

## CLINICAL REPORT

# Vulvar Lichen Sclerosus: 11 Women Treated with Tacrolimus 0.1% Ointment

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**Lichen sclerosus is a chronic relapsing disease, usually treated with ultra-potent corticosteroids. As immunological alterations are considered important aetiopathogenetic factors in lichen sclerosus, the new immunomodulating topical agents, such as tacrolimus and pimecrolimus, have been employed sporadically as alternative therapies. The aim of this study was to evaluate the therapeutic effects of tacrolimus 0.1% ointment in lichen sclerosus in 11 patients unresponsive or poorly responsive to previous treatments. Tacrolimus 0.1% ointment was applied twice daily for 6 weeks, then tapered over a further 6 weeks. Symptoms and objective parameters were evaluated and quantified at the start, after 6 weeks, at the end of the topical treatment, and at follow-up visits. Improvement or remission of symptoms was observed in the patients who completed the study, while objective parameters were poorly influenced and often were not related to symptom behaviour. Topical tacrolimus can be considered an alternative treatment for lichen sclerosus. Key words: vulvar lichen sclerosus; immunomodulating topical agents; vulvar disease.**

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Lichen sclerosus (LS) is a chronic inflammatory disease that occurs most commonly on the skin and mucosae of the anogenital area. Caucasians are most susceptible to LS; both sexes may be affected, but women are more often affected than men. The condition may be observed at any age, although two peaks of incidence occur, in the prepubertal and postmenopausal periods. Multiple autoimmune diseases, such as vitiligo, hypothyroidism, thyrotoxicosis, pernicious anaemia and alopecia, may be associated with LS.

Among the multiple aetiopathogenetic factors immunological alterations seem to be crucial (1–3). Langerhans' cells, T lymphocytes and imbalance of interleukin production play a role in LS (1, 3, 4).

Topical administration of ultra-potent corticosteroids is now considered the first-line treatment for LS; nevertheless the condition frequently recurs (5).

Tacrolimus, a new immunomodulating topical agent, calcineurin inhibitor, originally used for atopic dermatitis (6, 7), has been administered in other immuno-mediated skin diseases (8–16) and recently also in LS (17–20).

We employed tacrolimus ointment in a selected group of patients affected by vulvar LS with the aim of evaluating the efficacy of this product in the management of the disease.

## PATIENTS AND METHODS

Between September 2004 and May 2005, 12 women affected by vulvar LS that was unresponsive or poorly responsive to previous super-potent or potent topical corticosteroids, were selected in our vulva clinic and included in the study. The ineffectiveness of at least two cycles of 3 months each, one with corticosteroids, was an inclusion criteria for the prescription of tacrolimus ointment. One woman was excluded from the study as she had a previous allergy to macrolides. At enrolment, the 11 patients had a mean age of 54 years (range 32–80 years) and a mean duration of vulvar disease of 4.8 years (range 12–252 months).

Treatment was scheduled with the application of tacrolimus 0.1% ointment (Protopic® 0.1% ointment, Astellas Fujisawa GmbH, Munich, Germany) on the involved vulvar regions. Considering the chronicity of the disease, it was decided to apply the ointment twice daily for 6 weeks, then once a day for 15 days, and finally twice weekly for a further 4 weeks. Subjects gave their informed consent at the beginning of the study.

Subjective and objective evaluations were carried out at the start, after 6 weeks, and at the end of the treatment, using the following scores:

*Subjective evaluation* of itching, burning and dyspareunia was obtained by interview using a visual analogue scale (VAS); a score of 10 was attributed to the highest intensity of the symptoms, and 0 to their absence. A global score was obtained by summing each symptomatological parameter.

Thirteen *objective parameters* (leukoderma, sclerosis, atrophy, fine wrinkling, lichenification, hyperkeratosis, erosions, oedema, erythema, purpuric lesions, linear itching-related excoriation, mono- or bilateral labial adhesion) were considered and respectively graded, by the same doctor, on the following numeric scale: 0 = absent; 1 = slight; 2 = moderate; 3 = severe. A global score was obtained by summing the value of each parameter.

The variations between initial and final scores were expressed with a percentage value. An arbitrary percentage, >55%, was considered a good improvement, and <55% a slight improvement. Biopsies, confirming the clinical diagnosis, were obtained from the most significant area for all the patients before enrolment, and for patients 1 and 2 also at the end of the treatment.

The women were examined every 2–3 months; the maximum period of follow-up was 7 months.

## RESULTS

The subjective and objective score variations are shown in Table I, together with the percentage score variations obtained at the end of treatment.

Complete remission of subjective symptoms was obtained in 4 out of 11 patients. A good improvement was reported by 4 patients, and a slight improvement by 2 patients. No subject worsened. Regarding the objective evaluation, resolution of the clinical aspects was obtained in one patient, while a good improvement was seen in another (Fig. 1). In 6 patients a slight clinical improvement in the vulvar dermatitis was observed, while no variation was seen in one patient and, the condition in another worsened. One subject did not attend for the final visit. At the end of the 3-month treatment period, 3 women showed patches of brown pigmentation on the labia majora.

Side-effects, described as a "peculiar, tacrolimus-related itching and burning" after topical administration, were reported by 3 patients; these effects were slight, always transient and disappeared after a few applications.

Comparison of the biopsy specimens, performed on 2 cases at the beginning and at the end of the study, revealed a consistent reduction in histopathological alterations (Fig. 2).

Follow-up, ranging from 2 to 7 months, was obtained in 10 subjects and was negative for recurrences in all cases.

## DISCUSSION

LS is a disease with a chronic and/or relapsing course (1–3). Ultra-potent corticosteroids, despite their positive therapeutic effects, do not prevent recurrences, which may be unpredictable (1–3, 5).

Aetiopathogenetic evidence supports the use of topical immunomodulating agents (TIMs), such as ta-

crolium and pimecrolimus, in LS (1–4). Some recent reports from the literature appear to confirm their effectiveness in this disease. It has been reported that these topical agents reduce pruritus and burning and improve histopathological alterations (17–20).

We therefore used tacrolimus ointment in a selected group of patients affected by chronic or relapsing LS. The higher potency molecule tacrolimus was used, rather than the lower potency pimecrolimus, because of the severity and chronicity of the disease. A standardized regimen was chosen, rather than symptom-related drug application.

Analysis of subjective score variations shows a clear positive influence of the drug on itching, burning and dyspareunia. In all patients the remission of, or reduction in, symptoms occurred within a few days. The 2 subjects who showed moderate improvement were satisfied with their new condition.

The patients who complained of drug-related side-effects could clearly distinguish the pruritus and "scalding" sensation as being induced by tacrolimus rather than by the disease itself. In no case was it necessary to withdraw the topical administration, and rapid disappearance of these adverse events was reported.

Analysis of the objective score variations, on the other hand, shows a poor influence of the treatment on the parameters evaluated. Six out of 11 patients achieved only a slight improvement in clinical signs, while no variation was seen in one patient and a worsening in another. Complete remission was reported in only one case, and a remarkable improvement in another. The 2 patients (patients 1 and 2) who repeated biopsies at the end of the treatment obtained almost complete resolution of the histopathological features of LS, although clinical improvement was considered slight. Similar histological findings were described by Assmann et al. (17) after administration of tacrolimus in one case, and

Table I. Subjective and objective score and percentage variations of improvement. Values = 100 were considered complete remissions; values > 55% were considered good improvement, while values < 55% were considered slight improvement; negative values were considered worsening. Example of percentage calculation (patient 2):  $100:27 = x:8$ .  $x = 29.6$ ,  $100-29.6 = 70.4 \approx 70$  percentage of improvement

| Patients No./age (years) | Symptoms (itching, burning, dyspareunia)<br>VAS: 0–10 for each symptom <sup>1</sup> |             |                 | Objectivity (13 parameters)<br>Score: 0–3 for each parameter <sup>1</sup> |             |                  |
|--------------------------|-------------------------------------------------------------------------------------|-------------|-----------------|---------------------------------------------------------------------------|-------------|------------------|
|                          | Initial score                                                                       | Final score | Improvement (%) | Initial score                                                             | Final score | Improvement (%)  |
| 1/70                     | 3                                                                                   | 0           | Remission (100) | 15                                                                        | 10          | Slight (34)      |
| 2/63                     | 27                                                                                  | 8           | Good (70)       | 12                                                                        | 7           | Slight (42)      |
| 3/64                     | 8                                                                                   | 0           | Remission (100) | 5                                                                         | 4           | Slight (20)      |
| 4/54                     | 20                                                                                  | 0           | Remission (100) | 5                                                                         | 4           | Slight (20)      |
| 5/62                     | 9                                                                                   | 1           | Good (89)       | 9                                                                         | 2           | Good (78)        |
| 6/57                     | 24                                                                                  | 2           | Good (92)       | 2                                                                         | 0           | Resolution (100) |
| 7/33                     | 3                                                                                   | 0           | Remission (100) | 13                                                                        | 9           | Slight (31)      |
| 8/38                     | 7                                                                                   | 2           | Good (71)       | 4                                                                         | 4           | Unchanged (0)    |
| 9/80                     | 16                                                                                  | 10          | Slight (37)     | 18                                                                        | 15          | Slight (17)      |
| 10/61                    | 5                                                                                   | Drop out    | Drop out        | 11                                                                        | Drop out    | Drop out         |
| 11/35                    | 18                                                                                  | 16          | Slight (11)     | 12                                                                        | 13          | Worsened (–8)    |

<sup>1</sup>sum of score is shown  
VAS, visual analogue scale.

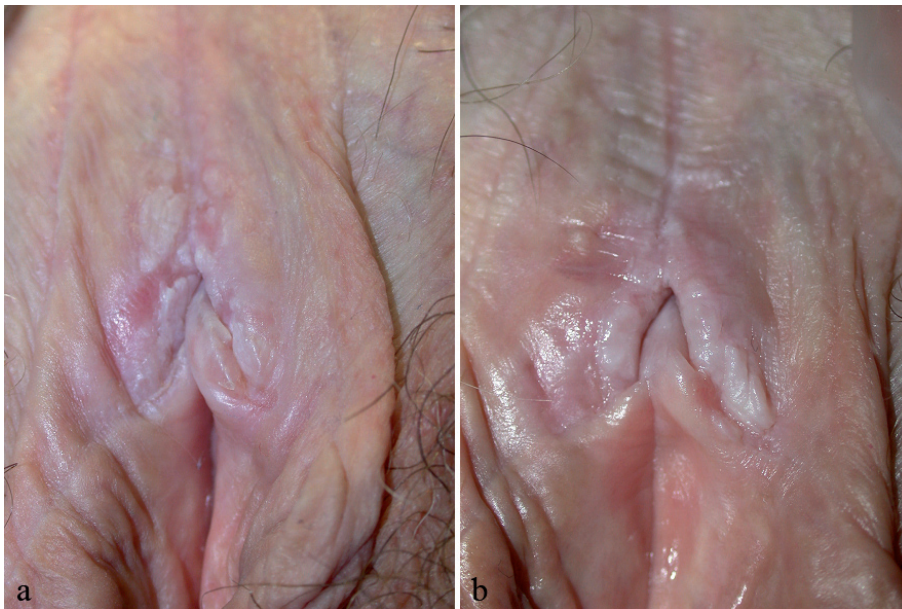


Fig. 1. Patient 5 (a) before and (b) after treatment: evaluated as good improvement.

by Goldstein et al. (20) after administration of pimecrolimus in 2 cases, but they were associated with a more marked improvement in the vulvar appearance.

Recently, the influence of calcineurin inhibitors on melanocytes has been evidenced. Fricain et al. (21) observed that, in lichen planus, topical tacrolimus increases the melanogenesis and melanocyte density of the inflamed mucosae, probably as a consequence of enhanced penetration of the drug. However the re-pigmenting effects of the skin reported by some authors in patients with vitiligo (8, 9, 22) seem to be dependent on exposure to ultraviolet light and on epidermal thickness, being restricted to the face. In 3 cases the appearance of new “brown spots” on the vulva or an increased pigmentation of some lenticular maculae were observed. This local side-effect could be considered positive, as LS is characterized by small, white, depigmented areas and is also known as white spot disease.

No recurrences of LS have been reported in the literature after withdrawal of TIM application (17–20); furthermore, to date the follow-up performed in all our cases remains negative. Despite these positive data, a

longer period of observation is necessary to evaluate the real influence of tacrolimus and/or pimecrolimus on the prevention of relapses in comparison with other conventional treatments.

The potential risk of systemic immunosuppression and carcinogenicity due to topical tacrolimus seems to be very low. However, a prolonged study is required to determine whether the intrinsic risk of LS evolving towards skin cancer (estimated to be about 5%) is increased due to these new TIMs (1–3, 23).

Further studies are necessary to define the best modalities and lengths of treatment with TIMs: to date there is notable diversity amongst the available protocols.

Whilst awaiting confirmation of the long-term safety and real efficacy of topical tacrolimus, which will probably emerge from future controlled multicentric studies, we conclude that tacrolimus may be an alternative therapeutic approach in LS when conventional therapies fail.

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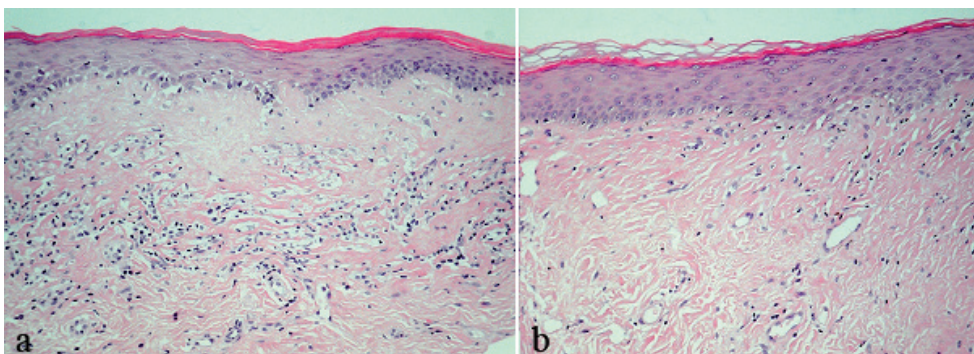


Fig. 2. Histology of lichen sclerosus (patient 2) (a) before treatment: showing homogenization of the collagen and inflammatory infiltrate in the dermis (20 $\times$ ) and (b) clear improvement in the sclerosis and the inflammatory infiltrate after therapy with tacrolimus (20 $\times$ ).

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