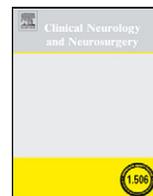




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# Endermology: A treatment for injection-induced lipoatrophy in multiple sclerosis patients treated with sub cutaneous glatiramer acetate

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### ABSTRACT

**Objective:** To evaluate sessions of endermology (LPG) on patients with lipoatrophy, due to GA injections in an open-labelled study.

**Background:** Glatiramer acetate (GA) is an immunomodulatory drug, with an excellent safety profile, that is currently used for treatment of multiple sclerosis and is administered as daily subcutaneous injections of 20 mg. The most common adverse effects, which occur in approximately 20–60% of the patients, include pain, inflammation and induration at the injection sites. Another adverse effect is frank panniculitis followed by localized lipoatrophy at the injection sites, which has been described in half of the patients receiving treatment with glatiramer acetate injections. No treatment has been found for established lipoatrophy.

**Patients and methods:** All patients underwent LPG twice a week during 30 min. A cycle of two months was initially proposed. If the patient was satisfied with the result, sessions were continued with one session per week until the 4th month.

**Results:** Eight Patients treated with GA and presenting with lipoatrophy were prospectively recruited. None of them complained of any adverse events. After 8 weeks of treatment, all had a visible reduction of lipoatrophic area. MRI showed no major subcutaneous changes except for a reduction in and repartition of fatty tissues.

**Conclusion:** The LPG cellu M6 keymodule is a mechanotransduction machine that stimulates the skin's surface in triggering cells to activate lipolysis and collagen production. It has never been used for treatment of lipoatrophy due to drug treatment or in specific diseases associated with lipoatrophy (diabetes, HIV). The prevention and management of lipoatrophy includes patient education, regular examination and manual palpation of all injection sites. LPG endermology can help patients to resolve this side effect and to continue immunomodulatory treatment.

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## 1. Introduction

Glatiramer acetate (GA) is an immunomodulatory drug containing four naturally occurring amino acids: L-glutamic acid, L-alanine, L-tyrosine, and L-lysine. It simulates myelin basic protein and is currently used for treatment of multiple sclerosis because it has been shown to be effective in reducing relapse and in diminishing the disability of patients with relapsing–remitting multiple sclerosis [1]. The drug is administered in daily subcutaneous injections of 20 mg with an excellent safety profile. The most common adverse effects, which occur in approximately 20–60% of the patients, include pain and inflammation at the injection sites, all of which spontaneously disappear within hours or a few days. Another

adverse effect is frank panniculitis followed by localized lipoatrophy at the injection sites, which has been described in half of the patients receiving treatment with glatiramer acetate injections [2–6]. In reports of this adverse effect, the authors only described lipoatrophy, in some cases even without histopathologic study of the lesions [2,4] and in others with vague histopathologic descriptions of “inflammatory infiltrate involving the subcutaneous tissue” [3]. A recent report noted progressive lipoatrophy after cessation of GA injections [7].

## 2. Methods

Patients treated with GA and presenting with visible lipoatrophy were prospectively recruited. Informed consent explaining the aim of the visits, MRI procedures and LPG technique was signed. The LPG (Louis Paul Guitay) cellu M6 keymodule is a unique mechanotransduction machine (LPG endermology, USA). The treatment head stimulates the skin's surface and simultaneously signals to

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**Table 1**

Clinical characteristics of patients developing localized panniculitis at the sites of glatiramer acetate injections.

Case/age, y/sex	EV/33/F	DD/52/F	GMP/38/F	LP/46/F	ZA/36/F	FM/37/F	SG/32/F	VM/45/F
RRMS duration, years	17	12	6	29	6	6	4	6
Other SC treatments before GA, years	Yes IFNb 1b 6	Yes IFNb 1b 2	No	No	Yes IFNb 1a 2	No	No	Yes IFNb 1b 1
GA treatment duration, years	8	5	1	3	1	4	3	5
GA treatment ongoing	Yes	No	No	Yes	Yes	No	No	Yes
Erythematous nodule after GA injections	Yes	Yes	Yes	EOD	Yes	EOD	Yes	Yes
Panniculitis	Yes	Yes	Yes	Yes	Yes	EOD	Yes	Yes
Administered topical treatments	NSAI gel Warm patch	NSAI gel	Cold patch	No	NSAI gel	No	NSAI gel	No
Time Interval between first injection and development of lipoatrophy, yrs	5	1	0.2	0.2	0.5	3	0.6	0.5
Highest measurement of lipoatrophy cmxcmxcm	18/12/2	6/4/0.5	15/10/0.5	20/10/1.2	5/8/0.5	10/5/0.4	10/7/0.8	12/12/1.2
Time between lipoatrophy and LPG (months)	36	108	14	64	2	26	45	52
Visual analogue scale	9/7/3	9/5/4	6/4/2	9/6/4	8/6/4	7/5/3	8/5/3	8/6/4
Thigh diameter D0, D30, D60 (cm)	47/49/50	57/55/53	52/51/50	50/50/51	57/56/54	48/48/48	50/49/48	55/55/54.5
Weight D0, D30, D60 (kg)	50/51/50	73/73/72	53/54/53	63/64/64	67/65/65	53/54/54	57/57/57	59/57/57

EOD: every other day; NSAI: non-steroid anti-inflammatory.

cells that trigger targeted actions (lipolysis and collagen production) [8]. All patients underwent LPG therapy twice a week during 30 min. A cycle of two months was initially proposed. If the patient was satisfied with the result continuation with one session per week until the 4th month was proposed. All patients had been instructed initially in self-injection techniques to assure the safe administration of a daily subcutaneous injection of 20 mg of glatiramer acetate. The commercially available form is a white, sterile, lyophilized powder containing 20 mg of glatiramer acetate and 40 mg of mannitol supplied in refrigerated single-use vials for subcutaneous administration after reconstitution with sterile water. As a regular procedure, prefilled syringe packages from the refrigerator were kept at room temperature for 20 min before injection to allow the solution to warm to room temperature. The patients injected the drug into the subcutaneous fat at the recommended sites (periumbilical skin, upper side aspects of arms, hips, and front of thighs) and they did not use any site more than once each week. The patients denied constitutional symptoms, trauma, or other skin problems, and they were not taking any other medications at the time. Four patients received previous treatment with subcutaneous injections of interferon beta, but this therapy had been withdrawn at least 1 month before treatment with glatiramer acetate injections was initiated. Patients visited monthly during 6 months. Clinical measurements, visual analogue scales, pictures and MRI were performed at baseline, month 2, 4 and 6. The MRI protocol was run on a Sigma 1.5 T (GE medical system, Milwaukee, USA), with axial T2-weighted sequences on lipodystrophic areas as

follow: TR/TE 2360/82.1 ms; thick: 3 mm, gap: 7 mm; field: 42 × 29.4; matrix: 288 × 256.

### 3. Results

The clinical characteristics of our series are summarized in Table 1. Briefly, all 8 patients were female, with an age range between 29 and 52 years (mean: 39.9 years). The instructions for preparation, storage, and injection of GA were verified and followed accurately, and the injection site was correctly rotated. In all cases, lipoatrophy developed in areas in which the patients had complained of transient burning and pain or induration. Routine laboratory tests were always normal, excluding systemic diseases.

All patients showed asymptomatic, well-circumscribed skin depressions on the lateral side of the thighs, upper arms, and the peri-umbilical area, the usual injection sites. The overlying skin did not exhibit inflammation, sclerosis, or hyperpigmentation. The lesions developed generally with preceding inflammation and were about 12–60 cm<sup>2</sup> in area and 1–2 cm deep (Fig. 1). They were located at the injection sites, and all patients developed subcutaneous erythematous nodules in several areas (periumbilical skin, upper side aspects of arms, hips, and front of thighs) during treatment. Only occasionally, the glatiramer acetate injection was followed by a transient burning sensation, mild pain, and wheals. The duration of glatiramer acetate treatment before localized panniculitis at the injection sites was 1–2 months. In all patients,



**Fig. 1.** Persistent lipoatrophy on the top of the right thigh (right), left arm (middle) and peri-umbilical area (left).

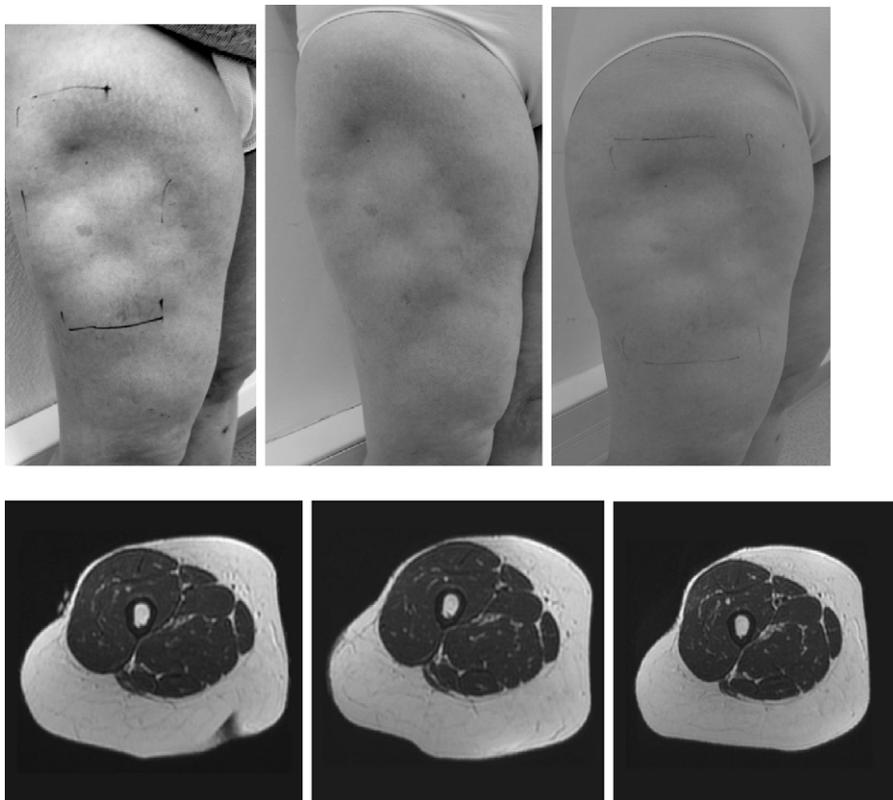


Fig. 2. Result of LPG treatment on lipoatrophy (A) and MRI (B) on the top of the right thigh at baseline (right), after 4 weeks (middle) and 8 weeks (left).

residual lesions of lipoatrophy developed in previously inflamed sites without hyperpigmentation.

The LPG sessions were well tolerated without pain. All patients reported to be well after each session and cutaneous benefits begun to be visible after 3 weeks without significant changes in thighs diameter or weight (Fig. 2A and Table 1). MRI follow-up showed no difference in the thickness of sub-cutaneous signal (Fig. 2B). After 3 months, all the patients agreed to continue both their immunomodulatory treatment and LPG sessions once a month to keep benefit on cutaneous aspect. Considering the visual analogue scale use, patients and medical observers both reported a mean improvement of more than 60% of the cutaneous aspect (Table 1). After a mean of one year follow-up, no adverse event were reported due to LPG sessions.

#### 4. Discussion

LPG endermology was originally developed in the late 70s in France by Louis Paul Guitay to soften scars and standardize physical therapy. However, patients treated with the LPG machine showed improvement in body contour and skin texture. Since then, endermology has been used in France, in the United States, and many other nations as an alternative method to altering fat distribution in the subcutaneous plane [8]. Because this technique is operator dependant, which may explain the variable results that have been reported, the opinions as to its efficacy in the plastic surgical community vary widely, from those who condemn it openly without having any experience with it, to enthusiastic believers.

Concerning injection-site reactions to GA, erythema (66% of patients), inflammation (49%), pain (73%), and pruritus (40%) are the most commonly described local side effects. Lipoatrophy and localized panniculitis have been described as complications of daily subcutaneous glatiramer acetate injections for the treatment of relapsing–remitting multiple sclerosis. It was initially reported to

be a relatively rare event; however, more recent studies indicate that it affects 45–64% of MS patients treated with GA [4]. Drago et al. [6] were the first authors to point out localized lipoatrophy at the sites of subcutaneous injections in 6 female patients with multiple sclerosis receiving treatment with glatiramer acetate. They reported that the lesions developed without any preceding inflammation and the overlying skin did not exhibit inflammation, sclerosis, or hyperpigmentation. Finally, Edgar et al. [4] described 5 female patients with lipoatrophy at the sites of glatiramer acetate injections but a biopsy was performed only in two cases.

Lipoatrophy is a localized loss of subcutaneous adipose tissue without significant inflammation. It is a well-described and common reaction at injection sites. Most injection site reactions show involuntional lipoatrophy or a foreign body reaction. Other described histological reactions at injection sites include allergic contact dermatitis, lipogranulomas, local necrosis, sterile and infectious abscesses, necrotizing, necrobiotic and sarcoidal granulomas, cutaneous lymphoid hyperplasia, lupus profundus-like and morphea-like reactions.

Soos et al. [2] were the first to recognize a panniculitic stage previous to the lipoatrophy that was induced by the glatiramer acetate injections. Lipoatrophy secondary to subcutaneous injections has been described in conjunction with several drugs, including insulin, corticosteroids, vasopressin, antibiotics, human growth hormone, iron dextran, diphtheria–pertussis–tetanus immunization serum, and antihistamines. The mechanism is probably different for each drug and predominates in females, probably due to specificities in fat tissues [9–11]. Trauma alone, like acupuncture, may induce lipoatrophy, possibly via macrophage cytokines that enhance lipocyte catabolism and inhibit lipogenesis. In acupuncture-related lipoatrophy there is an involuntional pattern with thin and elongated fat lobules. Although different pathogenic mechanisms have been proposed for each of these drugs, lipoatrophy is the common late or residual stage of a previous drug-induced localized panniculitis.

In the literature on biopsied cases, in more than half of the GA treated patients, typical epidermal and dermal changes of discoid lupus erythematosus are described. These include atrophy of the epidermis, vacuolar change at the dermoepidermal junction, thickened basement membrane, interstitial mucin between collagen bundles of the dermis, and superficial and a deep perivascular inflammatory infiltrate of lymphocytes involving the dermis. These cases seem to be related to long-term GA treatment. In the other half of the cases, the changes are confined to the subcutaneous fat, with no anomalies in the dermis or epidermis. There is a mostly lobular panniculitis with an inflammatory infiltrate predominantly composed of lymphocytes. A characteristic feature, found in more than half of the patients, is the presence of lymphoid follicles. It could probably correspond to a Koebner phenomenon or isomorphic response, referring to skin lesions appearing on lines of trauma for patients with auto-immune diseases.

Generally, panniculitis appears within 2 months of starting glatiramer acetate therapy and spontaneous involution of panniculitis within 3 months of cessation of therapy is usual. It is likely that the drug itself induces a local inflammatory response as a result of a direct toxic effect on the adipocytes, and this inflammatory stage is followed by a hypersensitivity reaction and residual lipoatrophy. When glatiramer acetate injections are withdrawn, the cutaneous lesions disappear, but they recur when the injections are reintroduced. This adverse event appears to be independent of the injection technique. A recent case reported lipoatrophy that continued to progress despite cessation of GA in the absence of any other known causative agent [7]. MRI examination of lipoatrophy by other causes shows a reduction in the T2-hypersignal due to disappearance of subcutaneous fat. Limitations of our study include the low number of patients and the lack of cutaneous biopsy. As MRI follow-up showed no difference in the sub-cutaneous signal, we could not affirm that the visible improvement of lipoatrophy is partly due to effect on surrounding tissues. Nevertheless, LPG has a great impact on cutaneous aspect and helped patients to continue SC glatiramer injections.

The prevention and management of lipoatrophy include patient education, regular examination and manual palpation of all injection sites [4]. No treatment has been proposed when lipoatrophy is established. Even if, as expected, LPG induces no change of subcutaneous fat tissues on MRI, it helps patients to continue their GA treatment and to have a great improvement of body contour and skin aspect, with reduction of lipoatrophic area. If these results are confirmed, LPG could be proposed preventively to reduce such adverse event, especially in female patients.

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