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

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Background: Lichen sclerosus (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 2011;64:e99-104.)

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

Lichen sclerosus (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 sclerosus
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 finding 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 effect 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.

CAPSULE SUMMARY

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

This study demonstrates that:

- Both clobetasol and pimecrolimus are effective in decreasing the inflammation and symptoms associated with lichen sclerosus.
- 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 sclerosus.

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