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ORIGINAL RESEARCH

Benefit of Endermology on Indurations and Panniculitis/Lipoatrophy During Relapsing–Remitting Multiple Sclerosis Long-Term Treatment with Glatiramer Acetate

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ABSTRACT

Introduction: Use of endermology (Endermologie®), which consists of a deep mechanical massage, in patients with multiple sclerosis receiving glatiramer acetate suggested improvements in injection-site indurations and panniculitis/lipoatrophy in our previous pilot experience. We aimed to assess the effect of endermology in a larger population of patients with multiple sclerosis receiving glatiramer acetate in clinical practice.

Methods: This was the extension phase of our pilot experience, carried out in patients with relapsing–remitting multiple sclerosis (RRMS) and indurations and/or panniculitis/lipoatrophy associated with long-term glatiramer acetate administration. Patients underwent endermology sessions twice per week, for 6 weeks, according to clinical practice.

Results: Seventy evaluable patients were included (mean age, 42.7 ± 9.3 years; female, 95.7%; mean multiple sclerosis duration, 9.2 ± 8.6 years; mean glatiramer acetate duration, 46.7 ± 29.9 months). Fifty (71.4%) patients showed indurations and 58 (82.9%) panniculitis/lipoatrophy. After 12 endermology sessions, the number of patients with indurations significantly decreased (71.4% vs. 28.6%; $p < 0.001$), as did the number of their indurations (4.2 ± 3.6 vs. 3.7 ± 3.4; $p < 0.001$). Although the number of patients with panniculitis/lipoatrophy did not significantly decrease, there was a significant reduction in

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the number of areas of panniculitis/lipoatrophy (4.3 ± 2.6 vs. 3.9 ± 2.2; $p < 0.05$). Forty-nine (98.0%) patients with indurations and 57 (98.3%) patients with panniculitis/lipoatrophy felt satisfied/very satisfied with treatment and considered endermology useful/very useful. Endermology was well tolerated, as some pain was reported in eight (11.4%) patients, discomfort in three (4.3%) patients, and local blotch/swelling and transient bruise in one (1.4%) patient each. Endermology enabled glatiramer acetate tolerance to be enhanced in 42 (60.0%) patients.

Conclusion: This project represents the largest experience available supporting the benefit of endermology in the reduction/disappearance of indurations and improvement in panniculitis/lipoatrophy in patients with RRMS receiving long-term glatiramer acetate treatment. Moreover, these benefits also contributed to enhancing glatiramer acetate tolerance.

Keywords: Endermologie; Endermology; Glatiramer acetate; Induration; Lipoatrophy; Multiple sclerosis; Panniculitis

INTRODUCTION

Glatiramer acetate is one of the main first-line immunomodulatory treatments currently approved for reducing the frequency of relapses in ambulatory patients with relapsing–remitting multiple sclerosis (RRMS). Its subcutaneous once-daily administration is generally well tolerated; however, patients may experience local reactions such as pain, inflammation or indurations at the injection site [1]. Though these injection-site reactions are usually transient, they may persist and even lead to localized panniculitis followed by subcutaneous lipoatrophy [2, 3]. It has been reported that up to 45% of patients receiving glatiramer acetate for long-term periods may experience localized lipoatrophy, and despite not being considered a serious event, its disfiguring effect and restriction of areas of injection often lead patients to reduce adherence or even discontinue treatment [4].

Endermology is a non-surgical therapy developed by Louis Paul Guitay (LPG) in the late 1970s to soften scars, regain skin elasticity and restore muscle function (Endermologie®; LPG Systems, Valence, France). It consists of a mechanical body massage performed using a treatment head composed of two independent motorized rollers and a regulated suction system that grasp the skin creating a fold [5]. The pressure difference and the rolling motion provide a smooth and deep massage that improves blood/lymph microcirculation [6, 7], stimulates fibroblasts [8, 9] and mobilizes subcutaneous fat [10, 11]. This therapy has been successfully used to improve skin texture and body contour [6, 12–17], as well as to treat several conditions such as radiation-induced skin fibrosis [18], lymphedema [19–21], morphea [22], or fibromyalgia [23].

Lebrun et al. [24] were the first to assess the effect of endermology in a series of eight patients with injection-induced lipoatrophy during the treatment of multiple sclerosis with glatiramer acetate. The benefit suggested by this project led us to conduct a multicenter pilot experience in 13 patients treated with glatiramer acetate who showed induration and/or panniculitis/lipoatrophy at the injection site [25]. The results obtained in our small series of patients also supported the benefit of endermology. In fact, indurations were reduced or even disappeared, panniculitis/lipoatrophy was considerably improved, and glatiramer acetate tolerance was also enhanced.

In view of these benefits, we conducted an extension phase of our pilot experience to expand the information available on the effect of endermology on indurations and/or panniculitis/lipoatrophy associated with glatiramer acetate administration in a larger population of patients with multiple sclerosis.

METHODS

Project Design

This project represents the extension phase of the previously reported multicenter pilot experience to assess the effect of endermology on local indurations and panniculitis/lipoatrophy associated with long-term subcutaneous administration of glatiramer acetate for RRMS treatment [25].

Eligible patients were identified from Multiple Sclerosis Units at 17 Spanish hospitals. Patients received onsite endermology treatment or were referred to cosmetic clinics depending on endermology availability at the site; ten cosmetic clinics participated in the project.

Patient Population

The patient population comprised men or women aged between 18 and 65 years, diagnosed with RRMS, who showed indurations and/or panniculitis/lipoatrophy associated with long-term subcutaneous administration of glatiramer acetate. Patients with active malignancies and/or those with peripheral venous insufficiency were excluded.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000 and 2008. Informed consent was obtained from all patients included in the project.

Measurements

Patients were assessed at the beginning of endermology therapy (baseline visit) and again after 12 endermology sessions (final visit) (Fig. 1). At the baseline visit, information on demographics and history of multiple sclerosis were retrieved from patients' medical charts. A physical examination, including visual inspection and manual palpation, and photographic assessments of indurations and areas of panniculitis/lipoatrophy were also performed. Patients then underwent endermology sessions of 15–40 min, twice per week for 6 weeks, to reach a total of at least 12 sessions. LPG Cellu M6® (LPG Systems, Valence, France) modules were used during endermology sessions. Trained nurses or technicians operated these modules according to routine clinical practice and following the manufacturer's recommendations. During endermology sessions, the operator moved the treatment head of the instrument forward, backwards, sidelong and diagonally. This movement exerted a mechanical massage through the two motorized rollers of the head of the instrument, whose independent directions of rotation induced a roll-in, roll-up or roll-out effect on the skin and subcutaneous tissues. In addition, the intensity of aspiration of the suction system was regulated to adjust the height of the skinfold created inside the vacuum chamber between the two rollers, which enabled the depth of the massage to be controlled. The movement of the treatment head and the suction intensity were adapted according to patient tolerance and taking into account the manufacturer's recommendations.

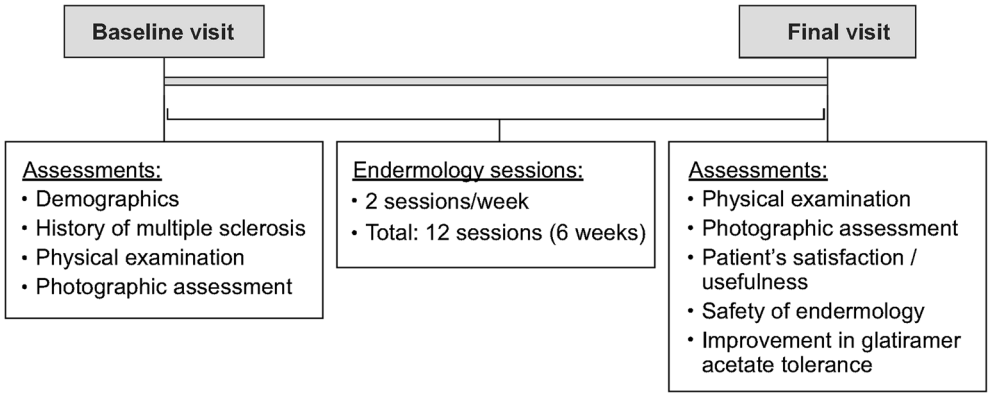

Fig. 1 Overall project design

At the final visit, changes in indurations and areas of panniculitis/lipoatrophy were evaluated by physical examination, including visual inspection and manual palpation, and photographic assessments. Patients' satisfaction with endermology treatment and its perceived usefulness were evaluated using three-point scales ranging from very satisfied/useful to not satisfied/useful and additional questions on its positive/negative effects. Data on adverse events reported during endermology treatment and improvement in glatiramer acetate tolerance were also collected.

All patients received glatiramer acetate (Copaxone®; Teva Pharmaceuticals Ltd., London, United Kingdom) from commercial sources, administered as once-daily subcutaneous injections according to the Summary of Product Characteristics. Glatiramer acetate treatment was prescribed as per routine clinical practice and without any interference with patients' participation in the project.

Statistical Considerations

The primary endpoint was the change in local indurations and areas of panniculitis/lipoatrophy from the baseline visit to the final visit. Secondary endpoints include patients' satisfaction with and perceived usefulness of endermology treatment, improvement in glatiramer acetate tolerance and endermology safety in terms of adverse events reported at the final visit. Descriptive analyses were performed, including the calculation of absolute frequencies and valid percentages for qualitative variables, and mean and standard deviation (SD) for quantitative variables. Comparisons were carried out using McNemar's tests, Chi squared tests or Wilcoxon tests, where appropriate.

Missing data were not considered in the analyses, which were performed with a significance level of 0.05 and using the Statistical Package for the Social Sciences (SPSS) version 17.0 (SPSS Inc., Chicago, Illinois, USA).

RESULTS

Patient Characteristics

A total of 84 patients were screened between April 2011 and June 2013. Three patients were screened for failures and 11 patients were considered non-evaluable; details on patient disposition are shown in Fig. 2. Therefore, the

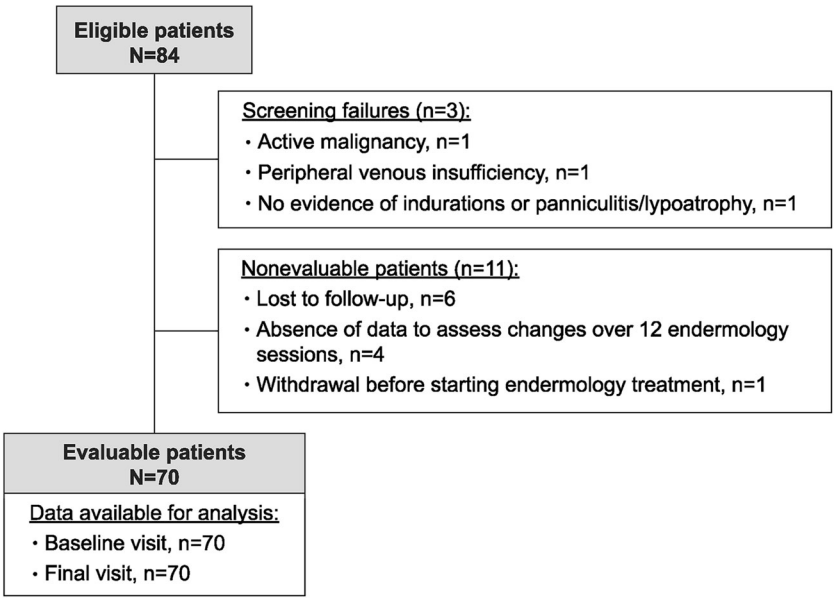

Fig. 2 Summary of patient disposition

evaluable population comprised a total of 70 patients, whose characteristics are described in Table 1.

Patients had a mean (±SD) age of 42.7 (±9.3) years, were mostly women (67 [95.7%] patients) and reported a mean (±SD) multiple sclerosis duration of 9.2 (±8.6) years. Fifteen (21.4%) patients had received previous therapies for multiple sclerosis and the mean (±SD) duration of glatiramer acetate treatment at baseline visit was 46.7 (±29.9) months.

Efficacy

At baseline, 50 (71.4%) patients showed a mean (±SD) of 4.2 (±3.6) indurations, which were mainly located on the abdomen and thighs (Table 2). After 12 endermology sessions, the number of patients showing indurations significantly decreased by 60%, to just 20 (28.6%) patients ($p < 0.001$), and the mean (±SD) number of their indurations was significantly reduced to 3.7 (±3.4) ($p < 0.001$) (Table 2).

Fifty-eight (82.9%) patients showed a mean (±SD) number of 4.3 (±2.6) areas of panniculitis/lipoatrophy in thighs, abdomen, buttocks and arms at baseline (Fig. 3). Even though the number of patients with panniculitis/lipoatrophy did not significantly decrease at the final visit (53 [75.7%] patients), the number of areas of panniculitis/lipoatrophy was significantly reduced to 3.9 (±2.2) ($p < 0.05$).

When patients with indurations were questioned about their satisfaction with the endermology treatment and their perception of its usefulness, 49 (98.0%) patients reported feeling satisfied or very satisfied and considered it useful or very useful (Table 3). Similarly, 57 (98.3%) patients with panniculitis/lipoatrophy reported being satisfied or very satisfied with endermology effect and considered it useful or very useful (Table 3). Furthermore, 64 (91.4%) patients reported improvements in skin condition and 42 (60.0%) in glatiramer acetate tolerance, especially with regard to decreased injection-related pain ($n = 27$).

Table 1 Baseline patient characteristics

Patient characteristics	(*N* = 70)
Age (years), mean ± SD	42.7 ± 9.3
Gender, *n* (%)	
Female	67 (95.7)
Male	3 (4.3)
Caucasian, *n* (%)	70 (100)
Patients previously treated for multiple sclerosis, *n* (%)	15 (21.4)
Previous therapies for multiple sclerosis, *n* (%)[a]	
Interferon beta-1a s.c.	10 (14.3)
Interferon beta-1b s.c.	3 (4.3)
Interferon beta-1a i.m.	1 (1.4)
Mitoxantrone	1 (1.4)
Glatiramer acetate	1 (1.4)
Duration of multiple sclerosis (years), mean ± SD	9.2 ± 8.6
Duration of glatiramer acetate treatment (months), mean ± SD[b]	46.7 ± 29.9
Patients with indurations or panniculitis/lipoatrophy, *n* (%)[c]	
Indurations	50 (71.4)
Panniculitis/lipoatrophy	58 (82.9)

i.m. Intramuscular, *s.c.* subcutaneous, *SD* standard deviation

[a] Multiresponse variable, patients may have received more than one therapy

[b] Missing data, $n = 20$

[c] Multiresponse variable, patients may have had indurations and/or panniculitis/lipoatrophy

Safety

Endermology sessions were well tolerated; only some pain and discomfort were reported by eight (11.4%) and three (4.3%) patients, respectively. Local blotch/swelling and transient bruise were each reported in one (1.4%) patient. Seven (10.0%) patients complained about the logistics of endermology administration (i.e., the need to go to the hospital/clinic or timetables for endermology sessions).

DISCUSSION

We provide the largest evidence currently available about the effect of endermology on indurations and panniculitis/lipoatrophy occurring during long-term glatiramer acetate administration in patients with RRMS. The administration of 12 endermology sessions reduced the number of indurations, leading to their complete disappearance in 60% of patients. Even though some areas of panniculitis/lipoatrophy still remained, endermology helped to reduce their number and improve skin condition. In fact, the vast majority of patients felt satisfied or very satisfied with endermology effect and considered it useful or very useful. These findings are consistent with previous assessments of endermology for the treatment of indurations or panniculitis/lipoatrophy in two small series of patients receiving glatiramer acetate [24, 25]. Cutaneous benefits began to be visible after six sessions [24] and, after 12 sessions, endermology enabled indurations to be reduced or even eliminated from the most frequent injection sites and panniculitis/lipoatrophy to be ameliorated [25]. Based on these results, further benefits that might even lead to the complete recovery from panniculitis/lipoatrophy are likely to be achieved by increasing the number of endermology sessions.

Indurations and panniculitis/lipoatrophy are common events after the administration of injected therapies, especially subcutaneous ones. Many factors may be involved in their

Table 2 Changes in indurations during endermology treatment

Characteristics of indurations	Baseline visit	Final visit
Patients with indurations	$n = 50$	$n = 20$*
Number of indurations, mean ± SD[b]	4.2 ± 3.6	3.7 ± 3.4*
Location of indurations, *n* (%)[cd]		
Abdomen	30 (60.0)	7 (35.0)[a]
Thighs	22 (44.4)	5 (25.0)[a]
Buttocks	19 (38.0)	4 (20.0)[a]
Arms	17 (34.0)	3 (15.0)[a]

SD Standard deviation

* $p < 0.001$ versus baseline

[a] Non-significant differences versus baseline

[b] Missing data: baseline visit, $n = 2$

[c] Missing data: baseline visit, $n = 3$; final visit, $n = 1$

[d] Multiresponse variable, patients may have had indurations in more than one location

development, including the inflammatory local reactions derived from the injection itself, fat tissue damage caused by cytokine release triggered by needle trauma or specific drug-related mechanisms [24]. Histologic studies at the sites of glatiramer acetate injection revealed inflammatory infiltrates, which mainly consisted of lymphocytes and macrophages engulfing lipids from destroyed fat cells, and increased fibrosis in subcutaneous tissues [2, 26, 27]. Endermology has been reported to contribute to reducing inflammation and indurations in patients with morphea [22]; to ameliorate indurations and improve suppleness in areas of radiation-induced fibrosis [18]; and to improve subcutaneous fibrosis and lymphovenous circulation in patients with lymphedema [19–21]. In addition, endermology has also been used to enhance skin texture or body contouring by mobilizing subcutaneous fat [12–17].

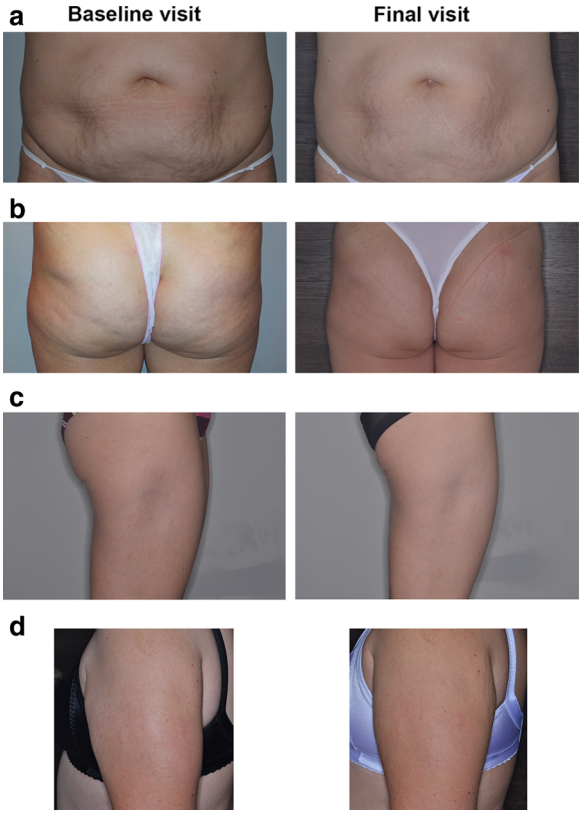

Fig. 3 Changes in panniculitis/lipoatrophy on **a** abdomen, **b** buttocks, **c** thighs and **d** arms

The underlying mechanism of endermology involved in such improvements is still unclear, but it is believed to be associated with the pressure exerted on subcutaneous tissues and the stimulation of lymphatic flow while the skinfold is created by the suction system and moving rollers of the treatment head [13]. In fact, forces on the skinfold have been shown to induce architectural changes resulting from redistribution of collagen bands within the subcutaneous layer in the swine model [8]. Ultrasound assessments on human volunteers reported structural changes in the interface of the dermis and fat tissue, with a reduced surface area during the endermology treatment that led to an improved cellulite appearance of the skin [6, 15]. Endermology may contribute to this restructuring by stimulating fibroblasts, as

Table 3 Summary of patients' satisfaction and perceived usefulness of endermology treatment

Satisfaction/ usefulness	Patients with indurations ($n = 50$)	Patients with panniculitis/ lipoatrophy ($n = 58$)
Satisfaction, *n* (%)		
Very satisfied	30 (60.0)	30 (51.7)
Satisfied	19 (38.0)	27 (46.6)
Not satisfied	1 (2.0)	1 (1.7)
Usefulness, *n* (%)		
Very useful	28 (56.0)	29 (50.0)
Useful	21 (42.0)	28 (48.3)
Not useful	1 (2.0)	1 (1.7)

increased fibroblast number and nuclei surface have been reported after 14 sessions [9]. Another study carried out in pigs and human volunteers suggested that endermology might also alter the physiologic and metabolic activity of fat, based on its findings with regard to redistribution of free fat, enhanced blood perfusion and lymphatic drainage within subcutaneous fat tissues [7]. Several studies have supported the effect of endermology on subcutaneous fat and/or fluid mobilization using different objective methods [10, 11, 19–21]. In addition, a recently published study showed that endermology promotes changes in the expression of genes involved in metabolic pathways—especially of those that enhance lipolytic response—and in chemokine signaling pathways [10]. Nonetheless, other factors such as circulating estradiol might also play a role in the mechanism of action of endermology [28].

The effects described above might have contributed to enhancing the skin condition of our patients, which in turn enabled glatiramer acetate tolerance to be improved, especially in terms of pain. A similar improvement in skin condition accompanied by improved tolerance to glatiramer acetate was also reported in our previous pilot experience on the effect of endermology on indurations and panniculitis/lipoatrophy in patients receiving glatiramer acetate [25]. Another small patient series assessing its effect on injection-induced lipoatrophy at glatiramer acetate injection sites also showed improved skin appearance and supported the contribution of endermology to maintaining glatiramer acetate treatment [24]. Indurations and areas of panniculitis/lipoatrophy need to be avoided as injection sites, which may considerably limit their rotation and even cause the remaining sites to become more sensitized or damaged. In addition, endermology has successfully been used to reduce pain in patients with fibromyalgia [23] or those undergoing colectomy [29]; though local sensory stimulation might have played a role, the mechanism of action is not yet known. Endermology therefore not only represents a useful tool to reduce injection-site reactions, but it may also help patients to continue glatiramer acetate treatment. Thus, it might contribute to increasing the chances of optimal long-term treatment of multiple sclerosis. The Food and Drug Administration recently approved a new formulation of glatiramer acetate that contains a higher dose (40 mg) and is administered three times per week. Even though its safety profile has shown to be consistent with that of the approved once-daily (20 mg) formulation and may even lead to potentially reduce injection-site reactions [30], further observation is needed to confirm its specific effects on skin and subcutaneous tissues. This new formulation of glatiramer acetate is not yet available in Europe.

Endermology has been widely shown to have excellent tolerance when used either to ameliorate subcutaneous reactions during glatiramer acetate treatment [24, 25], to improve skin texture/body contour [6, 15–17] or to treat other conditions [19, 22, 29]. The only complaints consisted of localized stinging pain, redness, bruising or increased urination likely related to fluid mobilization [15, 17, 19]. Our results also support the good tolerance of endermology, as only eight patients reported some pain, three patients some discomfort and two patients local blotch/swelling or transient bruise.

Project limitations such as its non-randomized open-label design and the absence of a comparator group should be considered when interpreting these results. Although no comparator group was included in our project, the detection of significant improvements from baseline allowed assessment of the benefit obtained after 12 endermology sessions. In addition, potential biases derived from the open-label design were minimized using objective measurements whenever possible and photographic assessments. Thus, we believe that this project provides physicians with valuable information to be taken into account when treating multiple sclerosis with glatiramer acetate in clinical practice.

CONCLUSION

In conclusion, our project provides the largest evidence currently available on the beneficial effect of endermology to treat indurations and panniculitis/lipoatrophy associated with the long-term administration of glatiramer acetate in patients with RRMS. Twelve endermology sessions administered over 6 weeks enabled patients to reduce the number of indurations and areas of panniculitis/lipoatrophy, as well as to achieve a complete recovery from indurations and improved skin condition. Patients were highly satisfied with the results obtained with endermology, though further sessions might still be needed to completely recover from all areas of panniculitis/lipoatrophy. Endermology effects on indurations and panniculitis/lipoatrophy allowed the recovery of injection areas and even enhanced glatiramer acetate tolerance, which represent conspicuous benefits in terms of treatment adherence and maintenance of long-term therapy. Nevertheless, further research is needed to confirm our findings, as well as to determine the duration of endermology effect and the most appropriate time interval for subsequent supplemental endermology sessions in patients receiving glatiramer acetate for multiple sclerosis.

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Conflict of interest. CM has acted as a board member for Merck and has received honoraria as a consultant and speaker fees and support for traveling to meetings from the following companies: Novartis, Biogen, Merck, Teva, Glaxo, and Genzyme. LVC has acted as a board member for Teva and has received honoraria as a speaker for Novartis, Biogen, Merck, and Teva. RDN has received honoraria as a consultant and speaker fees and support for traveling to meetings from: Novartis, Biogen, Merck, Teva, Glaxo, and Genzyme. DR has received honoraria as a consultant and speaker fees and support for traveling to meetings from the following companies: Novartis, Biogen, Merck, Teva, Glaxo, and Genzyme. PFM is an employee of Teva Pharma Spain, who works at the Medical and HEOR Department. RSR is an employee of Teva Pharma Spain, who works at the Medical and HEOR Department.

Compliance with ethics guidelines. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000 and 2008. Informed consent was obtained from all patients included in the project.

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