

Dalfampridine improves slowed processing speed in multiple sclerosis patients with mild motor disability: post hoc analysis of a randomized controlled trial

Carlo Pozzilli^{ID}, Luca Prosperini, Silvia Tommasin, Claudio Gasperini, Elena Barbuti and Laura De Giglio

Abstract

Objective: To evaluate baseline characteristics predictive of improving information processing speed in multiple sclerosis (MS) and the relationship between cognitive and motor response to dalfampridine (DA) treatment.

Methods: This is a post hoc analysis of a randomized, double-blind, placebo-controlled trial in patients with MS randomized to receive DA 10 mg or placebo twice daily for 12 consecutive weeks. Here, we include only data from 71 patients in the arm treated with DA. According to the median value of Symbol Digit Modalities Test (SDMT) response, patients were categorized as “full responders” (FR) or “partially responders” (PR).

Results: There was higher possibility of being FR in the presence of a baseline lower Expanded Disability Status Scale [odds ratio (OR) 0.69; 95% confidence interval (CI) 0.5–0.97, $p=0.034$], a higher Multiple Sclerosis Functional Composite value (OR 1.37; 95%CI 1.05–1.8, $p=0.022$), a lower Timed 25-Foot Walk Test (OR 0.76; 95% CI 0.6–0.98, $p=0.033$), and a lower 9-Hole Peg Test with dominant hand (OR 0.92; 95% CI 0.86–0.99, $p=0.029$). FR group did not show any significant improvement of motor performance compared with PR group.

Conclusion: The current analysis shows that in MS patients with cognitive deficit, the greatest improvement in SDMT provided by DA was observed in patients with milder motor impairment; cognitive and motor responses to treatments are not related.

Trial registration: EU Clinical Trials Register; ID 2013-002558-64 (<https://www.clinicaltrialsregister.eu/ctr-search/search?query=2013-002558-64>)

Keywords: dalfampridine, multiple sclerosis, processing speed, response to treatment

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Introduction

Dalfampridine (DA) has been shown to improve walking ability in a subset of patients with multiple sclerosis (MS).^{1,2} More recent experiences with DA showed that benefits to MS patients may be broader than just on walking speed, with improvements in gait pattern, manual dysfunction, walking endurance, balance, fatigability, cognitive dysfunction and quality of life.^{3–12}

Recently, we demonstrated in a randomized, double-blind, placebo-controlled trial the efficacy of DA treatment in improving information processing speed in patients with MS and a documented deficit in this cognitive domain.¹³ This was the only randomized, double-blind, placebo-controlled trial of class I which demonstrated the cognitive efficacy of DA with a medium effect size.¹⁴ Proper selection of patients experiencing

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Correspondence to:

Carlo Pozzilli
Department of Human
Neuroscience, Sapienza
University, Viale
dell'Università 30, Rome,
00185, Italy

MS Center Sant'Andrea
Hospital, Sapienza
University of Rome, Rome,
Italy

carlo.pozzilli@uniroma1.it

Luca Prosperini
Claudio Gasperini

Department of
Neuroscience San
Camillo-Forlanini Hospital,
Rome, Italy

Silvia Tommasin
Department of Human
Neuroscience, Sapienza
University of Rome, Rome,
Italy

Elena Barbuti
MS Center Sant'Andrea
Hospital, Sapienza
University of Rome, Rome,
Italy

Laura De Giglio
Medicine Department,
Neurology Unit San Filippo
Neri Hospital, Rome, Italy

clinical benefits in Symbol Digit Modalities Test (SDMT)¹⁵ from DA has not yet been reported.

Therefore, here we report a post-hoc analysis aimed to test the predictive value of a set of demographic and clinical criteria baseline characteristics. Moreover, it is unknown whether the beneficial effects of DA on cognition are limited to patients showing poor SDMT response or extended to patients with deficit regarding motor function. This implies that responsiveness to DA should be evaluated in the clinical setting separately for cognitive and motor function.

Materials and methods

Patients and procedures

This post hoc analysis included patients who received DA in the trial. The study design for the DA trial study has been previously reported.¹³ Briefly, this was a randomized, double-blind, placebo-controlled trial in which 120 patients with MS were randomized in a 2:1 ratio to receive DA 10 mg or placebo twice daily for 12 consecutive weeks.

The study was sponsored by an investigator initiated trial grant from Biogen, who reviewed the protocol and provided both DA and matching placebo.

We enrolled patients from two regional referral MS Centers in Rome from February 2015 to June 2016. Patients were referred to the trial in the clinics, based on their subjective cognitive complaints. Eligible participants were patients with a diagnosis of MS according to the revised McDonald criteria,¹⁶ with an age ranging from 18 to 65 years (inclusive) and a score in the SDMT below the 10th percentile of normative values of the Italian population.^{17,18} Exclusion criteria were: (1) the occurrence of a clinical relapse in the previous 60 days; (2) history of major depression or psychosis; (3) severe or moderate depression according to Beck Depression Inventory-II (with a cut-off score of 19);^{19,20} (4) history of seizures; (5) conditions that would interfere with study conduction; (6) introduction or modification of any medication including medication for mood, fatigue or cognition in the previous month. Eligible patients completed the whole cognitive battery, the clinical evaluation and other study questionnaires according to the study protocol.

After 12 weeks patients came back to the Centers to repeat the tests.

Outcome measures

The main endpoint of efficacy–response to treatment was an improvement in the SDMT, calculated as the number of patients presenting at least an improvement of four points in the raw SDMT.

The administration of SDMT was preceded by a learning sequence at all time-points; furthermore, to reduce the learning effect, two alternative versions of the test were presented.^{15,17,21} Other outcomes of the study included the 9-Hole Peg Test (9HPT), the Timed 25-Foot Walk Test (T25-FWT) and the 3-s version of Paced Auditory Serial Addition Test (PASAT)²² seconds rate, which were used to calculate the Multiple Sclerosis Functional Composite (MSFC) score.²³

Statistical methods

Data management and analyses were performed on available data by an independent research organization (TFS Trial Form Support S.L., Rome, Italy) with no role in the study design and data collection. Previous results from the trial¹³ showed at the 12-week assessment a raw score increase in the SDMT from baseline of 9.9 [95% confidence interval (CI) 8.5–11.4] for patients treated with DA and of 5.2 (95% CI 2.8–7.6) for patients in the placebo group ($p=0.0018$). In the present analysis, we included only data from patients in the arm treated with DA. Since the median value of improvement in treated patients at the SDMT performance at the end of the treatment period was 10 points, we chose this value as cut-off to categorize patients as “full responders” (FR) or “partially responders” (PR).

Statistical analyses were performed using Stata 14.2. Two-tailed p -values < 0.05 were considered as significant.

We used a univariate logistic regression considering baseline characteristics to identify predictors of response. Moreover, to explore potential predictors of better response to DA, we ran a three-step hierarchical linear regression model (stepwise fashion) to identify which demographic variables (step 1), clinical factors (step 2) and motor and cognitive scores (step 3) were associated with

Table 1. OR of baseline clinical characteristics for dalfampridine responders.

	PR <i>n</i> = 37	FR <i>n</i> = 34	OR	95% CI	<i>p</i>
Gender, <i>n</i> (%)					
Male	19 (51.4)	11 (32.4)	1		
Female	18 (48.7)	23 (67.7)	2.21	0.8–5.8	0.108
Age years, mean (SD)	49.0 (8.2)	48.1 (7.2)	1.00	0.9–1.1	0.924
Formal education, mean (SD)	13.1 (3.5)	12.5 (3.5)	0.95	0.8–1.1	0.477
Phenotypes, <i>n</i> (%)					
Relapsing remitting	34 (91.9)	29 (85.3)	1		
Secondary progressive	3 (8.1)	4 (11.8)	1.56	0.3–7.6	0.579
Primary progressive	0 (0.0)	1 (2.9)			
Patients under DMT, <i>n</i> (%)					
No	13 (35.1)	13 (38.2)	1		
Yes	24 (62.2)	21 (61.8)	0.91	0.3–2.4	0.854
Disease duration, years, mean (SD)	15.2 (8.0)	12.5 (9.0)	0.96	0.9–1.0	0.179
EDSS, median (range)	4 (3–5)	3 (1.5–4.5)	0.69	0.5–0.97	0.034
<i>p</i> values refer to univariate logistic regression. CI, confidence interval; DMT, disease modifying treatment; EDSS, Expanded Disability Status Scale; FR, fully responders; OR, odds ratio; PR, partially responders.					

change in raw SDMT score from baseline assessment (dependent variable).

Results

Out of 120 randomized to receive DA (*n* = 80) or placebo (*n* = 40), 71 patients allocated to the DA group completed 12 weeks of treatment.

Briefly, the sample consisted of 41 women and 30 men with a mean \pm standard deviation (SD) age of 49.1 ± 7.7 years, mean (SD) disease duration of 13.9 ± 8.6 years, mean SDMT raw score of 30.2 ± 7.8 and median (range) Expanded Disability Status Scale (EDSS) score of 3.5 (1.0–6.0). Of them, 63 had a relapsing–remitting, seven a secondary progressive and one a primary progressive phenotype; 45 were on-treatment and the remaining 26 were off-treatment with disease-modifying drugs (Table 1 reports baseline clinical characteristics for both FR and PR groups).

According to our definition, 34 patients were classified as FR and 37 as PR.

The FR group consisted of 23 women and 11 men with a mean age of 48.1 ± 7.2 years; in the PR group we found 18 females and 19 males with a mean age of 49.0 ± 8.2 years. We did not find differences between groups in baseline characteristics (Table 1) except for median EDSS, which was lower in FR group compared with PR [3.0, range 1.5–4.5 *versus* 4.0, range 3.0–5.0, odds ratio (OR) 0.69; 95% CI 0.5–0.97, *p* = 0.034].

The FR group also presented a better performance in MSFC (0.79 ± 1.99 *versus* -0.40 ± 1.96) with a higher possibility of being FR in presence of a better MSFC value (OR 1.37; 95%CI 1.05–1.8, *p* = 0.022); in particular FR group presented a lower T25-FWT and a lower 9HPT with dominant hand compared with PR group (6.63 ± 1.86 *versus* 8.04 ± 2.96 ; OR 0.76; 95% CI 0.6–0.98,

Table 2. OR of baseline cognitive and motor scores for dalfampridine responders.

	PR	FR	OR	95% CI	<i>p</i>
	37	34			
PASAT 3 raw, mean (SD)	26.35 (11.26)	30.79 (14.46)	1.03	0.99–1.07	0.152
PASAT 3 adjusted, mean (SD)	-1.53 (0.93)	-1.16 (1.19)	1.39	0.89–2.19	0.152
T25-FWT, mean (SD)	8.04 (2.96)	6.63 (1.86)	0.76	0.60–0.98	0.033
9HPT dominant hand, mean (SD)	29.26 (14.25)	22.97 (6.33)	0.92	0.86–0.99	0.029
9HPT no dominant hand, mean (SD)	29.48 (10.47)	25.75 (8.44)	0.96	0.90–1.01	0.117
MSFC	-0.40 (1.96)	0.79 (1.99)	1.37	1.05–1.80	0.022

p values refer to univariate logistic regression.
 9HPT, 9-Hole Peg Test; CI, confidence interval; FR, fully responders; MSFC, Multiple Sclerosis Functional Composite; OR, odds ratio; PASAT, Paced Auditory Serial Addition Test; PR, partially responders; T25-FWT, Timed 25-Foot Walk Test.

$p=0.033$ and 22.97 ± 6.33 versus 29.26 ± 14.25 , OR 0.92; 95% CI 0.86–0.99, $p=0.029$) (Table 2).

Univariate and multivariable hierarchical linear regression models predicting change in SDMT score at week 12 in patients treated with dalfampridine ($n=71$) are shown in Table 3. The strongest predictor of univariate linear regression was 9HPT dominant hand. ($p=0.011$). The hierarchical linear regression model did not reveal any demographic variable (step 1) predicting the outcome. The introduction of baseline clinical variables (step 2) revealed that the EDSS score contributed significantly to the regression equation ($F_{1,69}=4.10$, $p=0.047$), although explaining only 5% of the variance in outcome. Finally, entering in the model the baseline motor and cognitive scores (step 3) revealed other significant independent predictors (9HPT dominant hand, SDMT and PASAT) that explained 24% of the variance in outcome, and this R^2 -change was significant ($F_{1,63}=4.83$, $p=0.032$).

In Table 4, mean changes from baseline of 9HPT dominant hand, 9HPT no dominant hand and T25-FWT are reported for patients PR and FR to DA treatment. FR group did not show any significant improvement of motor performance compared with PR group. Mean changes of SDMT from baseline were not different comparing two groups of patients as divided according to their response to measures of motor functions (data not shown).

Discussion

The mechanisms underlying the observed changes in responsiveness of DA remain speculative.

A neurophysiological study suggests that patients with MS with a normal pre-therapy central motor conduction time (CMCT) are very unlikely to benefit from DA, whereas patients with a prolonged CMCT have a higher chance to respond to treatment.²⁴ Given that DA may improve signal conduction by blocking potassium channels along demyelinated axons, patients with extensive demyelination might benefit more from this treatment. In addition to that, in experimental models, Dietrich *et al.*²⁵ demonstrated that 4-aminopyridine could prevent axonal loss.

Few attempts have aimed to predict clinical responsiveness to DA in MS patients. Some studies provide evidence that walking function at baseline can accurately predict the responder status, patients more disabled at baseline having the best outcome.^{26–28} On the other hand, original works by Goodman *et al.*,^{1,2,29} as well as work by Allart *et al.*,³ showed that responders and non-responders had similar baseline characteristics.

In our study the positive effect of DA on processing speed was specific to the primary outcome of SDMT. Patients were recruited based on a specific impairment in processing speed, while the impairment in other domains was not necessary. Therefore, processing speed impairment in MS should be associated with higher amount of axonal demyelination within the neural cognitive

Table 3. Univariate and multivariable hierarchical linear regression models predicting change in SDMT score at week 12 in patients treated with dalfampridine ($n=71$).

	β	95% confidence intervals		<i>p</i> -value	Adjusted R^2
		Lower bound	Upper bound		
Univariate analysis					
Sex (male <i>versus</i> female)	1.45	-1.43	4.34	0.32	
Age (each year)	0.02	-0.17	0.20	0.86	
Formal education (≤ 13 <i>versus</i> > 13 years)	0.32	-3.11	3.76	0.85	
Disease duration (each year)	-0.07	-0.23	0.10	0.43	
Phenotype (SP/PP <i>versus</i> RR)	0.99	-3.54	5.52	0.66	
EDSS score (each step)	-0.98	-1.94	-0.02	0.047	
DMT exposure (yes <i>versus</i> no)	-0.63	-3.60	2.35	0.68	
T25-FWT (each second)	-0.58	-1.14	-0.01	0.047	
9HPT dominant hand (each second)	-0.16	-0.28	-0.04	0.011	
9HPT non-dominant hand (each second)	-0.15	-0.29	-0.01	0.044	
SDMT (each point)	-0.07	-0.26	0.12	0.47	
PASAT (each point)	0.11	0.01	0.22	0.048	
Multivariable hierarchical analysis					
Step 1					
No predictors					
Step 2					0.05
Constant	13.61	9.86	17.36	<0.001	
EDSS score (each step)	-1.11	-2.12	-0.10	0.033	
Step 3					0.24
Constant	22.44	14.50	30.39	<0.001	
9HPT dominant hand (each second)	-0.30	-0.48	-0.12	0.001	
SDMT (each point)	-0.27	-0.47	-0.07	0.01	
PASAT (each point)	0.13	0.01	0.26	0.032	
9HPT, 9-Hole Peg Test; DMT, disease-modifying treatment; EDSS, Expanded Disability Status Scale; PASAT, Paced Auditory Serial Addition Test; PP, primary progressive; RR, relapsing–remitting; SDMT, Symbol Digit Modalities Test; SP, secondary progressive; T25-FWT, Timed 25-Foot Walk Test.					

network, providing more targets for DA to reinforce processing speed.

In the present study, EDSS score, as well as motor functions (T25-FWT and 9HPT),

predicted improvement in information processing speed by DA. The strongest predictor in the univariate analysis was 9HPT in dominant hand, indicating the best response in patients with preserved manual abilities. Lower EDSS value and

Table 4. Mean (SD) changes of motor tests from baseline measured in partially responders (PR) and fully responders (FR) to dalfampridine treatment.

	PR <i>n</i> = 37	FR <i>n</i> = 34	<i>p</i>
9HPT dominant hand, mean (SD)	-2.92 (11.23)	-5.87 (7.96)	0.211
9HPT no dominant hand, mean (SD)	-2.88 (9.42)	-5.27 (7.23)	0.238
T25-FWT, mean (SD)	-9.79 (11.87)	-8.69 (11.44)	0.700

p values refer to univariate logistic regression.
9HPT, 9-Hole Peg Test; T25-FWT, Timed 25-Foot Walk Test.

better performance at T25-FWT were also predictive of a good response.

Patients with an impairment of information processing speed, as those enrolled in the present study, showed lower deep gray matter volume, less white matter integrity, but also stronger increases in functional connectivity.³⁰ EDSS had a direct linear relationship with lesion load and inverse of thalamic volume, while it benefitted from functional connectivity, representing mechanisms of adaptation to structural damage and inflammation.³¹ Although it is quite difficult to apply cut-offs of EDSS to individual patients, functional connectivity generally decreases in comparison with structural measure at EDSS score greater than 3.0, which may be critical and indicate exhaustion of compensatory mechanisms.³¹ Similarly, it has been demonstrated that impaired finger dexterity in MS is associated with a decreased functional connectivity in several regions involved in motor functions such as superior frontal gyrus, lingual gyrus and posterior cerebellum.³² In our patients, a poor response should reflect failure of functional connectivity, interfering with the action of DA, which primarily involves an enhanced conduction in demyelinated pathways.

An interesting issue, also emerging from the present study, is that the motor response to DA is similar in FR and PR at SDMT, corroborating the hypothesis of different networks involving motor control and sustained attention. Correlations between functional connectivity clinical and neuropsychological variables in MS showed that a higher EDSS score correlated with a maladaptive neuronal response in the supplementary motor area bilaterally and in the right precentral operculum,³³ as well as with a more rigid (less fluid) global connectivity.³⁴ Conversely, temporal network and

relay areas the cerebellum and brainstem correlated with cognitive performances.³⁴⁻³⁶ Prosperini *et al.*¹¹ in a sub-study of the present trial demonstrated that patients classified as responders to DA according to SDMT improved also their postural sway, thus confirming the hypothesis of an overlap between the two networks connecting balance and information processing speed.^{37,38}

A limitation of this post hoc study is that PR and FR subgroups were defined retrospectively. The similar sample size of the two subgroups PR *n* = 37 and FR *n* = 34, however, may enhance statistical comparisons.

Conclusion

We have previously demonstrated that DA administered for 12 weeks improves information processing speed in patients with MS showing poor SDMT performance; here we found that favored response is extended to patients with motor deficit. However, a greater response to DA was observed only in a subpopulation of patients who had a lower EDSS and a better performance on tests of walking and hand dexterity. A maladaptive structural and functional plasticity in more motor disabled patients might account for these findings. These findings could help us to select the best candidate for DA treatment, even though further studies are required to confirm our hypothesis and to explore other predictors of treatment response.

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Authors of this article meet all the four International Committee of Medical Journal Editors (ICMJE) criteria for authorship, take responsibility and are accountable for the work. All authors have given their approval for this version of the article to be published.

Conflict of interest statement

CP reports: scientific advisory boards for Actelion, Biogen, Genzyme, Hoffmann-La Roche, Merck-Serono, Novartis, Sanofi and Teva; consulting and/or speaking fees, research support and travel grants from Allergan, Almirall, Biogen, Genzyme, Hoffmann-La Roche, Merck-Serono, Novartis, Sanofi and Teva. LP reports: consulting fees from Biogen, Novartis and Roche; speaker honoraria from Biogen, Genzyme, Merck Serono, Novartis and Teva; travel grants from Biogen, Genzyme, Novartis and Teva; research grants from the Italian MS Society (Associazione Italiana Sclerosi Multipla) and Genzyme. ST has nothing to disclose. CG reports: fees as invited speaker or travel expenses for attending meeting from Biogen, Merck-Serono, Teva, Sanofi, Novartis and Genzyme.

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Ethics statement and informed consent

All procedures performed in the study were in accordance with the Helsinki Declaration as revised in 2013 or comparable ethical standards. The study was reviewed and approved by the Ethical Committee of Sapienza University in Rome (Prot. 1074/13, Rif. 2991/28.11.2013) and all patients signed an informed consent prior to any study-related procedure. The study was prospectively registered to the (2013-002558-64) EU Clinical Trials Register (<https://www.clinicaltrialsregister.eu/>) with the ID 2013-002558-64).

ORCID iD

Carlo Pozzilli  <https://orcid.org/0000-0002-6360-4798>

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