

Tolerance and Efficacy of Fampyra[®] in Real-Life Cohort of Patients with Multiple Sclerosis

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Abstract

Background: Prolonged-release Fampridine is a selective potassium channel blocker licensed for the improvement of walking in adult patients diagnosed with multiple sclerosis (MS). The objective of this study was to evaluate the efficacy and safety of prolonged-release Fampridine in our regional MS cohort.

Methods: Descriptive analysis data of Prolonged-release Fampridine (10 mg twice daily) patients were extracted from the European Database for Multiple Sclerosis (EDMUS) for the period since Fampridine became available in clinical practice. Data were collected on all patients in Alsace region of France. The patients had a mean EDSS score of 5.5 at baseline. The primary outcome was to determine the proportion of timed-walk responders at day compared to day 0 (baseline). The secondary outcome was the amplitude of this response in terms of time to walk and the 12-item Multiple Sclerosis Walking Scale (MSWS-12) score. Additional analysis was conducted to determine the incidence of reported adverse events. The proportion of AE reports was estimated by event, as classified at the MedDRA preferred term level. Commonly reported AEs were defined as those with a prevalence $\geq 2\%$ of all reported AEs.

Results: Of 467 patients who received Fampyra[®] 453, 332 women (73.3%) and 121 men (26.7%), were included in the study. The proportion of patients in this cohort who were classed as responders was 73.5% (333 of 453). Responders walked 8 sec faster at day 15 compared to baseline (18.0 ± 12.9 sec versus 25.6 ± 22.2 sec; $p < 0.001$). The average improvement from baseline for the responders was 30.2% for walking speed and 33.1 for the MSWS-12).

Conclusions: Our study confirms the efficacy of Fampridine with a high level of responders (73%). The intensity of the improvement concerning walking capacity was around 30% for both evaluations (walking speed and MSWS-12 score). In view of the low level of side effects the benefit/risk ratio of Fampridine appears favorable.

Keywords: Fampyra[®]; Multiple sclerosis; Real-life cohort; Tolerance; Efficacy

Introduction

Multiple sclerosis (MS) is primarily an inflammatory disorder of the central nervous system (CNS) in which focal lymphocytic infiltration leads to damage of myelin and axons [1]. Myelin deficit leads to exposure of paranodal, fast, voltage-gated potassium (K⁺) channels, and the attendant abnormal K⁺ conductance impairs action potential electrogenesis, repetitive axonal discharge, and propagation [2,3]. Impaired ability to walk constitutes one of the major disabling neuromuscular deficits associated with multiple MS [4-6]. It is often the most visible sign of MS and has been reported to affect 80% of persons within 15 years of disease onset [4,7,8]. As a consequence of compromised activities of daily living that involve walking about the home or in the community, gait impairments lead to loss of independence, decreased sense of self-worth due the external

appearance of disablement, lost employment opportunities and reduced quality of life [6,9].

Conventional approaches to management of gait impairment primarily involve physical rehabilitation and functional retraining of gait. This may be coupled with pharmacological management of symptoms that compromise gait, such as spasticity. Pharmacologic agents for the management of spasticity reduce abnormalities of tone that impair locomotor capacity, but do so without reversing the underlying gait deficit. Disease modifying therapies designed to slow progression of the disease do not provide direct symptomatic relief of gait disorders. Against the backdrop of this conventional management of impaired gait in MS, there has been considerable interest in the development of a new class of pharmacotherapeutics designed to reverse the underlying neurologic deficits associated with demyelination of axons within the central nervous system (CNS). Fampyra[®] is the first drug in this class to be approved by the European Medicines Agency (EMA), (approval granted in July 2012). Fampridine (Fampyra[®]) is broad spectrum potassium (K⁺) channel blocking agent,

with the capacity to improve conduction across demyelinated internodes in axons of the CNS. Approval was based on phase II and two Phase III clinical trials, which demonstrated an increase in walking speed using the timed 25-Foot Walk [10-12]. However, there are only a few studies in real life situation. These studies are necessary as patients in phase II and III studies are highly selected. The objective of this study was to evaluate the efficacy and safety of prolonged-release Fampridine tablets 10 mg twice daily in real life using our regional MS-cohort registry.

Methods

Descriptive analysis data were extracted from the European Database for Multiple Sclerosis (EDMUS) from the date on which Fampyra® became available for use in clinical practice. The study included all patients in the Alsace region of France who had MS, as defined by the 2005 McDonald criteria [13] and had received Fampyra® treatment at any time between July 2012 and October 2014. Variables analyzed included age; gender; disease duration, EDSS score; walking speed; and 12-item Multiple Sclerosis Walking Scale (MSWS-12 score) immediately before receiving Fampyra (baseline: day 0) and after day 15 of treatment; percentage of timed walk responders (TWRs); MSWS-12 score; adverse events (AEs); and reasons for discontinuation. The first objective of this study was to evaluate the proportion of timed-walk responders based on consistency of response in terms of walking speed on Timed 25-Foot Walking. As in phase III studies, patients were considered responders to treatment if at day 15 visit, an improvement of 20% in walking speed compared to baseline. The secondary outcomes were the amplitude of the improvement in walking speed and MSWS-12 score in the responder population. All patients gave their written consent to participate in this study.

Statistical analysis was done using the t-student test with *p* value of ≤0.05 indicating statistical significance.

Results

Demographic and clinical characteristics of patients (n=467)

	Total cohort (n=453)	Responders (n=333)	Nonresponders (n=120)	<i>p</i>
Initiation age, mean (SD)	53.4 (11.2)	52.8 (11.2)	55.2 (10.8)	ns
Female n (%)	332 (73.3)	243 (72.9)	89 (74.2)	ns
Relapsing-remitting, n (%)	155 (34.2)	116 (34.8)	39 (32.5)	
Primary progressive, n (%)	54 (11.9)	36 (10.8)	18 (15.0)	ns
Secondary progressive, n (%)	244 (53.8)	181 (54.4)	63 (52.5)	
Disease duration, yrs, n (SD)	19.7 (10.5)	19.6 (10.4)	20.3 (10.6)	ns
EDSS score, mean (SD)	5.5 (1.1)	5.5 (1.1)	5.5 (1.0)	ns

EDSS: Expanded Disability Status Scale; P values reported from t-test comparisons

Table 1: Demographic and baseline clinical characteristics of patients.

Table 1 compares Fampyra® responders and non-responders patients by examining the demographic and baseline clinical characteristics. Of the 467 patients who received Fampyra®, only 453 had usable data and were included in this study. For 14 other patients, we did not have complete data. Of the 453 patients analyzed, 332 were women (73.3%) and 121 were men (26.7%); this female-to-male ratio (2.74) was similar to that of the MSF204 Phase 3 trial study [12]. About half of the patients had secondary progressive MS, a third had relapsing remitting MS, and most of the remainder had primary progressive MS. In terms of all the variables listed in Table 1, there were no significant differences between responders and non-responders.

Efficacy of fampridine

The proportion of patients in our cohort study who were classed as responders was 73.5% (333 of 453).

Time to complete 25-foot walk: Figure 1 compares Fampyra® responders and non-responders patients by examining the time to complete the 25-foot walk. At baseline, responder patients took mean 25.6 seconds to cover the distance of the walk test, and at end of the efficacy analysis period (day 15) mean walking time was 18.0 seconds. Table 2 compares walking speed at baseline and at day 15 in responders and shows an improvement of 30.2% (95% CI, 22.3-29.6).

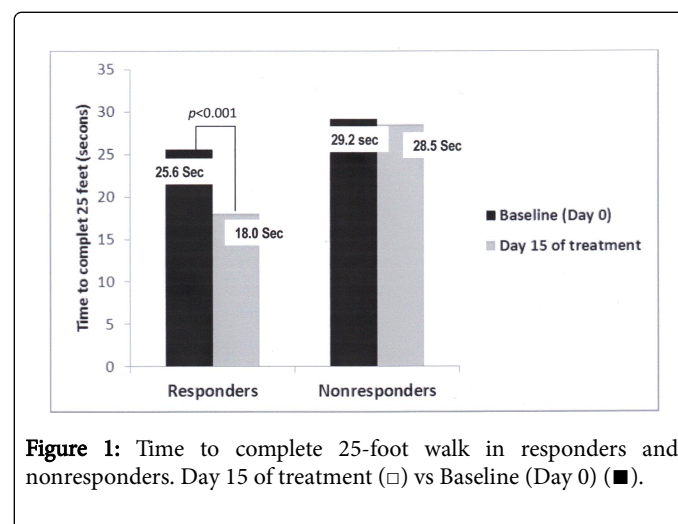


Figure 1: Time to complete 25-foot walk in responders and nonresponders. Day 15 of treatment (□) vs Baseline (Day 0) (■).

	Responders (n=333)	Nonresponders (n=120)	<i>p</i>
Baseline walking speed (ft/sec), mean (SD)	0.97 (0.83)	0.86 (0.59)	ns
Walking speed (ft/sec) at Day 15, mean (SD)	1.39 (1.41)	0.88 (0.71)	0.001
Absolute difference	0.42	0.02	
Gain relative to baseline (%) (95% confidence Interval)	30.2% (22.3 to 29.6)	2.3 (0.1 to 6.7)	0.001

Table 2: Walking speed (ft/sec).

MS walking Scale (MSWS-12): Table 3 summarizes the result of the MSWS-12, which assesses perceptions of walking problems in daily life. Responders also showed a significantly greater improvement in MSWS-12 score than non-responders: 48.4% versus 72.3% (*p*<0.001).

The average change from baseline in responders' MSWS-12 score was 33.1% (95% CI, 36.7-30.1).

	Responders (n=333)	Nonresponders (n=120)	p
Baseline MSWS-12 score, % (SD)	72.3 (19.7)	64.8 (23.5)	
MSWS-12 score at Day 15, % (SD)	48.4 (23.7)	63.1 (25.5)	0.001
Absolute difference	-23.9	-1.7	
% of change in MSWS-12 (Day 0 to Day 15), (95% confidence Interval)	-33.1 (-36.7 to -30.1)	- 2.6 (-2.8 to -2.4)	0.001

Table 3: MS walking Scale (MSWS-12).

Safety profile

Table 4, shows another goal of this study namely adverse events (AEs) of Fampyra®. A total of 296 AEs were reported in our cohort study, and the most frequently reported AEs are shown in the table.

In our cohort study, 49 (10.8%) patients, discontinued treatment due to AEs; five within a week of starting treatment, and 44 after day 15 of treatment. One patient experienced an epileptic fit.

	n (% of total events)
Insomnia	25 (8.4)
Dizziness	20 (7.1)
Balance disorder	19 (6.4)
Nausea	18 (6.0)
Asthenia	16 (5.4)
Headache	13 (4.4)
Back pain	8 (2.9)

Table 4: Most frequently reported adverse events, defined as having a prevalence of ≥ 2% of all reported events (n=298).

Discussion

Our study confirms the efficacy of Fampridine observed in phase II and III studies with a high percentage of responders (73.5%). This percentage was higher than in pivotal studies but the criteria were less stringent. The changes from baseline in responders were relatively high for both walking speed (30.2%) and MSWS-12 (33.1%). Furthermore, safety profile was very good without any new unexpected side effects.

The magnitude of the improvement indicates that the changes associated with response were clinically meaningful, further validating the relevance of the responder criterion used for analysis [14]. Our study is a short term evaluation but long-term, open-label extensions of the two pivotal clinical trials (MS-F203/4) in which maximum exposure was up to 5 years demonstrated that, among dalfampridine extended release (dalfampridine-ER) responders, walking speed remained improved compared with nonresponders, although mean improvement relative to baseline declined over time [15], likely as a result of MS progression [16]. Evidence from two recent studies also

suggests that, in addition to improvement in walking speed, treatment with dalfampridine-ER may improve walking distance. In one study, designed as an open-label withdrawal study in subjects who were considered timed-walk responders, walking distance measured using the 2-minute walk test was significantly greater on drug relative to off drug by 25.4 feet ($p=0.006$) [17]. In the other study, in which walking distance was measured using the 6-minute walk test at a subset of study sites, dalfampridine-ER resulted in a mean improvement from baseline in walking distance of 128.6 feet which was significantly greater than the 41.7 feet improvement with placebo ($p<0.05$) [18].

Fampyra® was generally well tolerated in clinical trials. The incidence of AEs among patients treated with Fampyra in our cohort study was 83% similar to that reported in the two phase III trials (84% and 86% in MS-F203 and MS-F204, respectively). The majority of AEs were of mild or moderate severity. The results of this evaluation show that the AEs reported in a clinical setting were relatively consistent with expectations based on clinical trials, and no new AEs emerged compared with the randomized studies. The AEs in our cohort included urinary tract infection, insomnia, dizziness, asthenia, balance disorder, headache, and nausea but no new unexpected side effects. Fampyra is contraindicated in patients with a history of seizure and in those with moderate or severe renal impairment. In our study, one patient had an epileptic fit. The dose-ranging studies indicated that AEs were dose-dependent, especially those related to the CNS such as balance problems, dizziness, and insomnia [10-19].

Based on the efficacy demonstrated in the pivotal clinical trials and the overall safety profile, Fampyra®, was approved by the EMA in July 2012 to improve walking in patients with MS. This was demonstrated by an increase in walking speed. Since its introduction into clinical practice, post-marketing data on dalfampridine-ER have become available for 1- and 2-year periods after approval [20,21]. These data have a safety profile consistent with the clinical trials and are in accordance with the present study. Several published studies on utilization and outcome of dalfampridine-ER in clinical practice, representing populations more heterogeneous than in clinical trials, have suggested that a wider range of both short-and long-term benefits of treatment may be obtained, including improvements in arm and lower body function [22-24]. In these studies, therapeutic benefits were observed at the first follow-up, at 2 weeks after initiating treatment [25], with approximately 60% of the patients still on therapy and showing benefits after 9-12 months in the studies that continued follow-up for this duration [22-24].

The main limitation of our study is the lack of comparison with an untreated or placebo control group. A further limitation is the short-term evaluation. However, as many adverse events and positive effects are observed during the first day of treatment it seems likely that most of them would have been observed by the end of the follow-up in our study.

In conclusion, our study confirms the good efficacy of Fampridine in real life with a high level of responders (73.5%) and a marked degree of improvement (around 30%) for both walking speed and MSWS-12 score. Furthermore, we confirm the good tolerance profile of Fampridine with only expected side effects. Overall, the efficacy/risk ratio of Fampridine seems to be largely favorable.

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Conflict of interest

The authors declare no conflicts of interest

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