

Contribution of Endermology to Improving Indurations and Panniculitis/Lipoatrophy at Glatiramer Acetate Injection Site

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ABSTRACT

Introduction: Endermology is a mechanical massage therapy that enables fat mobilization and body contouring. The authors' aim was to assess the effect of endermology on indurations and panniculitis/lipoatrophy associated with subcutaneous administration of glatiramer acetate in patients with multiple sclerosis (MS).

Methods: This was a multicenter pilot experience carried out in patients with MS treated with glatiramer acetate who showed indurations and/or panniculitis/lipoatrophy at the injection site. Patients underwent endermology and glatiramer acetate treatment according to clinical practice. The primary endpoint was the change in indurations and/or panniculitis/lipoatrophy after 12 endermology sessions.

Results: Between April and July 2011, a total of 13 evaluable patients were included (mean age, 40.7±3.1 years; female, 100%; white, 100%; mean MS duration, 10.1±2.3 years; previous MS treatment, 46.2%; mean glatiramer acetate treatment duration, 27.3±9.5 months). Eleven patients (84.6%) showed local indurations (mean diameter, 3.4±0.5 cm; mean number, 9.0±1.0) and six patients (46.2%) areas of panniculitis/lipoatrophy (mean number, 5.0±1.1). After 12 endermology sessions, patients with indurations reported having experienced a reduction in size (10 patients [90.9%]; mean diameter, 0.1±0.05 cm; $P<0.001$) and number of indurations (nine patients [81.8%]; mean number, 2.3±1.1; $P<0.005$). These indurations completely disappeared from arms, thighs, buttocks, and abdomen in six (75.0%), six (75.0%), two (50.0%), and three (42.9%) patients,

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respectively. Three of these patients (27.3%) recovered from all indurations. Although panniculitis/lipoatrophy did not completely disappear, all patients reported improvements. Most patients with indurations (63.6%) felt very satisfied and considered endermology very useful for reducing indurations. All patients with panniculitis/lipoatrophy were satisfied and considered to be endermology useful in improving it. In addition, endermology enabled glatiramer acetate tolerance to be improved in most patients (60.0%).

Conclusion: Endermology may contribute to improving indurations and panniculitis/lipoatrophy at the site of subcutaneous injection of glatiramer acetate in patients with MS, enabling areas of injection to recover, and treatment tolerance to increase.

Keywords: Endermology; Glatiramer acetate; Induration; Injection; Lipoatrophy; Multiple sclerosis; Panniculitis; Recovery

INTRODUCTION

Glatiramer acetate is a mixture of synthetic polypeptides, obtained by polymerizing l-glutamic acid, l-alanine, l-tyrosine, and l-lysine, that modulates the immunologic pathways involved in the pathogenesis of multiple sclerosis and stimulates the secretion of brain-derived neurotrophic factor in the central nervous system [1–3]. The drug is indicated for reducing the frequency of relapses in ambulatory patients with relapsing–remitting multiple sclerosis, administered once daily as a subcutaneous injection. Although administration of glatiramer acetate has widely proved to be well tolerated, injection-site-related reactions such as pain, inflammation, or indurations have often been reported as the most frequently observed adverse events [4]. These

injection-site-related reactions occur regardless of injection technique and last from several hours to several days. Persistent indurated areas develop that are avoided as injection sites, diminishing the rotation of injection sites and leading to more frequent injecting at other sites, in turn increasing the probability of panniculitis and lipoatrophy at those sites. Persistent panniculitis at the injection sites may potentially lead to localized lipoatrophy [5, 6], which was initially described as a rare event, but later reported in up to 45% of the patients receiving treatment with glatiramer acetate [7]. Since no known treatment for lipoatrophy has been described, the only way to minimize it appears to be to use appropriate injection techniques [4]. Thus, even though injection-site lipoatrophy is not a serious adverse event, it often causes distress and concern that may even lead to discontinuation of glatiramer acetate treatment, despite its being effective against multiple sclerosis.

In the late 1970s, Louis Paul Guitay (LPG) suffered muscle and skin damage as a result of a motor vehicle accident. The scarring that resulted was treated by therapeutic massage to soften this tissue and restore muscle function. These massage sessions, which lasted 3–4 hours a day, consisted of rigorous routines of manually rolling the skin in order to regain its elasticity. Guitay was dissatisfied with this massage because the therapy was time-consuming, labor-intensive, and the outcome varied widely based on the skill of the individual therapist. As a result, Guitay designed the Endermologie® system (LPG Systems, Valence, France). Endermologie is a nonsurgical therapy consisting of an intense and deep massage of skin and subcutaneous tissue, performed using a treatment head composed of two motorized rolls. As the practitioner moves the head across the skin, creating a fold with the help of a vacuum, the surface of the skin

is stimulated and fat distribution is altered. This technique is contraindicated in patients with active cancer and peripheral venous insufficiency. The technique also involves some adverse events, such as pain, bruises, and the time of exposure, though these have to be considered subjective to the patient's tolerance of the technique. The underlying mechanism of action appears to be stretching of the vertical connective tissues and stimulation of lymphatic flow as a result of the pressure difference and the rolling motion [8]. Additionally, the positive pressure from rolling and the negative pressure from suction are believed to cause sublethal damage to subcutaneous adipocytes, which subsequently go through a process of healing that results in an improved distribution of subcutaneous fat and body contour [8]. For this reason, this technique has been widely used to soften scars, improve skin texture, and enhance body contour.

However, endermology has also been reported to be beneficial in treating radiation-induced skin fibrosis [9], secondary arm lymphedema [10], and morphea [11], and improving postoperative results after external ultrasound-assisted lipoplasty [12]. In addition, a recently published study suggests its potential beneficial effect on glatiramer acetate injection-induced lipoatrophy in patients with multiple sclerosis, which not only might improve lipoatrophic areas, skin appearance, and body contour, but might also help patients to continue glatiramer acetate treatment [13].

In view of the above, the aim of the present authors was to expand the information available regarding the use of endermology in patients with multiple sclerosis, assessing its effect on cutaneous side effects such as local indurations and panniculitis/lipoatrophy associated with subcutaneous administration of glatiramer acetate.

MATERIALS AND METHODS

This multicenter pilot study was conducted in 10 Spanish cosmetic clinics. Patients aged between 18 and 65 years who were diagnosed with relapsing–remitting multiple sclerosis and undergoing treatment with subcutaneous glatiramer acetate were eligible to participate. Eligible patients also had to have local indurations, panniculitis, or lipoatrophy associated with the subcutaneous administration of glatiramer acetate. Exclusion criteria were any active malignant neoplasm and peripheral venous insufficiency.

Patients who gave their written informed consent for the technique underwent endermology treatment for 30–40 minutes once or twice a week according to clinical practice. The LPG Cellu M6 Keymodule® (LPG Systems) was used during endermology sessions. Glatiramer acetate (Copaxone®; Teva Pharmaceuticals Ltd., London, UK) was administered from commercial sources according to routine clinical practice conditions. The commercially available form is a solution for injection containing 20 mg of glatiramer acetate, supplied in a refrigerated, prefilled syringe for subcutaneous administration once daily.

Patients were assessed at the beginning of endermology treatment (baseline assessment) and after receiving 12 endermology sessions (final assessment). Changes in indurations and panniculitis/lipoatrophy were evaluated by clinical examination and digital photography. There was no control group in this study; each patient was her own control, with the authors comparing the last data available with the patient's initial data. Patient satisfaction and perception of the usefulness of the technique were assessed according to three-point scales ranging from very satisfied/useful to not satisfied/useful.

Improvements in cutaneous lesions were also assessed according to changes in terms of injection-site reactions reported by patients.

The primary efficacy endpoint was the change in local indurations or panniculitis/lipoatrophy associated with subcutaneous administration of glatiramer acetate from baseline to final assessment. The secondary endpoints were patient satisfaction and perception of usefulness as recorded at the moment of the final assessment, and improved tolerance to glatiramer acetate. Descriptive analyses of these endpoints were performed.

STATISTICAL ANALYSIS

Quantitative variables were described using mean and standard error (SE), and qualitative variables using frequencies and valid percentages. Comparisons of the number of indurations and their diameter between baseline and final assessments were performed using Student's *t*-test, and a significance level of 0.05 was used for statistical testing. The statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS) version 18.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Between April 2011 and July 2011, a total of 16 patients were screened, two of whom were rejected by screening: one suffered from an active malignant neoplasia and the other from peripheral venous insufficiency. Another patient decided to withdraw before starting endermology treatment. Therefore, the evaluable population comprised a total of 13 patients (mean age, 40.7±3.1 years; female, 100%; white, 100%; mean duration of multiple sclerosis, 10.1±2.3 years; previous multiple

sclerosis treatment, 46.2%; mean glatiramer acetate treatment duration, 27.3±9.5 months). One of the 13 withdrew before the final assessment and was lost to follow-up. Baseline characteristics of the evaluable patients are described in Table 1. Eleven patients (84.6%) showed local indurations and five (38.5%) showed panniculitis/lipoatrophy at the injection site of glatiramer acetate. The former group had a mean (± SE) number of 9.0±1.0 indurations, with a mean (± SE) diameter of 3.4±0.5 cm, mainly located on arms and thighs (nine patients [82%] each), followed in order of frequency by abdomen (eight patients, 73%) and buttocks (five patients, 45%) (Fig. 1). The latter group showed a mean (± SE) number of 5.0±1.1 areas of panniculitis/lipoatrophy, which were primarily located in thighs (four patients, 80%), but also

Table 1 Baseline patient characteristics (*n*=13)

Patient characteristics	Value
Mean age, years (± SE)	40.7±3.1
Female, <i>n</i> (%)	13 (100)
White, <i>n</i> (%)	13 (100)
Mean duration of multiple sclerosis, years (± SE)	10.1±2.3
Patients previously treated for multiple sclerosis, <i>n</i> (%)	6 (46.2)
Previous treatments for multiple sclerosis, <i>n</i> (%) ^a :	
Interferon beta-1a s.c.	4 (30.8)
Interferon beta-1b s.c.	2 (15.4)
Interferon beta-1a i.m.	1 (7.7)
Mean duration of glatiramer acetate treatment, months (± SE)	27.3±9.5
Patients with indurations, <i>n</i> (%)	11 (84.6)
Patients with panniculitis/lipoatrophy, <i>n</i> (%)	6 (46.2)

i.m. intramuscular, *s.c.* subcutaneous, *SE* standard error

^aMultiresponse variable

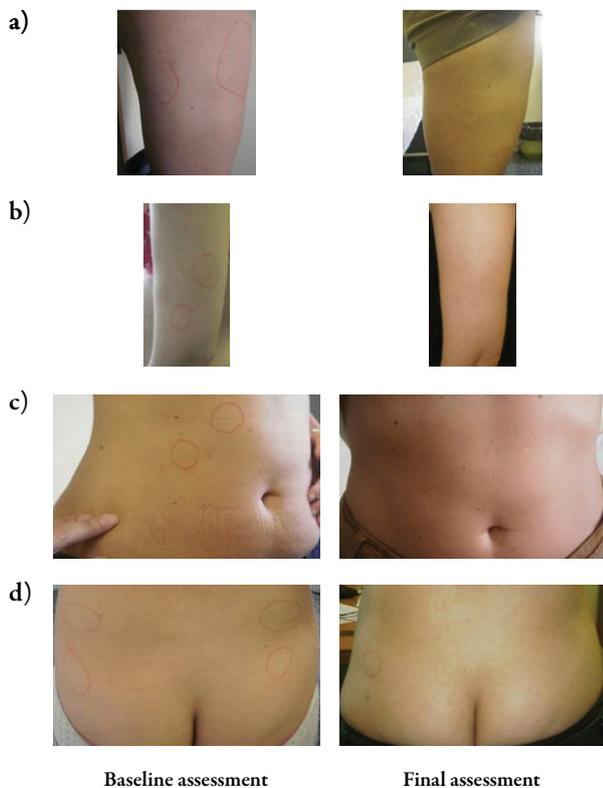


Fig. 1 Indurations on thighs (a), arms (b), abdomen (c), and buttocks (d)

appeared in the abdomen (two patients, 40%), buttocks (two patients, 40%), and arms (one patient, 20%) (Fig. 2).

After 12 endermology sessions, patients with indurations reported having experienced a reduction in size (10 patients, 90.9%) and number of indurations (nine patients, 81.8%) (Fig. 1), reaching a statistically significant lower mean (\pm SE) diameter of 0.1 ± 0.05 cm ($P < 0.001$) and a lower mean (\pm SE) number of 2.3 ± 1.1 indurations ($P < 0.005$). In fact, complete disappearance of indurations from arms, thighs, buttocks, and abdomen was reported in six (75.0%), six (75.0%), two (50.0%), and three patients (42.9%), respectively; and a complete recovery from all indurations was observed in three patients (27.3%). Even though panniculitis/lipoatrophy did not completely disappear, all patients showing areas of panniculitis/

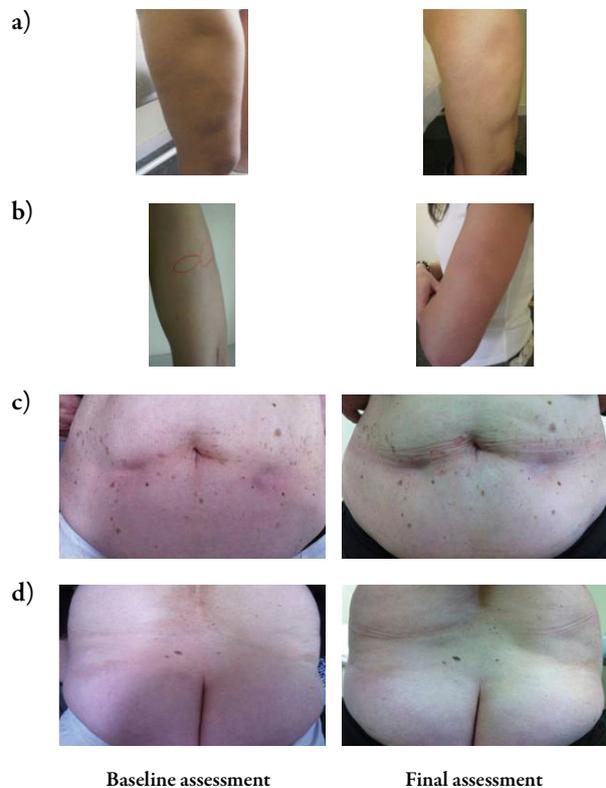


Fig. 2 Panniculitis/lipoatrophy on thighs (a), arms (b), abdomen (c), and buttocks (d)

lipoatrophy at baseline reported improvements following endermology treatment (Fig. 2).

Most patients with indurations felt very satisfied with the results achieved by endermology (seven patients, 63.6%), and also considered the treatment very useful for reducing indurations related to glatiramer acetate administration (seven patients, 63.6%) (Table 2). In addition, all patients with panniculitis/lipoatrophy were satisfied with endermology and considered it useful for improving the condition (Table 2).

At the final assessment none of the patients studied complained of any adverse events (pain, subcutaneous changes except for a reduction in and redistribution of fatty tissues) and the technique was well tolerated. Endermology was also reported to enhance tolerance to glatiramer acetate

Table 2 Endermology treatment: satisfaction and perceived usefulness

Satisfaction and perceived usefulness	Patients with indurations (<i>n</i> =11)	Patients with panniculitis/lipoatrophy (<i>n</i> =6)
Satisfaction, <i>n</i> (%) ^a :		
Very satisfied	7 (63.6)	0 (0.0)
Satisfied	2 (18.2)	5 (100)
Not satisfied	2 (18.2)	0 (0.0)
Perceived usefulness, <i>n</i> (%) ^a :		
Very useful	7 (63.6)	0 (0.0)
Useful	2 (18.2)	5 (100)
Not useful	2 (18.2)	0 (0.0)

^aMissing data in patients with panniculitis/lipoatrophy, *n*=1

administration in six patients (60.0%) (one patient's data omitted) at the final assessment, was considered less painful, and decreased cutaneous reactions.

DISCUSSION

The results of this pilot study show that endermology treatment can contribute to improving indurations and panniculitis/lipoatrophy associated with subcutaneous administration of glatiramer acetate in patients with relapsing–remitting multiple sclerosis. Reductions in the size and number of indurations were observed in the large majority of patients, allowing indurations to disappear from the most frequent injection sites and even leading to their complete recovery in more than one fourth of the patients. Although the areas of panniculitis/lipoatrophy did not disappear, endermology treatment contributed to their improvement. Thus, the recovery or improvement achieved by endermology on indurations and panniculitis/lipoatrophy also enabled of injection areas to recover, and the great majority of patients felt satisfied with the results achieved. These results are in line with those reported by the only other

study previously carried out to assess the effect of endermology in patients with multiple sclerosis [13]. Patients included in this study showed areas of lipoatrophy at the sites of glatiramer acetate injection on thighs, upper arms, and the periumbilical area, where they had complained of transient burning and pain, or induration. Cutaneous benefits began to be visible after 3 weeks of twice-weekly endermology sessions, and after 3 months all patients agreed to continue with both immunomodulatory treatment and once-monthly endermology sessions to maintain the benefit achieved in cutaneous appearance. Magnetic resonance imaging did not show major subcutaneous changes in subcutaneous fat tissues, but the improvement achieved in body contour and skin appearance helped patients to continue their therapy with glatiramer acetate.

Although the information currently available in patients with multiple sclerosis is very limited, the beneficial effect of endermology on skin and subcutaneous tissues has been previously reported in other patient populations. Endermology was originally developed by LPG to standardize physical therapy and facilitate his own recovery from burns and traumatic scars.

However, endermology has not only been shown to soften burn scars [14], it has also enabled cellulite to be reduced [8, 15–17]. In addition, endermology has been used after liposuction to improve the final outcome [18, 19], assisting the distribution of residual fat and mobilizing the interstitial edema fluid into the capillary circulation [19]. Improved postoperative results were reported when endermology was used after ultrasound-assisted lipoplasty, in terms of reduction in cellulite appearance and body contouring [12]. Its use in patients with secondary arm lymphedema also led to reductions in edema volume, improvements in fibrotic indurations in some lymphatic territories, and an increase in patient-reported range of arm movement [10]. Additionally, endermology has been shown to enable large improvements in the clinical appearance of lesions and indurations and in pain in patients with morphea [11]. Similarly, patients with cutaneous fibrosis after breast cancer treated with radiotherapy also showed decreased erythema, pain, pruritus, and feeling of induration of the skin after receiving endermology treatment [9].

Lipoatrophy is a localized loss of subcutaneous adipose tissue without significant inflammation. In the literature of biopsied cases, half of the patients treated with glatiramer acetate have typical epidermal and dermal changes of discoid lupus erythematosus, but in the other half of the cases the changes are confined to the subcutaneous fat, with no anomalies in the dermis or epidermis [13]. The beneficial effect of endermology on cutaneous reactions might be associated with architectural changes deriving from accumulation of collagen bands in the subdermal tissue layer [20], modification of the physiological and metabolic activity of adipose tissue [20, 21], or increased perfusion [19, 21] and lymphatic drainage [21]. However, its mechanism of action is not completely

understood, and many other factors, such as plasma levels of estradiol [22] or expression of genes involved in metabolic pathways, may also have an influence [23].

Additionally, in the present study, endermology contributed to an increased tolerance to glatiramer acetate treatment in nearly two thirds of patients. This improved tolerance is especially relevant in patients with multiple sclerosis because, even though cutaneous reactions, such as indurations or panniculitis/lipoatrophy, are not usually serious, they often cause distress that may lead patients to discontinue effective treatments against the multiple sclerosis. Therefore, any improvement in treatment-related reactions might also improve patients' adherence to multiple sclerosis treatment. This is also in line with the only other previous report of endermology use in patients with multiple sclerosis, which concluded that endermology helped patients to continue with their glatiramer acetate treatment [13]. However, further studies are still required.

Several limitations should be considered when interpreting the results from the present study. These limitations include the small sample size and the lack of a comparator group. In addition, potential biases derived from the open-label design cannot be ruled out. Even though these results should be interpreted with caution and cannot be generalized to the whole patient population, the authors believe that they provide helpful information for further research about the effect of endermology on cutaneous adverse events associated with subcutaneous administration of glatiramer acetate in patients with multiple sclerosis.

CONCLUSION

The present results suggest the usefulness of endermology for improving indurations and panniculitis/lipoatrophy associated with

subcutaneous administration of glatiramer acetate in patients with relapsing–remitting multiple sclerosis. Endermology enabled the recovery of injection areas for further administration of multiple sclerosis treatment and even improved tolerance to subcutaneous administration of glatiramer acetate. In addition, the great majority of patients felt satisfied with the results achieved by endermology and considered it useful for improving indurations and panniculitis/lipoatrophy. However, the present results should still be regarded as preliminary and need to be confirmed in controlled studies carried out in larger patient populations.

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The authors declare that Pablo Francoli Martínez and Rainel Sánchez-De la Rosa are employees of the Medical Department at TEVA Pharma S.L.U. The rest of the authors have no conflict of interest to disclose.

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PRESENTATION OF DATA AT SCIENTIFIC MEETINGS

Preliminary results were partially presented at the following scientific meeting: XVIII Reunión

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