

A double-blind, randomized controlled trial of clobetasol versus pimecrolimus in patients with vulvar lichen sclerosis

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Background: Lichen sclerosis (LS) is a lymphocyte-mediated chronic cutaneous disorder with a predilection for the vulva. The current gold standard treatment is topical ultrapotent corticosteroids such as clobetasol.

Objective: We sought to compare the safety and efficacy of clobetasol and pimecrolimus in the treatment of vulvar LS.

Methods: This double-blind, randomized trial enrolled 38 women with biopsy-proven vulvar LS. This study consisted of a 2-week screening period and a 12-week treatment period. The primary efficacy variable was the change in inflammation, as determined by a dermatopathologist, on the biopsy specimens obtained at screening and at the week 12 visit. Secondary efficacy variables included the change from baseline in pruritus and burning/pain as assessed by patients using a visual analog scale and a clinical evaluation by the investigator.

Results: Clobetasol was found to be superior in improving inflammation when compared with pimecrolimus ($P = .015$). Both groups showed improvement in pruritus and burning/pain but this difference was not statistically significant ($P = .32$ and $.93$, respectively). Both clobetasol and pimecrolimus were found to be effective in decreasing both the total score on the Investigator Global Assessment ($P = .001$) and all 3 subscales. Serum levels of pimecrolimus and clobetasol did not approach levels of concern during the study period. No adverse events were reported.

Limitations: This study was limited by the relatively short study duration.

Conclusion: Both clobetasol and pimecrolimus appear efficacious and well tolerated for the treatment of vulvar LS; however, clobetasol is more effective than pimecrolimus and should remain first-line therapy for LS. (J Am Acad Dermatol 10.1016/j.jaad.2010.06.011.)

Key words: calcineurin inhibitor; corticosteroid; lichen sclerosis; pimecrolimus; vulva.

Lichen sclerosis (LS) is a chronic cutaneous disorder with a notable predilection for the anogenital skin. Prevalence rates range from 1:70 to 1:1000 women, and affected female patients outnumber male patients by 10:1.^{1,2} Presenting symptoms may include intense pruritus, pain,

Abbreviations used:

IGA: Investigator Global Assessment
LS: lichen sclerosis
VAS-BP: visual analog scale-burning/pain
VAS-PR: visual analog scale-pruritus

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burning, and severe dyspareunia. The typical lesions of LS are white plaques and papules, often with areas of ecchymosis, excoriation, and ulceration.³

The histopathologic changes of LS are distinctive with pathognomonic findings on a biopsy specimen. Characteristic pathologic findings include hyperkeratosis of the epidermis, epidermal atrophy with loss of rete ridges, homogenization of the collagen in the papillary dermis, and a lichenoid (bandlike) inflammatory infiltrate in the dermis.³ Although there is no known cure for LS, the current gold standard treatment is ultrapotent corticosteroids.⁴

Although treatment with topical corticosteroids is effective, well-known side effects associated with long-term topical corticosteroid use include: thinning of the dermis, rebound reactions, striae formation, systemic absorption, hypo-thalamic-pituitary axis suppression, and fungal infections. Although these side effects are rare, long-term use of corticosteroids for the treatment of vulvar LS may increase these risks. Therefore, a treatment regimen that is shown to be effective, safe, and does not rely on corticosteroids may be beneficial.

Pimecrolimus cream 1% (Elidel, Novartis Pharmaceuticals Corp, East Hanover, NJ) is a topical calcineurin inhibitor that inhibits the proliferation of T cells after antigen-specific or nonspecific stimulation.⁵ As pimecrolimus does not inhibit collagen synthesis by keratinocytes, it does not cause skin atrophy.⁶ If one considers the method of action of pimecrolimus and the pathophysiology of vulvar LS, it is reasonable to theorize that pimecrolimus cream 1% may effectively treat LS without the potentially serious side effects that are associated with corticosteroids. The goal of this study was to evaluate the efficacy and safety of pimecrolimus for the treatment of vulvar LS and to compare it with clobetasol, an ultrapotent corticosteroid.

METHODS

This was a double-blind trial to evaluate the relative efficacy and safety of topical pimecrolimus cream 1% and clobetasol 0.05% cream for the treatment of vulvar LS. A total of 38 patients with a diagnosis of biopsy-proven active vulvar LS were

recruited from one center. This study consisted of a 2-week screening period and a 12-week treatment period. During the screening period, a 4-mm punch skin biopsy sample was collected from each patient to confirm the diagnosis of active LS and to rule out other diagnoses. Vulvoscopy was performed at the screening visit and after the 12-week treatment

period to rule out vulvar intraepithelial neoplasia or vulvar carcinoma. All eligible patients were randomized to either the pimecrolimus cream 1% or clobetasol group. Patients in the pimecrolimus cream group applied the medication twice daily for 12 weeks. Those in the clobetasol group applied an unmedicated vehicle cream in the morning daily and clobetasol cream 0.05% in the evening daily for 12 weeks.

The primary efficacy variable was the change in inflammation as determined by a dermatopathologist, on the biopsy specimens obtained during the screening period

and at the week 12 visit (0-4 scale). Secondary efficacy variables included the change from baseline in pruritus (VAS-PR) and burning/pain (VAS-BP) as assessed by patients using 0- to 10-point visual analog scale questionnaires. Additional secondary efficacy variables were based on clinical evaluation of an Investigator Global Assessment (IGA) of the severity of the disease (0-3 scale), clinical evaluation of lichenification (0-3 scale), and clinical evaluation of ulceration/fissuring (0-3 scale). Digital photographs were taken at baseline and at the week 4, 8, and 12 visits.

Safety assessments consisted of monitoring serum levels of pimecrolimus and clobetasol and evaluating total white blood cell count, lymphocytes, platelets, aspartate aminotransferase, alanine aminotransferase, creatinine, and blood urea nitrogen, and urinalysis at each visit. A urine pregnancy test was administered at screening and at each visit. All adverse events were recorded, including serious adverse events. The incidence of anogenital herpes simplex virus outbreaks over the study period was recorded.

Inclusion criteria included women who were 18 years or older with a diagnosis of biopsy-proven active vulvar LS, the ability to sign written informed

CAPSULE SUMMARY

This is, to our knowledge, the first randomized, controlled study comparing a calcineurin inhibitor and a corticosteroid for vulvar lichen sclerosis.

This study demonstrates that:

- Both clobetasol and pimecrolimus are effective in decreasing the inflammation and symptoms associated with lichen sclerosis.
- Clobetasol was more effective than pimecrolimus in decreasing inflammation on histologic examination.
- There was no difference in subjective improvement between women using clobetasol or pimecrolimus for lichen sclerosis.

consent, willingness and ability to comply with the study requirements, negative urine pregnancy test results for all women of childbearing potential before enrollment, two forms of birth control for women with childbearing potential, IGA at baseline of 1 or greater, and a score of 4 or greater (on a 0- to 10-point scale) on at least one of the two visual analog scales (VAS-PR, VAS-BP).

Exclusion criteria included receiving systemic immunosuppressants (eg, corticosteroids) within 4 weeks before participation in the study; treatment with topical therapy (eg, topical corticosteroids, pimecrolimus, and tacrolimus) at the affected area within 4 weeks before participation in the study; immunocompromise (eg, lymphoma, AIDS, Wiskott-Aldrich syndrome) or uncontrolled malignant disease; a history of lymphoma, lymphadenopathy, active vulvar herpes, molluscum, or condyloma; systemic or generalized infections (bacterial, viral, or fungal); a diagnosis of other vulvar dermatoses or carcinoma; a diagnosis of diabetes mellitus or Netherton syndrome; nursing mothers; known hypersensitivity to pimecrolimus or clobetasol or any of the components of the creams; severe medical conditions that, in the view of the investigator, prohibited participation in the study; and a history of substance abuse or any factor that would limit the participant's ability to cooperate with the study procedures.

This study was approved by the local institutional review board, all patients signed informed written consent, and the trial was listed on www.clinicaltrials.gov (NCT00393263).

Sample size

Using the assumption that the prevalence of symptomatic LS is 66% it was calculated that 38 participants would be required in each arm to detect a 40% difference in the primary efficacy variable. These assumptions are based on review of data from prior studies of vulvar LS.^{7,8}

Enrollment

A total of 38 women were enrolled in the trial. There were 3 screening failures. All 38 women completed the entire 14 weeks of the trial. Eighteen women were randomized to the pimecrolimus treatment arm and 20 women were randomized to the clobetasol arm. All 38 women had biopsy specimens that confirmed LS upon enrollment. At the end of the trial, all enrollment biopsy specimens were re-evaluated by a second dermatopathologist. It was determined that one participant's pretreatment biopsy specimen did not confirm LS. A third dermatopathologist concurred with the second

dermatopathologist that this participant did not have LS. Therefore, this participant was excluded from the analysis. In addition, a pretreatment biopsy slide of an additional participant was lost by the pathology laboratory. The laboratory made an additional slide from tissue that remained in the paraffin block, but it was not enough to be evaluated by the dermatopathologist. As there was no pretreatment biopsy specimen, this participant was also excluded from the analysis. Therefore, 36 women were included in the final analysis discussed below. Seventeen women were in the pimecrolimus arm and 19 women were in the clobetasol arm.

Randomization

Participants were assigned blinded treatment with consecutive numbers.

Statistical analyses

Analyses were undertaken following the intention-to-treat principle: women were analyzed in the treatment group to which they were randomized. Data analyses were performed with statistical software (SPSS, SPSS Inc, Chicago, IL). Descriptive statistics (means and SD or medians and interquartile ranges, as appropriate) were calculated for baseline data. The primary analysis, which compared the change in inflammation of the two groups, and the IGA were assessed using the Mann-Whitney U test. Continuous data, the VAS-PR, and the VAS-BP were assessed with a paired and an unpaired *t* test, as appropriate. A *P* value of .05 was considered to be statistically significant.

RESULTS

The improvement in inflammation as assessed by a dermatopathologist (primary efficacy variable) was significant both for the clobetasol and pimecrolimus groups (*P* = .001 and .008, respectively). In addition, clobetasol was found to be superior in improving inflammation when compared with pimecrolimus (*P* = .015). There were 9 nonresponders (ie, no improvement in inflammation), one in the clobetasol group and 8 in the pimecrolimus group. **Figs 1 and 2** show pretreatment and posttreatment photomicrographs of representative participants.

Both groups showed improvement in pruritus symptoms as assessed by the VAS-PR. The mean change in the VAS-PR score in the clobetasol and pimecrolimus groups were 4.5 and 3.5, respectively. However, this difference was not statistically significant (*P* = .319). Results were similar for the burning/pain symptoms assessed by the VAS-BP. The mean score in the pimecrolimus group was

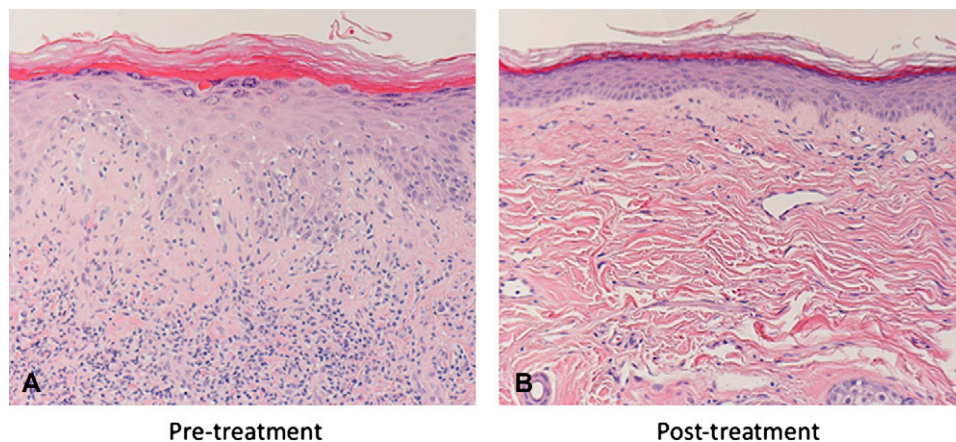


Fig 1. Photomicrographs of patient 17 before treatment showing severe inflammation (**A**) and after treatment with clobetasol showing decreased inflammation (**B**).

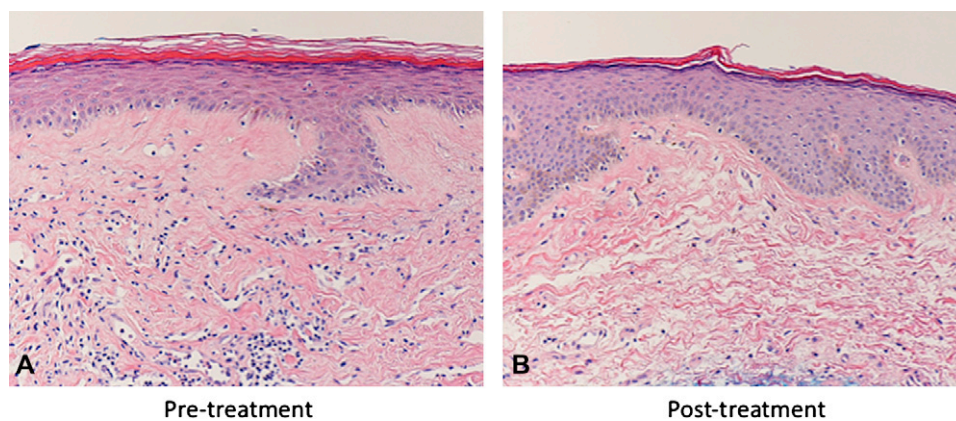


Fig 2. Photomicrographs of patient 8 before treatment showing severe inflammation (**A**) and after treatment with pimecrolimus showing decreased inflammation (**B**).

3.8, versus 3.7 in the clobetasol group, and this difference was not statistically significant ($P = .932$).

Both clobetasol and pimecrolimus cream were found to be effective in decreasing both the total score on the IGA ($P = .001$) and all 3 subscales (severity of disease, $P = .001$; lichenification, $P = .001$; and ulceration, $P = .025$). Figs 3 and 4 demonstrate before (baseline) and after (at 12 weeks) treatment photographs for both groups.

Serum levels of pimecrolimus and clobetasol did not approach pre-established cut-off levels for safety at any point during the study period. In addition, none of the serum laboratory parameters changed significantly during the study period. No adverse events were reported and no herpetic events occurred.

DISCUSSION

This study demonstrates that both clobetasol and pimecrolimus are effective in decreasing the inflammation and symptoms associated with LS. However, clobetasol was more effective than pimecrolimus in

decreasing inflammation. Although this finding was statistically significant, it may not be clinically significant, given that there was no difference in subjective improvement or objective assessment by the investigator between the two treatment groups.

The first case reports of vulvar LS successfully treated with pimecrolimus cream 1% were small case series.⁹⁻¹¹ One of these small series showed reversal of the characteristic histopathologic changes of LS.¹¹ A more recent pilot study evaluated the safety and efficacy of pimecrolimus cream 1%, applied twice daily for up to 6 months, in 29 women with severe LS previously unsatisfactorily treated with topical corticosteroids.¹² Of the 26 patients who completed the follow-up period, 24 showed improvement and 11 (42%) experienced remission. Biopsy specimens from 16 patients demonstrated increased collagen synthesis after 2 months of pimecrolimus treatment in comparison with baseline. Pimecrolimus levels were measured in 10 patients at the 2-month visit and were undetectable in all cases.



Fig 3. Photographs of patient 17 before treatment showing lichenification, ulceration, and ecchymosis (**A**) and after treatment with clobetasol showing significant improvement in lichenification and resolution of ulceration and ecchymosis (**B**).

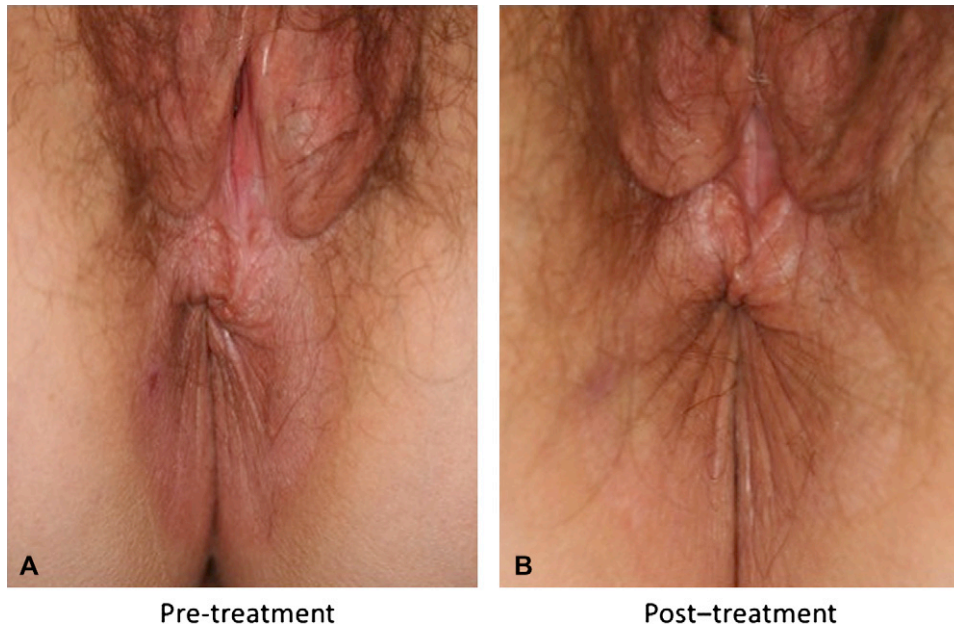


Fig 4. Photographs of patient 8 before treatment showing perianal lichenification (**A**) and after treatment with pimecrolimus showing significant improvement in perianal lichenification (**B**).

An additional study evaluated the efficacy of pimecrolimus cream 1% in 16 postmenopausal women with histologically proven vulvar LS.¹² After 3 months of treatment, complete disease remission was observed in 69% and partial remission in 25% of the patients. Lastly, a nonrandomized study evaluated 29 women with LS who had not responded to

conventional corticosteroid therapy. These patients applied pimecrolimus 1% cream twice daily for 2 months.¹³ As with the current study, posttreatment histologic examination showed decreased inflammatory lymphoid infiltrate.¹⁴

Potential limitations of this study include a relatively small sample size, although a statistically

significant difference was found between the treatment groups. The sample size was calculated based on prior efficacy studies of other medications used for the treatment of LS. It is possible that a larger sample would address safety concerns, however, pimecrolimus has been studied in thousands of patients and has an acceptable safety profile. Another concern is the relatively short study period and lack of long-term follow-up. With either corticosteroids or pimecrolimus, there is the potential for a rebound effect after discontinuing treatment. All patients in this study were evaluated upon completion of the trial and treatment with clobetasol was initiated. No rebound effects have occurred.

In conclusion, both clobetasol and pimecrolimus are efficacious and safe for the treatment of vulvar LS. This study suggests that clobetasol cream is more effective than pimecrolimus cream in LS and, therefore, clobetasol remains the most appropriate first-line therapy for vulvar LS. Pimecrolimus should be reserved for those patients who have failed therapy with ultrapotent corticosteroids, or who have a contraindication for the use of corticosteroids.

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