability to discriminate between the cohorts after matching

Figure 1. Candidate predictors of PR-FAM discontinuation due to LoE[a]



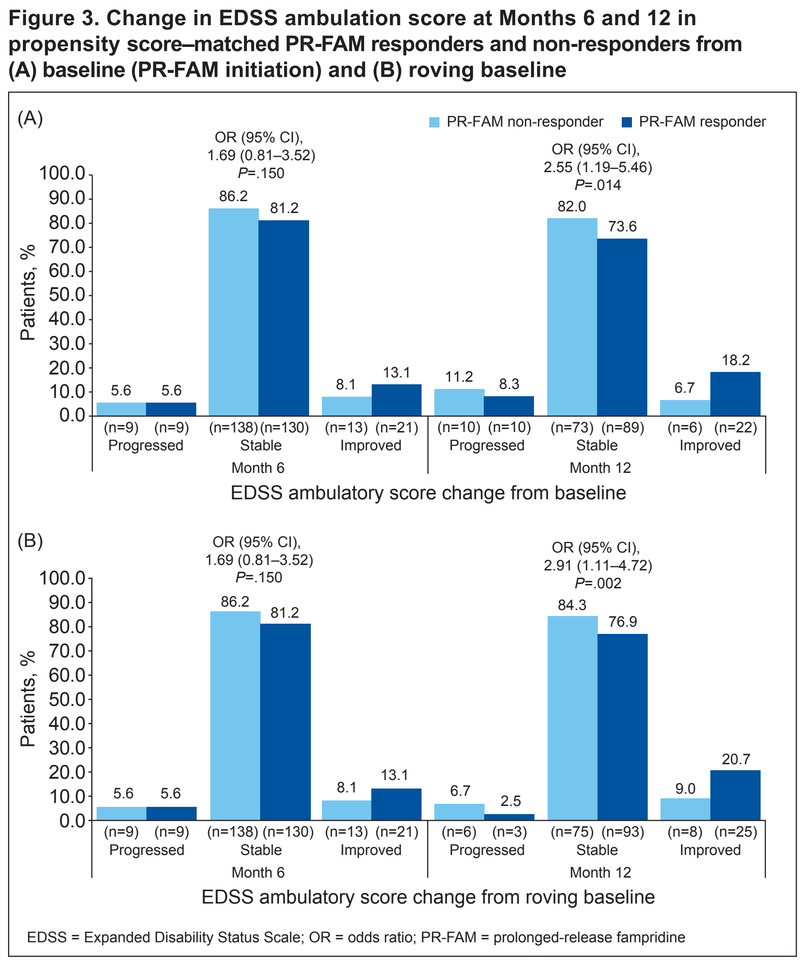
ARR = annualised relapse rate; DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale; GA = glatiramer acetate; HR = hazard ratio; LoE = lack of effectiveness; MSSS = Multiple Sclerosis Severity Score; PPMS = primary progressive multiple sclerosis; PR-FAM = prolonged-release fampridine; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis
[a]Includes 1104 patients with available data for all candidate predictors
[b]Reference category
[c]*P* values based on Wald test

Figure 2. Propensity score distribution (A) before and (B) after matching



PR-FAM = prolonged-release fampridine

Figure 3. Change in EDSS ambulation score at Months 6 and 12 in propensity score–matched PR-FAM responders and non-responders from (A) baseline (PR-FAM initiation) and (B) roving baseline



EDSS = Expanded Disability Status Scale; OR = odds ratio; PR-FAM = prolonged-release fampridine

Conclusions

- In this study of PR-FAM–treated patients in a real-world setting, 71% persisted on PR-FAM treatment for ≥3 months with a median (IQR) exposure of 32.9 (14.6–59.2) months for the responders group.
- PR-FAM discontinuation due to lack of effectiveness was not significantly associated with baseline disease characteristics; thus, PR-FAM has the potential to provide benefits across a broad range of MS populations.
- Responders were more likely than non-responders to show improvement vs. no improvement (stable or progressed) from baseline on EDSS ambulation score at Month 6 (OR [95% CI], 1.69 [0.81–3.52]) and Month 12 (OR [95% CI], 2.55 [1.19–5.46]).

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