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ORIGINAL ARTICLE

Effect of patients' expectations on clinical response to fampridine treatment

Filipa Ladeira[1] · Marcelo Mendonça[1,2] · André Caetano[1] · Manuel Salavisa[1] · Henrique Delgado[1] · Ana Sofia Correia[1,2] · Miguel Viana-Baptista[1,2]

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Abstract

Introduction Patient expectation of treatment outcome is one of the primary mechanisms underlying the placebo effect. In multiple sclerosis trials with symptomatic treatments, a robust placebo effect is observed, which might be related to patient expectations. The aim of this study was to evaluate whether patient expectations regarding fampridine treatment influence the clinical response after 4 weeks and 6 months of treatment.

Materials and methods We designed and carried out a prospective study from June 2015 to August 2017. Before treatment, patients completed a questionnaire including a scale evaluating their expectations regarding the treatment. The effect of baseline positive expectancy on the response status after 4 weeks and 6 months of treatment was analyzed through univariable and, when applicable, multivariable analysis.

Results A total of 47 consecutive patients were included in the study. At week 4, 37 (78.7%) patients were classified as responders; a one-point increase in the positive expectancy questionnaire was significantly associated with a fourfold increase in the likelihood of being a responder [OR = 4.020 (95% CI 1.082–14.933); $p = 0.038$]. At 6 months, 43 patients completed follow-up. The number of responders decreased to 28; at this point, positive expectancy at baseline was no longer associated with response status.

Conclusion Baseline positive expectancy regarding fampridine was determinant of the clinical response after 4 weeks of treatment. However, in the long term, fampridine efficacy was not dependent on expectations prior to treatment.

Keywords Beliefs · Expectations · Fampridine · Multiple sclerosis

Introduction

Expectations are known to influence the response to numerous treatments and are one of the major mechanisms underlying the placebo effect [1–4]. In multiple sclerosis (MS), the effect of patients' expectations on the outcomes of symptomatic treatments has not been studied yet. However, in clinical trials on fatigue, pain, spasms, and spasticity, a robust placebo effect has been observed. [5–7] These placebo effects might, at least partly, be related to the expectations and beliefs of patients regarding the treatment and its efficacy. Moreover, several other factors have been shown to influence treatment

✉ Filipa Ladeira
filipaladeira@msn.com

Marcelo Mendonça
marcelomendoncasousa@gmail.com

André Caetano
andre.p.caetano@gmail.com

Manuel Salavisa
mteixeira1@campus.ul.pt

Henrique Delgado
riquedelgado@hotmail.com

Ana Sofia Correia
ana_sofiacorreia@hotmail.com

Miguel Viana-Baptista
mvianabaptista@nms.unl.pt

[1] Department of Neurology, Hospital Egas Moniz, Centro Hospitalar de Lisboa Ocidental, Serviço de Neurologia, Hospital Egas Moniz, Rua da Junqueira 126, 1349-019 Lisbon, Portugal

[2] CEDOC Nova Medical School/ Faculdade de Ciências Médicas, Universidade Nova de Lisboa, Campo Mártires da Pátria 130, 1169-056 Lisbon, Portugal

expectations, such as the patient's emotional state prior to treatment, information and communication prior to initiation of the drug regimen, and the expected outcome [8–10].

Fampridine has recently become available as a symptomatic drug for the treatment of walking impairment in MS patients. In the clinical trials that led to the drug's approval, the responder status was based on multiple clinical evaluations for a period of 9 to 14 weeks. In clinical practice, however, where the responder definition is dependent on a single evaluation after only 4 weeks, the response rate was much higher (78.5%) [11–13]. Although the different definition in clinical trials and clinical practice might justify the different response rates, we wonder whether the higher response rate in the short-term could relate to a transient effect of expectation.

The aim of this study was to evaluate if patient expectations regarding fampridine treatment at baseline are associated with response status after 4 weeks and 6 months of treatment.

Material and methods

We designed a cohort study and invited all patients prescribed fampridine treatment in our center to participate. Patients were recruited in our Neurology Department, from June 2015 to August 2017. The inclusion criteria were the following: patients older than 18 years old, diagnosed with multiple sclerosis according to the 2010 McDonald Diagnostic Criteria, EDSS between 4 and 7, with a clinically apparent walking impairment, precribed fampridine treatment by the assisting physician, with a follow-up between 4 weeks and 6 months after starting the drug. Those patients with a follow-up superior to 4 weeks but inferior to 6 months were not excluded, but were included only in the results at 4 weeks, and excluded from the analysis of 6 months. Exclusion criteria included the presence of conditions listed as a contraindication to fampridine treatment in the European Medicines Agency guidelines. The local ethics committee approved the study. All patients included in the study gave written informed consent.

Demographic and clinical variables (age, disease duration, disease type, EDSS) were obtained from the patients' records.

Before commencing fampridine treatment, patients answered a questionnaire that contained a section on expectations using a Portuguese version of the Stanford Expectations of Treatment Scale (SETS)—a validated tool for measuring patients' expectations regarding treatments [14]. The SETS questionnaire includes three items concerning positive expectancy that relate to the placebo effect and three items regarding negative expectancy that relate to the nocebo effect. We only used the positive expectancy score, which ranges from 1 (low positive expectancy) to 7 (high positive expectancy).

Since emotional state and information/communication prior to treatment are known to influence patients' expectations, the questionnaire included a multiple choice question about the first source of information on fampridine treatment: "How did you become aware of fampridine? That is, the first time you were told of fampridine was through (select the most appropriate): a) assisting physician b) nurse c) patients' organizations/support groups d) Newsletters / material from pharmaceutical companies e) internet f) other patients g) other." A self-reported scale of anxiety and depression symptom—the Hospital Anxiety and depression scale (HADS) scale, validated among MS patients, was also included in the protocol.

Patients starting fampridine were evaluated and classified in accordance with the Portuguese Regulatory Agency: all patients were evaluated at baseline and at week 2 through a timed 25-ft walk test (T25FW), and a Portuguese validated version of 12-item Multiple Sclerosis walking scale (MSWS12) [15]. For patients with an improvement inferior to 20% on the timed 25-ft walk test (T25FW) but a reduction on the Multiple Sclerosis Walking Scale-12 (MSWS12) of at least 2 points at week 2, a subsequent follow-up was performed at week 4. Patients were considered responders at week 2 or 4 if there was a reduction of at least 20% on T25FW at week 2, or if there was an improvement of at least 2 points in MSWS12 at week 2 and a reduction of at least 20% on T25FW at week 4. Treatment response was reevaluated every 3 months in accordance with the local regulatory agency. Patients who failed to maintain a T25FW 20% decrement in subsequent evaluations, or did not comply were considered non-responders.

The number of patients prescribed fampridine treatment by the assistant physician determined the sample size. According to the response rate in a previous study [13] that applied the same responder criteria as in the current study, we expected that approximately 78% of patients would be classified as responders. We wanted to use the SETS score to predict the response variable. Using a two-tailed test, we determined that a sample size of 37 patients would be needed to detect an increase of 20% in the response rate in patients who scored one standard deviation above the mean SETS score (power of 0.8, significance level of 0.05, OR = 4).

To reduce interview bias, the patients were not informed about the study hypothesis before completing the baseline questionnaire. Considering that previous knowledge of the T25FW results at week 2 might influence the subjective evaluation of walking reported in MSWS-12, the MSWS-12 test was conducted prior to the T25FW test in all patients.

IBM SPSS Statistics 22 software was used to perform the data analysis.

In the statistical analyses, response status at 4 weeks and 6 months was treated as the outcomes. Factors considered to be potential determinants were demographic variables (age, gender); clinical variables (disease duration, EDSS score, disease type); source of information regarding fampridine treatment;

positive expectancy regarding treatment evaluated through a positive SETS expectancy score; emotional status prior to treatment evaluated through HADS depression and anxiety scores; and baseline T25FW and MSWS-12 scores. Follow-up T25FW and MSWS-12 scores were excluded from the analysis since they are implicit in the response status. Quantitative data were analyzed through mean or median values and respective standard deviation or interquartile ranges. The categorical variable "source of information regarding fampridine treatment" was dichotomized as assistant physician vs. other informant and the categorical variable "disease type" was dichotomized as relapsing-remitting and progressive forms of the disease.

A univariable logistic regression was performed to evaluate the influence of each variable in response status and a multivariable regression was carried out for variables reaching statistical significance ($p \leq 0.05$) in the univariate analysis or for variables considered clinically relevant. Emotional status at the start of treatment and information prior to treatment are known to influence expectations regarding treatments and were considered to be clinically relevant variables.

Results

Baseline characteristics

Of the 59 patients prescribed fampridine treatment in our department during the recruitment period, 47 were considered to be eligible for participation in the study (Fig. 1).

The study cohort comprised, therefore, 47 patients, with an average age of 53.1 ± 12.4 years, 68.1% ($n = 32$) were women.

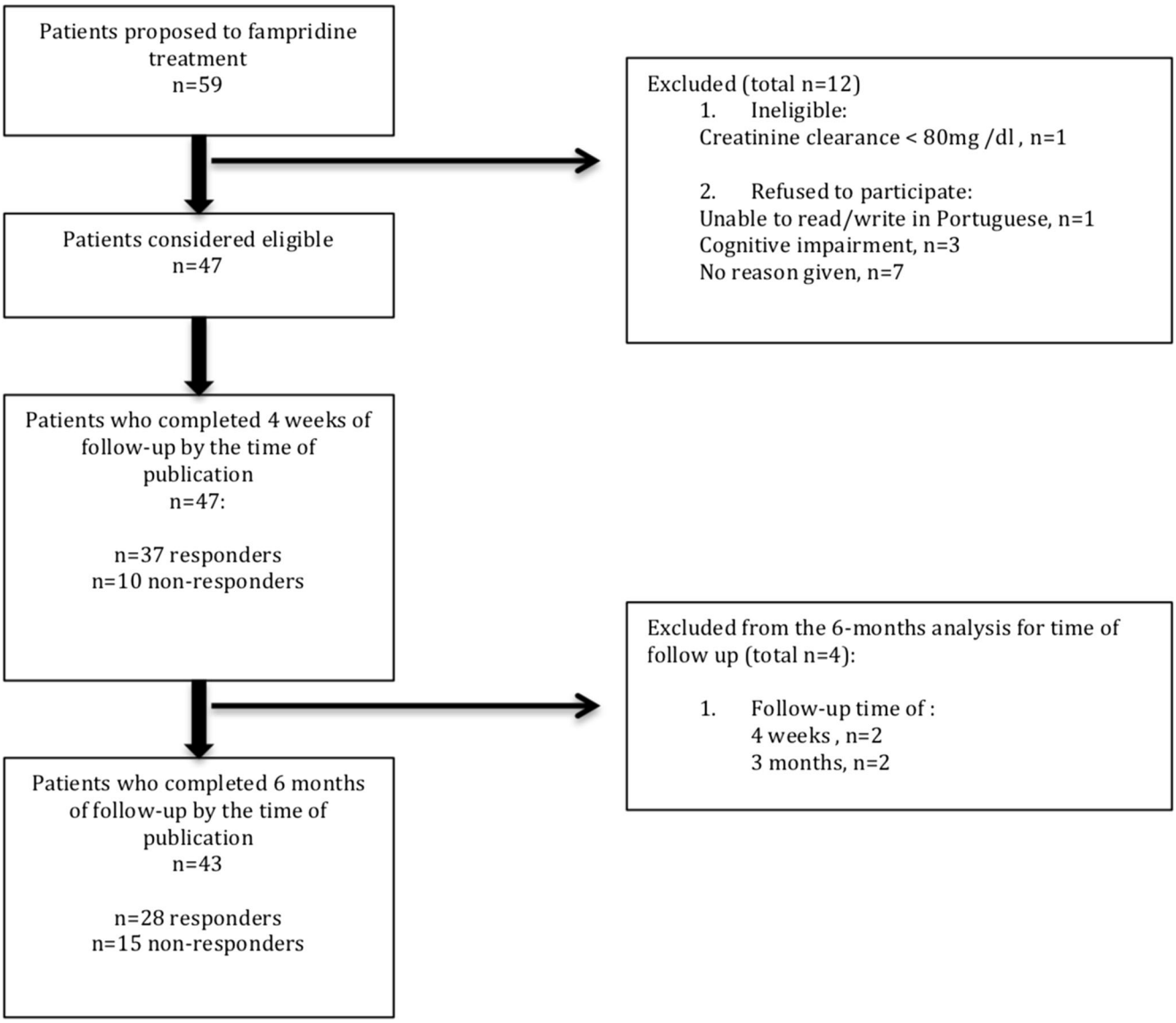

Fig. 1 Patients' recruitment and follow-up flow

The median EDSS was 5.5 and mean disease duration was 17.4 ± 9.6 years (Table 1). Regarding disease type, 38.3% ($n = 18$) patients were classified as relapsing-remitting MS, 21.3% ($n = 10$) as secondary-progressive MS, and 40.4% ($n = 19$) as primary-progressive or progressive-relapsing MS.

Patients presented a mean positive expectancy score on the SETS of 5.5 ± 1.9 prior to treatment, reflecting high expectations regarding fampridine. The first source of information regarding fampridine treatment was the assistant physician for the majority of patients (61.7%), followed by the internet in 19.1% of cases. Other sources, such as nurses, patient organizations, pharmaceutical companies, and other, were less frequently reported (8.5%, 6.4%, 2.1%, and 2.1%, respectively). The mean HADS sub-scores for depression (HADS-D) and anxiety (HADS-S) were 7.5 (± 4.0) and 6.8 (± 3.9), respectively, reflecting low levels of anxiety and depression symptoms prior to treatment. Twenty-two of the patients had a HADS depression score above the cut-off of 8, but only three had a score that indicated severe depression (> 15). Regarding the HADS anxiety score, 19 patients had a score above the cut-off of 8, but only two had a score above the cut-off for severe anxiety (> 15).

Response at week 4

Thirty-seven (78.7%) patients were considered responders at week 4. Patient characteristics, according to response status at week 4, are presented in Table 1.

We performed a univariable regression analysis to ascertain the effect of positive expectancy on the likelihood of response to fampridine treatment and found that for every one-point increase in the SETS positive expectancy score, the likelihood of response to fampridine treatment increased 3.7 times [OR = 3.658 (95% CI 1.176–11.383); $p = 0.025$]. After adjustment for possible confounders (for depression, anxiety and source of information regarding fampridine treatment), a one-point increase in the SETS positive expectancy score was still significantly associated with a fourfold increase in the likelihood of being a responder at week 4 [OR = 4.020 (95% CI 1.082–14.933); $p = 0.038$].

Response after 6 months

Among the 43 patients who completed 6 months of follow-up, the number of non-responders increased to 15. The effect of baseline expectations observed in the clinical response at week 4 was lost after 6 months of treatment (Table 2). There were no differences in the SETS positive expectancy scores regarding treatment between the group of patients who continued to respond ($n = 28$) and the group that no longer responded ($n = 5$) after 6 months of therapy (5.2 ± 1.0 vs. 5.6 ± 1.1; $p = 0.340$). We could not find any clinical or demographic characteristic associated with a clinical response after 6 months of treatment.

Table 1 Demographic and clinical characteristics of the patient's cohort at different time points

Variables	Total sample ($n = 47$)	Response status at 4 weeks		Response status at month 6	
		Benefit ($n = 37$)	No benefit ($n = 10$)	Benefit (n = 28)	No benefit ($n = 15$)
Age, mean (SD), years	53.1 (12.5)	53.7 (12.6)	51.0 (12.5)	52.3 (12.6)	54.7 (12.8)
Female, n (%)	32 (68.1)	23 (73)	9 (90)	18 (64.3)	12 (80.0)
Disease duration, (mean), (SD), years	17.4 (9.6)	16.9 (9.3)	19.3 (11.2)	16.8 (9.9)	19.0 (9.5)
EDSS score, median (IQR)	5.5 (2.0)	5.5 (2.0)	6.0 (2.1)	5.3 (2.4)	6.0 (2.0)
Disease type, n (%) RRMS SPMS/ PPMS	18 (38.3) 29 (61.7)	15 (40.5) 22 (59.5)	3 (30.0) 7 (70.0)	12 (42.9) 16 (57.1)	4 (26.7) 11 (73.3)
Patients who reported the assistant physician as source of information regarding fampridine's treatment, *n* (%)	28 (59.6)	20 (54.1)	8 (80.0)	15 (53.6)	9 (60.0)
T25FW mean (SD), seconds Week 0	28.2 (36.6)	30.9 (40.1)	18.0 (17.1)	25.7 (29.0)	36.9 (51.2)
MSWS-12 score, mean (SD) Week 0	47.4 (7.8)	47.3 (8.2)	47.7 (6.3)	46.5 (8.7)	48.9 (5.6)
SETS positive expectancy score, (mean)	5.5 (1.9)	5.7 (2.0)	4.5 (0.7)	5.4 (0.9)	5.0 (1.1)
HADS depression score (SD)	7.5 (4.0)	6.9 (4.0)	9.6 (3.3)	6.4 (3.8)	8.9 (4.0)
HADS anxiety score (SD)	6.8 (3.9)	6.9 (4.2)	6.5 (3.0)	6.8 (3.9)	6.4 (3.7)

EDSS, expanded disability status score; *HADS*, Hospital Anxiety and depression scale; *IQR*, interquartile range; *MSWS-12*, Twelve Item MS Walking Scale; *PPMS*, primary-progressive multiple sclerosis; *PRMS*, progressive-relapsing multiple sclerosis; of treatment scale; *RRMS*, relapsing-remitting multiple sclerosis; *PRMS*, progressive-relapsing multiple sclerosis; *SD*, standard deviation; *SETS*, Stanford expectations of Treatment Scale; *SPMS*, secondary-progressive multiple sclerosis; *T25FW*, timed 25-ft walk

Table 2 Logistic regression evaluating the influence of positive expectancy and other covariates in response status at week 4 and at month 6

	Week 4 ($n = 47$)		Month 6 ($n = 43$)	
Variables	Odds ratio (95%CI)	p value	Odds ratio (95%CI)	p value
Univariate analysis				
Gender	0.183 (0.021–1599)	0.125	0.450 (0.102–1.982)	0.291
Age	1.018 (0.961–1.078)	0.549	0.985 (0.936–1.036)	0.556
Disease duration	0.975 (0.909–1.046)	0.477	0.977 (0.915–1.042)	0.474
EDSS	0.738 (0.384–1.418)	0.362	0.701 (0.389–1.264)	0.238
Disease type	0.629 (0.140–2.826)	0.545	0.485 (0.124–1.903)	0.299
Source of information regarding treatment	0.313 (0.058–1.682)	0.176	0.833 (0.231–3.003)	0.780
Baseline T25FW	1.017 (0.982–1.053)	0.341	0.992 (0.976–1.009)	0.372
Baseline MSWS-12 score	0.994 (0.907–1.089)	0.898	0.959 (0.880–1.044)	0.333
SETS positive expectancy score	*3.658 (1.176–11.383)*	*0.025*	1.659 (0.807–3.413)	0.169
HADS depression score	0.841 (0.697–1.014)	0.070	0.845 (0.704–1.013)	0.068
HADS anxiety score	1.025 (0.854–1.230)	0.792	1.028 (0.869–1.215)	0.749
Multivariate analysis				
SETS positive expectancy score	*4.020 (1.082–14.933)*	*0.038*		
Source of information regarding treatment	0.260 (0.034–2.017)	0.198		
HADS depression score	0.798 (0.611–1.042)	0.097		
HADS anxiety score	1.115 (0.804–1.547)	0.514		

Italicized entries represent statistical significance ($p < 0.05$)

EDSS, expanded disability status score; *MSWS-12*, Twelve Item MS Walking Scale; *HADS*, Hospital Anxiety and depression scale; *SETS*, Stanford expectations of Treatment Scale; *T25FW*, timed 25-ft walk

Discussion

To our knowledge, this is the first study to examine the contribution of patient expectations to the clinical response to fampridine treatment.

In our cohort, high expectations were observed regarding fampridine treatment, reflected by the mean SETS positive expectancy scale score of 5.5. The response rate at week 4 was 78.7%. A recent systematic review reported a highly variable response rate to fampridine in previous studies, depending on the adopted responder criterion [16]. In the ENABLE study [13], a previous real-world assessment of response to fampridine treatment that used the same responder criteria as the current study, the response rate was very similar to ours (78.5%). Positive expectancy scores were shown to be associated with a clinical benefit at week 4 in our sample while the remaining clinical variables did not seem to influence the response. After 6 months of treatment, the response rate decreased to 65.1% and expectations prior to treatment were no longer associated with response to fampridine treatment.

The influence of expectations on clinical outcomes has been demonstrated in other diseases, especially considering symptomatic treatments [4], and has been linked to the activation of several neurobiological pathways, depending on the therapeutic intervention [17]. Our observations suggest that positive expectancy potentiates the treatment efficacy of fampridine at week 4. Fampridine's effect has been attributed to the blockage of voltage-gated potassium channels potentiating the signal transmission through demyelinated axons, with some small sample reports demonstrating an actual improvement in neurophysiological parameters [18–20]. Positive expectancy might modulate, to some extent, the frontostriatal brainstem pathways that improve sensory and motor transmission in the central nervous system, reinforcing fampridine's effect.

After 6 months of treatment, the expectations prior to treatment seemed to no longer be associated with response to fampridine treatment. There are two possible explanations for these observations: the patients' expectations might have changed over time, although it might be reasonable to assume that expectations would be reinforced by the clinical improvement; alternatively, expectations are important for short-term improvement but not for sustained improvement (for that, the effect of the drug itself is the primary determinant). If patient expectations are indeed a determinant of clinical response to fampridine in the short term and if their effect is only transient, this could at least partly explain the different results observed in phase III and IV trials [11–13], in which a different follow-up period was applied. Furthermore, future clinical trials in symptomatic MS treatments should take the expectations effect into account.

According to the open-hidden paradigm [9], the removal of the psychosocial context of any therapy decreases the

response to active treatments. On the other hand, verbally induced expectations and social interactions play a crucial role in determining the therapeutic outcome. In clinical practice, this means that the establishment of an empathic doctor-patient relationship and providing accurate information about the treatment's efficacy and side effects might be useful in maximizing the effects of fampridine treatment. In the current sample, the source of information prior to treatment was not relevant to treatment outcomes; however, the quality of information was not evaluated.

We acknowledge that the use of a relatively small sample limits our conclusion and potential extrapolations to larger populations. However, a systematic assessment carried out in the same center could reduce possible bias. Other limitations include the single evaluation of patient expectations at baseline; further evaluation of expectations after 3 and 6 months of treatment would allow us to understand if the effect of patient expectations is indeed transitory. Furthermore, we only assessed the information provided prior to treatment by source and not by the quality of information, so the importance of the information quality prior to treatment cannot be ruled out in our study sample. Finally, it would have been interesting to include a cognitive evaluation of the patients since cognitive impairment may relate to a loss of the expectations component of the treatment outcome. Future studies with larger samples, including expectations reassessments in the long term and measurements of cognitive function, would be useful to confirm our hypothesis. Furthermore, the use of neurophysiological parameters in future studies could provide deep insights into the mechanism of the effects of patient expectations in motor improvement.

In conclusion, we found that patients' positive expectancy regarding treatment was associated with a therapeutic response at 4 weeks but not at 6 months. Baseline positive expectancy regarding Fampridine appears to be the main determinant of an early treatment response. A longer follow-up time seems to be needed to assess the sustained benefits of fampridine as this effect of positive expectancy does not persist over time.

Compliance with ethical standards

Conflict of interest Filipa Ladeira received travel support from Biogen, Teva, and Sanofi-Genzyme. Ana Sofia Correia received an educational sponsorship from Merck Serono; consulting and speaking fees from Novartis, Biogen Idec, and Merck; as well as research support from Biogen Idec and support for scientific meetings from Novartis, Biogen Idec, Sanofi Genzyme, Teva, and Bayer. Marcelo Mendonça, André Caetano, Manuel Salavisa, and Henrique Delgado have no conflicts of interest. Miguel Viana-Baptista received research support and travel grants from Sanofi-Genzyme.

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