Impact of fampridine on quality of life: clinical benefit in real-world practice

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ABSTRACT

Objectives To assess the effectiveness and tolerability of fampridine in patients with multiple sclerosis (MS) in real clinical practice and to analyse adherence to treatment and general satisfaction of patients in terms of quality of life (QOL).

Methods Patients who started treatment with fampridine from May 2014 to October 2014 were included. Primary and secondary outcomes were Timed 25-Foot Walk (T25FW) and MS Walking Scale-12 (MSWS-12) respectively, measured at baseline and 2 weeks, 3 and 6 months. Adherence was measured by the Morisky–Green questionnaire, patient satisfaction with a visual analogue scale (VAS) and QOL with improvement in mobility, self-care, daily activities, pain/discomfort or anxiety/depression.

Results 30 patients (46.7% women) of mean age 39 years, mean MS duration 13.7 years, mean Expanded Disability Status Scale score 5.8, 57% with relapsing-remitting MS were included. 22 patients (73%) continued to take treatment throughout the study period. Two weeks after treatment initiation all measures improved significantly from baseline (T25FW: −7.5 s, $p<0.05$; MSWS-12: −36.7, $p<0.05$). At 6 months, walking speed and self-perceived walking ability were significantly improved (T25FW: −3.8 s, $p<0.05$; MSWS-12: −30.0, $p<0.05$). Adverse events were reported by 30% of patients. Seizures were registered in one patient. 70% of patients were adherent with treatment. Median (IQR) general satisfaction VAS score was 8 (7–9). Patients reported an improvement in mobility (70%), anxiety/depression (33.3%), self-care (23.3%), daily activities (23.3%) and pain/discomfort (3.3%).

Conclusions Fampridine is effective and safe in patients with MS in real clinical practice up to 6 months. Adherence to treatment was suboptimal but patients' general satisfaction was high and fampridine improved several items of QOL.

INTRODUCTION

Mobility impairment, particularly walking, is reported by many patients with multiple sclerosis (MS) as a major concern,[1] and it is a limiting factor as disease progresses.[2] In a recent study, nearly half (45%) of patients reported experiencing mobility difficulties within a month of diagnosis and nearly all patients (93%) reported difficulties within 10 years.[3] Walking impairment can seriously impact daily activities and the emotional status of patients, thus decreasing health-related quality of life (QOL).[4]

Fampridine is a voltage-dependent potassium channel blocker that decreases abnormal potassium outward currents.[5] This results in an improvement in conduction in demyelinated nerves.[6] Two phase III studies demonstrated improved walking speed with fampridine in 35–43% of patients with MS, as measured by the Timed 25-Foot Walk (T25FW), compared with 8–9% of placebo-treated patients. Furthermore, it was associated with improvement in patient-perceived walking ability as measured by the 12-item MS Walking Scale (MSWS-12).[7 8]

Pivotal clinical trials evaluated the efficacy of fampridine after 14 weeks of treatment in terms of walking speed. The critical question remains whether treatment with this drug leads to long-term therapeutic benefits and which elements in walking improvement are of clinical meaningfulness (walking speed, walking ability, balance). Moreover, it remains unclear if an improvement in walking ability has a clinically significant effect on QOL or reduction of disability. These aspects must be measured in patients with MS in clinical practice in order to justify the costs of treatment.

The most common adverse effects of fampridine are balance disorders, anxiety, insomnia and urinary tract infection. Seizure disorders are a serious but rare adverse effect directly related to fampridine dose and plasma concentration.[9]

Adherence to fampridine in pivotal trials was high (>97%),[10] but potential barriers to therapeutic adherence were not analysed. Reasons for non-adherence have been fully assessed in patients with disease-modifying injection therapies.[11–14] Some of the reasons are not injection-related and could be potential causes of fampridine non-adherence, such as forgetting to take the medication, fatigue, inconvenient or difficult dosing schedule and depression. However, to date there have been no published studies that address this critical aspect of fampridine treatment.

The objective of our study was to assess the effectiveness of fampridine in real clinical practice and its maintenance after 6 months of treatment and to describe its tolerability and adverse effects as detected in our patients. A secondary objective was to analyse treatment adherence and general satisfaction of patients in terms of QOL.

METHODS

Patients and data

Patients with MS and walking impairment who started treatment with fampridine at our institution between May and November 2014 were included

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in the study. The follow-up period was from May 2014 to May 2015. Our institution is a university hospital with 1400 beds and a MS specialised unit. Patients were recruited in the ambulatory setting and were dispensed their MS medications in the hospital pharmacy. They were eligible for treatment if they had a diagnosis of MS, Expanded Disability Status Scale (EDSS) >4 and <7, absence of seizure disorder antecedents and normal renal function (creatinine clearance >80 mL/min). Exclusion criteria for treatment included disease instability as evidenced by recent MS relapse or change in immunomodulatory therapy.

Patients received fampridine 10 mg twice daily, which was initially dispensed in the hospital pharmacy for 14 days. According to the summary of product characteristics[15] and to select patients who responded to the drug, a clinical visit was scheduled after 2 weeks of treatment. Individuals with no significant adverse effects who reported a favourable response to the drug and showed an improvement of at least 20% in T25FW and any percentage in MSWS-12 continued taking the drug.

The primary outcome was the change in the T25FW test administered to the patient at baseline and each clinical visit (2 weeks, 3 months and 6 months). The T25FW is a component of the MS Functional Composite and assesses general walking speed in people with MS. It measures how many seconds the patient requires to walk a 25 foot (7.62 m) linear course.[16]

The secondary outcome was the change in the 12-item MSWS-12 administered to the patient at the same visits. The MSWS-12 is a reliable and valid patient-based measure of the impact of MS on walking. It captures patients' perspectives on their ambulatory disability in the following areas: standing, ability to run, need for support, moving around the home, concentration needed to walk, walking speed, maintaining balance, climbing stairs, walking distance, effort needed to walk, ability to walk and gait. Scores on the 12 items are summed and transformed into a 0–100 scale, with higher scores indicating greater impact of MS on walking.[17]

Clinical benefit was measured as a mixed variable including a ≥20% improvement in walking speed (T25FW) and any improvement reported in patient-reported walking ability (MSWS-12). This variable was defined in the Multiple Sclerosis Institution protocol and based in some studies that consider an improvement in walking speed of >20% as clinically relevant.[18]

Other clinical data were collected from patient charts: demographic information, disease duration and type of MS, EDSS at baseline and each visit, use of walking aids (cane, crutch) and immunomodulatory treatment. EDSS is a scale which quantifies disability in MS and monitors changes in the level of disability over time. It ranges from 0 to 10, with higher levels representing greater disability.[19]

Safety and tolerability were tracked by follow-up visits to the neurologist and pharmacist. Adverse drug reactions to fampridine were collected from clinical patient records.

In the outpatient pharmacy, the specialist pharmacist scheduled an interview with the patient between the third and sixth month of treatment, to ask about the degree of satisfaction with the treatment and adherence to it. We ask the patient to define his general satisfaction with treatment with a visual analogue scale (VAS) of 10 cm, where 0 was 'absolutely not satisfied' and 10 was 'very satisfied'.

At the same visit, patients answered a question about the items related to QOL that have improved with fampridine treatment (mobility, self-care, daily activities, pain/discomfort or anxiety/depression). These questions were based on the validated EuroQol-5D questionnaire and were asked as yes/no non-exclusive questions to the patients: "Do you believe that treatment with fampridine has implied an improvement in your mobility/self-care/daily activities/pain-discomfort or anxiety/depression?".

Finally, we assessed adherence to fampridine by the Morisky–Green (MG) test.[20] This test was selected because of its reliability (61%) and because it is presented in Spanish.[21] In addition, the MG test assesses attitudes towards treatment. According to the MG test, patients who answered the following four items correctly were considered to be fully adherent:

- Have you ever forgotten to take your medication? (No)
- Are you rigorous concerning your administration hours? (Yes)
- Do you skip your administration hours when you are feeling well? (No)
- When you feel worse due to the medicine, do you skip your administration? (No)

The review board of our institution approved this study and all patients provided informed consent to have their clinical data collected.

Statistical analyses

The effectiveness analysis was based on all patients who had at least one efficacy assessment of T25FW and MSWS-12 during the treatment period (intention-to-treat population). The safety analysis included all the patients who took at least one medication dose.

Continuous variables are presented as mean (SD) or median and IQR (p25, p75). For categorical variables, frequencies and percentages were used. The Kolmogorov–Smirnov test was performed to check the normality of variables. Non-parametric tests were used. The Mann–Whitney test was used to detect differences between independent groups and the Wilcoxon test for repeated measures. The χ^2 Pearson or exact Fisher test was used to detect differences in categorical variables. Statistical analysis was performed using IBM SPSS for Windows V.21.0. (IBM Corp, Armonk, New York, USA), with $p<0.05$ considered significant.

RESULTS

A total of 30 patients with MS were prescribed fampridine during the study period and were included in the study. Three patients discontinued before completing any efficacy measurements during the treatment period and were excluded from the intention-to-treat population. The mean age of the study population was 39 years, with an average duration of MS of 13.7 years; 14 patients (46.7%) were women. The majority of patients (17, 56.7%) had relapsing-remitting MS (RRMS), nine (30.0%) had secondary-progressive MS (SPMS), three (10.0%) had primary-progressive MS (PPMS) and one (3.3%) had progressive-relapsing MS (PRMS). Twenty-four patients (80%) needed walking aids for daily activities before treatment. Immunomodulatory treatments used concomitantly in patients, baseline EDSS, T25FW and MSWS-12 scores are shown in table 1.

Twenty-two patients (73%) continued fampridine treatment during the entire study period. Eight patients (27%) discontinued the drug, three of them after 15 days of treatment, two after 3 months and three after 6 months. Reasons for withdrawal were perceived lack of effectiveness in four patients (50%), poor tolerability in three patients (37.5%) and both poor effectiveness and tolerability in one patient (12.5%). There were no statistically significant differences in age, sex, disease duration, disease subtype or baseline walking measures

Table 1 Demographic and MS disease characteristics at baseline

	Entire cohort	Continued	Stopped	Comparison between continued and stopped
N (%)	30	22 (73.3%)	8 (26.7%)	–
Age (years), mean (SD)	39.1 (9.7)	38.2 (8.7)	41.7 (12.3)	p=0.50*
Women, n (%)	14 (46.7%)	9 (40.9%)	5 (62.5%)	p=0.295†
MS duration (years), mean (SD)	13.7 (6.4)	14.4 (6.6)	11.9 (5.8)	p=0.37*
MS types, n (%)				p=0.25†
RRMS	17 (56.7%)	13 (59.1%)	4 (50%)	
SPMS	9 (30%)	6 (27.3%)	3 (37.5%)	
PPMS	3 (10%)	3 (13.6%)	0 (0%)	
PRMS	1 (3.3%)	0 (0%)	1 (12.5%)	
Inmunomodulatory therapies				p=0.25†
Glatiramer acetate	6 (20%)	5	1	
Natalizumab	6 (20%)	4	2	
Interferon β-1a (Avonex)	3 (10%)	3	0	
Azathioprine	3 (10%)	3	0	
Interferon β-1a (Rebif)	3 (10%)	3	0	
Fingolimod	1 (3.3%)	1	0	
None	8 (26.7%)	3	5	
Use of walking aids, mean (SD)	24 (80%)	19 (86.4%)	5 (62.5%)	p=0.059*
EDSS, mean (SD)	5.8 (0.9)	5.9 (0.9)	5.4 (1.3)	p=0.65*
T25FW (s), median (IQR)	22.9 (18.4, 43.4)	24.1 (19.8, 39.1)	19.4 (12.7, 55.2)	p=0.39*
MSWS-12, median (IQR)	96.7 (88.3, 98.8)	95.8 (89.6, 98.3)	97.5 (83.8, 100.0)	p=0.70*

*Two-sample t-test.
†Fisher's test.
EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; MSWS-12, Multiple Sclerosis Walking Scale-12; PPMS, primary progressive multiple sclerosis; PRMS, Progressive-relapsing multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis; T25FW, Timed 25-Foot Walk.

between those who continued taking fampridine and those who discontinued the treatment (table 1).

At the first follow-up visit, 6 weeks after treatment initiation, a significant improvement was observed in median outcome measures (T25FW 2 weeks: −7.5 s, p<0.05; MSWS-12: −36.7 points, p<0.05). In addition, 3 and 6 months after treatment initiation, significant improvements in walking speed and self-perceived walking ability were observed compared with baseline performance (T25FW at 3 months: −7.0 s, p<0.05; MSWS-12 at 3 months: −30.8 points, p<0.05; T25FW at 6 months: −3.8 s, p<0.05; MSWS-12 at 6 months: −30.0 points, p<0.05). This improvement was demonstrated with a 32.8% reduction in median T25FW at 2 weeks, 30.5% at 3 months and 16.6% at 6 months. Median MSWS-12 improved 37.9% at 2 weeks, 31.9% at 3 months and 31.0% at 6 months. Over the 6-month assessment period the mean EDSS score remained stable in patients who continued treatment with fampridine (figure 1).

Clinical benefit based on a ≥20% improvement in walking speed (T25FW) and any improvement reported in patient-reported walking ability (MSWS-12) was observed in 73.3% of patients at the 2-week visit, in 53.3% at the 3-month visit and in 33.3% at the 6-month visit. The proportion of patients reporting improvement in walking ability by the MSWS-12 scale was higher than those reporting a benefit in walking speed (figure 2).

One patient no longer needed to use a cane as a walking aid after 2 weeks of treatment and this was maintained until the end of the follow-up period. The rest of the patients continued using the same walking aids as at the beginning of treatment.

Evaluation of the per cent change from baseline in walking speed demonstrated that the improvements were independent of baseline EDSS scores (figure 3). Patients demonstrated improvements in walking speed and in self-perceived mobility across EDSS scores at all the visits.

Adverse events were reported by 30% of patients. Most were mild and all were described in the summary of product characteristics:[15] dizziness (16.7%), asthenia (6.7%), constipation (6.7%), insomnia (3.3%) and pharyngolaryngeal pain (3.3%). A serious adverse event was registered in one patient (3.3%) with seizures, who discontinued treatment. Two more patients discontinued the treatment because of adverse events: one because of asthenia and another because of asthenia and insomnia.

According to the MG test, 21 patients (70%) adhered to treatment. Regarding the motives for non-adherence, seven patients (23.3%) had occasionally forgotten to take the drug, one patient (3.3%) did not administer the drug at the scheduled hours and did not respect the fasting period and two patients (6.7%) decided not to take the drug because of side effects.

The median general satisfaction VAS score was 8 (IQR 7–9). Patients reported an improvement in the following QOL items: mobility (70%), anxiety/depression (33.3%), self-care (23.3%), daily activities (23.3%) and pain/discomfort (3.3%); 20% of patients reported that fampridine improved their fatigue.

DISCUSSION

Our study demonstrates the benefits of fampridine on walking in people with MS in real clinical practice for up to 6 months. T25FW decreased 7.5 s at 2 weeks and 3.8 s at 6 months, which means improvements in walking speed of 32.8% and 16.6% at 2 weeks and 6 months, respectively. Self-perceived impact of MS on walking (MSWS-12 scale) improved 36.7 points (37.9%) at 2 weeks and 30 points (31%) at 6 months, confirming previous findings that fampridine improves both aspects of walking impairment in patients with MS.[7 8]

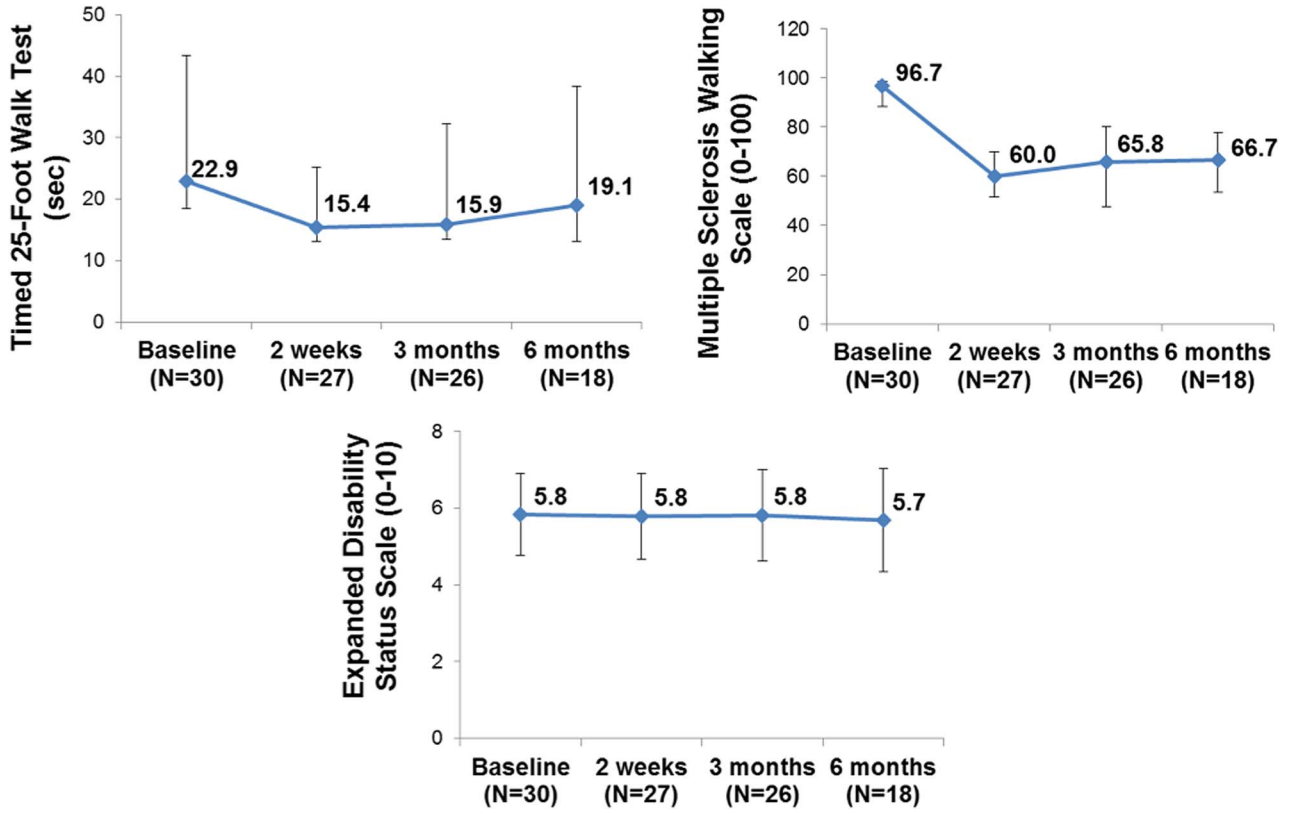

Figure 1 Changes in walking speed, patient-reported walking ability and Expanded Disability Status Scale over the 6-month follow-up period in patients treated with fampridine.

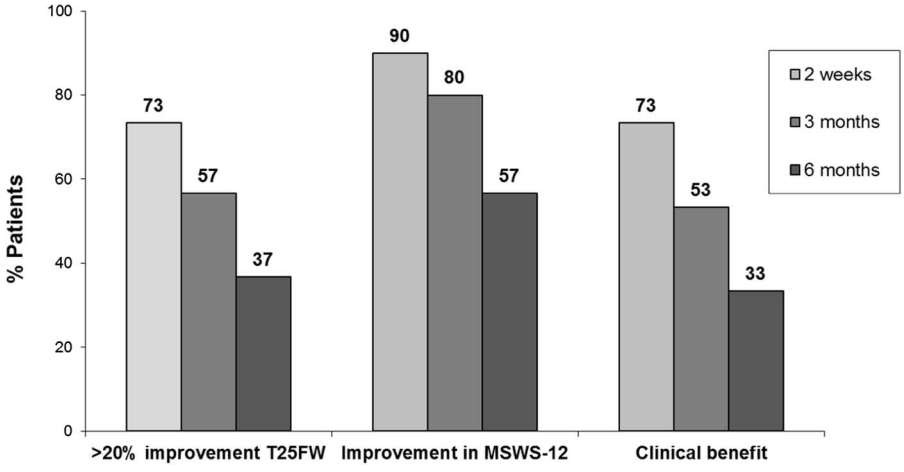

Figure 2 Proportion of patients experiencing clinical benefit from fampridine treatment according to response variables. Clinical benefit: mixed variable including an improvement of ≥20% in Timed 25-Foot Walk (T25FW) and any improvement reported in Multiple Sclerosis Walking Scale-12 (MSWS-12).

Other observational studies have reported less improvement in T25FW. Prugger and Berger[22] reported an improvement of 1.7 s at 4 weeks and 3.5 s at 6 months, and Cameron *et al*[23] found an improvement of 2.7 s at 6–8 weeks and 2.4 s at 6 months. However, different population characteristics might explain these findings. Our patients were mainly men (53%) and their mean age was 39 years, whereas the studies mentioned above were based on a majority of women and an older population (50 years). The low number of women in our study is surprising according to other studies, but it is not due to a selection bias as we analysed all consecutive patients treated in our centre with fampridine. The duration of MS and EDSS at baseline was similar to other studies. The type of MS in our group (RRMS 57%, SPMS 30%) differed from the pivotal trials and other studies (RRMS 30%, SPMS 50%). All these differences in the study populations make it difficult to compare results and to draw conclusions.

Previous studies have shown that improvements in T25FW speed of ≥20% are meaningful to people with MS[18] and the relationship between improvements in the MSWS-12 scale and health utility.[24] In our study, 73.3% of the patients prescribed fampridine experienced an improvement of >20% in walking speed at 2 weeks after initiation of treatment. This is a higher proportion than the 25–35% response rate reported in pivotal clinical trials of fampridine. In other observational studies, Prugger and Berger[22] reported a faster walking speed of >20% in 32.8% of patients after 4 weeks of treatment. Again, these discrepancies might be explained by differences in entry criteria, study

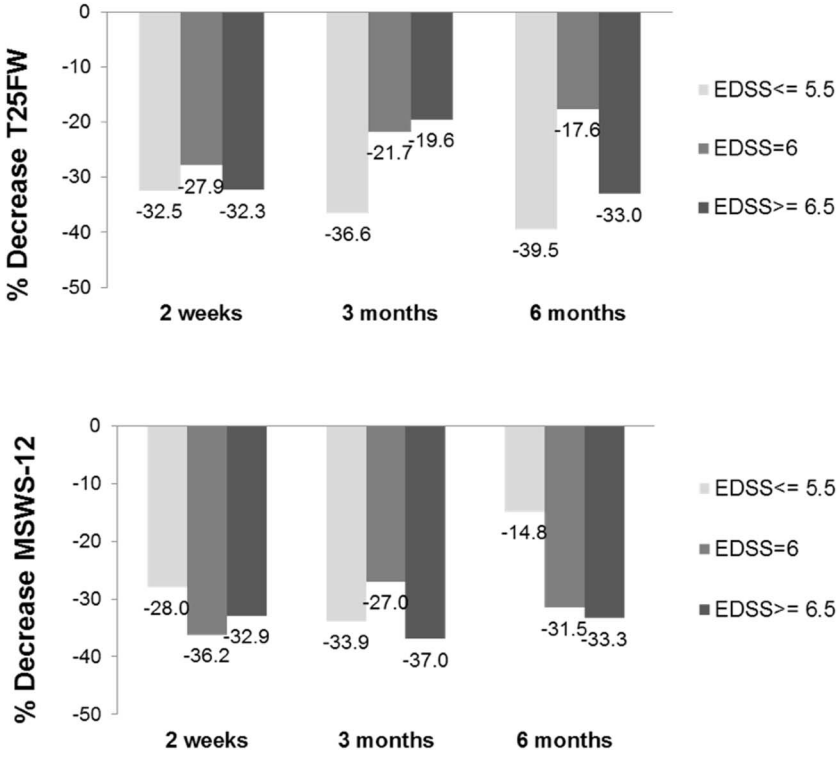

Figure 3 Per cent change in walking speed and in self-reported walking ability from baseline according to Expanded Disability Status Scale (EDSS) at baseline. T25FW, Timed 25-Foot Walk; MSWS-12, Multiple Sclerosis Walking Scale-12.

population and the definition of respondents in pivotal trials (T25FW improved in three of four visits, instead of T25FW improved after 2 weeks of treatment). Moreover, T25FW at baseline was lower in those studies (13 s) than in our population (22.9 s), suggesting greater walking impairment in our patients.

In spite of this improvement in walking speed, only one patient in our population improved in the use of walking aids (no longer needed to use a cane) with fampridine treatment. This emphasises the fact that QOL or disability are aspects that need to be measured in patients with MS because improvement in walking impairment itself is not sufficient to justify the clinical benefit of the treatment.

Response predictors to fampridine have not been determined in other studies, suggesting that benefits may be achieved regardless of demographic characteristics, clinical types of MS, disease duration and degree of walking impairment at baseline.[25] In our population, EDSS was not related to the response to treatment and fampridine has been effective in spite of population differences.

According to the MSWS-12 scale, 90% of patients perceived that they were benefitting from the treatment at initial follow-up. This high proportion may be due to the placebo effect in this unblinded study, but it was consistent with the high satisfaction scores given by patients in the interviews.

In this study, reduced effectiveness of the treatment was observed over the 6-month assessment period. The percentage of patients with an objective response measured by T25FW declined from 73.3% to 36.7% and the percentage with a subjective response measured by MSWS-12 declined from 90% to 56.7%. This effect has been reported in other studies[10] and it has been explained as being part of the natural history of MS. However, longer follow-up in our patients is needed to determine whether this reaches a steady state or whether the benefits of the drug disappear over time.

The rate of treatment discontinuation in our cohort was 27%. Perceived lack of efficacy was the most common reason for discontinuing fampridine, which was reported by 17% of the total population studied. Three patients (10%) discontinued the drug because of adverse events. This rate is higher than that observed in pivotal trials, where only 5% of patients in the fampridine-treated group discontinued the study because of adverse events. However, in other studies in real world practice, 20% of the patients discontinued the drug because of lack of effectiveness, which is consistent with our findings.[23] Non-serious adverse events were similar to those reported in pivotal trials (dizziness, asthenia, insomnia). In contrast, there was one serious adverse event of seizures in our population (3.3%), which is significant taking into account the small sample of patients.

Adherence to fampridine treatment in our patients was suboptimal. To date, there are no other published studies permitting comparison of this data, as most studies have assessed adherence in patients with MS with disease-modifying injection therapies.[12 14 26] In a comparative study of fingolimod versus other parenteral therapies in patients with MS, adherence to oral fingolimod was 80–90%, a good approximation as patients' characteristics might be similar.[27] In our study the adherence rate was only 70% and the principal reason for non-adherence was forgetting to take the drug in 23% of patients. This was consistent with published reasons for non-adherence in patients with MS.[11 13 14] This study was not designed and did not have enough power to determine whether adherence to fampridine may affect the effectiveness of the treatment. However, strategies should be implemented to improve this aspect, as most patients interviewed reported being aware of loss of effectiveness when they discontinued the treatment.

Study of QOL in MS should consider the use of an instrument which includes social, psychological, physical and mental aspects. Although many instruments have been applied to measure QOL in MS,[28–30] none is completely satisfactory. In our study we used an approximation to the EuroQol-5D questionnaire because it is a short questionnaire and can be easily

implemented in real-world practice. Treatment with fampridine was very satisfactory according to our patients, who reported improvement in several items of QOL including anxiety, depression, self-care and daily activities. Future investigations need to use a specific MS QOL questionnaire to further assess which specific aspects of QOL are improved by fampridine treatment.

This study has certain limitations including the open-label character, the small number of patients and being conducted in a single centre. Since it was based on collected data from clinical practice, follow-up was more incomplete than in a clinical trial setting. Moreover, there was no placebo or other control group, raising the possibility that some improvements were due to a placebo effect. Adverse events were collected from clinical records and corroborated to those described in the summary of the product characteristics,[15] but a method for imputation of causality was not used. However, our results have the advantage of reflecting actual clinical practice and assessing QOL as an outcome, which should be implemented when evaluating the clinical benefit of any drug.

Our study demonstrates the effectiveness and safety of fampridine in patients with MS in real clinical practice up to 6 months of treatment, but the decline observed in this effectiveness requires a longer follow-up period. Adherence to treatment was suboptimal and interventions should be addressed to improve it. However, patients' general satisfaction was high and fampridine improved several items of QOL in addition to mobility.

What this paper adds

What is already known on this subject

- Pivotal clinical trials have shown that fampridine improved walking speed after 14 weeks of treatment and this was associated with improvement in patient-perceived walking ability.
- However, data are limited about its effectiveness and safety in real clinical practice.
- There are no published studies on the association of the response to fampridine with an improvement in quality of life or its clinical impact in terms of patient satisfaction.

What this study adds

- Our study demonstrates the effectiveness and safety of fampridine in patients with multiple sclerosis in real clinical practice up to 6 months of treatment.
- However, the decline observed in this effectiveness requires a longer follow-up analysis.
- Adherence to treatment was suboptimal but patients reported high patient satisfaction and improvement in different items of quality of life.

Contributors Planning of the study including literature search and design of the intervention and data collection tools was performed by MBM-A and MLMB. The study was conducted by MBM-A and FR-D. Statistical design and analysis was done by MBM-A. MBM-A drafted the article which was revised by MLMB, JMGD, MLMG, AH and MS-S.

Competing interests None declared.

Patient consent Obtained.

Ethics approval Ethics approval was obtained from the Institutional Review Board.

Provenance and peer review Not commissioned; externally peer reviewed.

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