

Review

Topical calcineurin inhibitors for the treatment of vulvar dermatoses

Andrew T. Goldstein^{a,*}, Diamant Thaçi^b, Thomas Luger^c

^aDivision of Gynecologic Specialties, Department of Gynecology and Obstetrics, The Johns Hopkins School of Medicine, Baltimore, MD, USA

^bJohann Wolfgang Goethe University Hospital, Department of Dermatology and Venereology, Frankfurt am Main, Germany

^cDepartment of Dermatology, University of Muenster, Muenster, Germany

ARTICLE INFO

Article history:

Received 2 November 2008

Received in revised form 20 April 2009

Accepted 24 May 2009

Keywords:

Anogenital lichen sclerosis
Genital lichen planus
Topical calcineurin inhibitors
Vulvar dermatoses
Vulvar lichen simplex chronicus

ABSTRACT

Repeated courses of potent topical corticosteroids and maintenance therapy with moderately potent topical corticosteroids are frequently needed to treat various forms of vulvar dermatoses, which are often characterized by an abnormal proliferation or activation of T lymphocytes. Because such therapeutic regimen is associated with an increased risk of potential side effects, particularly skin atrophy, an anti-inflammatory alternative to topical corticosteroids is desirable. The two non-steroid topical calcineurin inhibitors pimecrolimus and tacrolimus are immunomodulators that block the release of inflammatory cytokines from T lymphocytes in the skin while promoting cutaneous innate host defences. They are currently approved in Europe and in the United States of America as second-line anti-inflammatory agents for the treatment of atopic dermatitis. We provide a comprehensive summary of existing case reports, series of cases, and open-label prospective studies concerning the use of topical pimecrolimus and tacrolimus for the treatment of anogenital lichen sclerosis, genital lichen planus, vulvar lichen simplex chronicus and related pruritic vulvar dermatoses (chronic vulvar pruritus and allergic contact dermatitis of the vulva). The available data suggest that both topical calcineurin inhibitors may be effective and well tolerated in these vulvar dermatoses, although topical pimecrolimus may exhibit a better long-term tolerability profile. Being devoid of steroid-related side effects, they may represent a useful second-line therapeutic option for patients who are intolerant of, or resistant to topical corticosteroids. Controlled clinical trials and comparative studies are warranted to substantiate the promising findings summarized in this review.

© 2009 Elsevier Ireland Ltd. All rights reserved.

Contents

1. Introduction	22
2. Methodology	23
3. Case report and study description by type of vulvar dermatosis	23
3.1. Anogenital lichen sclerosis	23
3.2. Genital lichen planus	26
3.3. Vulvar lichen simplex chronicus and related pruritic dermatoses	27
3.3.1. Vulvar lichen simplex chronicus	27
3.3.2. Chronic vulvar pruritus	27
3.3.3. Allergic contact dermatitis of the vulva (ACD-V)	28
4. Comment	28
References	28

1. Introduction

The non-steroid anti-inflammatory drugs pimecrolimus cream 1% and tacrolimus ointment belong to the class of topical calcineurin inhibitors (TCIs) [1–3] and are approved in Europe and in the United States of America for the treatment of atopic

* Corresponding author at: The Centers for Vulvovaginal Disorders, 3 Washington Circle NW, Suite 205, Washington, DC 20037, USA. Tel.: +1 202 887 0568; fax: +1 410 757 8741.

E-mail address: obstetrics@yahoo.com (A.T. Goldstein).

dermatitis in patients above the age of 2 years. Both agents are immunomodulators that block the proliferation of T lymphocytes and the release of inflammatory cytokines from these cells [1,2]. This mechanism of action is operative in vivo [4,5] and explains at least in part the therapeutic effect of calcineurin inhibitors in inflammatory skin diseases. However, additional benefit may derive from the ability of these agents to promote cutaneous innate host defences. For example, a recent in vitro study [6] has revealed that pimecrolimus at nanomole concentrations close to the therapeutic concentrations enhances the expression of antimicrobial peptides in keratinocytes and increases the ability of these cells to kill bacteria. As reviewed elsewhere [1,3], TCIs do not cause side effects that are known to be associated with prolonged use of topical corticosteroids (TCSs) [7], including skin atrophy, and impairment of the epidermal barrier function. Therefore, they represent a useful second-line therapeutic option for patients intolerant of TCSs or when TCSs are contraindicated [1,3].

This article provides a comprehensive summary of the available case reports and studies on the use of TCIs in various forms of vulvar dermatoses [8], including anogenital lichen sclerosis, genital lichen planus, vulvar lichen simplex chronicus and related pruritic dermatoses such as chronic vulvar pruritus and allergic contact dermatitis of the vulva (ACD-V). All these disorders are considered to be associated with an abnormal proliferation or activation of T lymphocytes, and disease relapses are commonly treated with potent or superpotent TCSs [8]. The intermittent use of these drugs is effective in many patients and bears little risk [8], especially if TCSs are accurately applied in very small amounts only to the lesional area as recommended [8,9]. However, continuous treatment with superpotent TCSs for at least 3 months is often required to control the inflammatory process [8], and such therapeutic regimen increases the risk of potential steroid-related side effects [7]. The atrophogenic effect of TCSs is a particular disadvantage in lichen sclerosis, because this condition is inherently associated with variable degree of atrophy in the lesional area [8]. Therefore, a non-steroid anti-inflammatory therapeutic alternative may be desirable. The case reports, series of cases and open-label prospective studies summarized in this article (Tables 1 and 2) [10–25] suggest that TCIs may represent an effective second-line therapeutic option for lichen sclerosis and other often frustrating and difficult-to-treat forms of vulvar dermatoses, although the data supporting their use in these pathological conditions are still limited.

2. Methodology

We performed a literature search through 31 December 2007, using PubMed and the search terms 'tacrolimus', 'pimecrolimus' or 'calcineurin inhibitors' and 'vulvar dermatosis', 'vulvar dermatitis', 'vulvar eczema', 'chronic vulvar pruritus', 'genital lichen', 'genital lichen sclerosis', 'genital lichen planus', 'vulvar lichen' or 'vulvar lichen simplex chronicus'. Cross-references of the retrieved articles were also checked to identify other case reports or studies. The search revealed seven case reports, 2 series of cases, three pilot studies and 4 open-label prospective studies concerning the use of topical pimecrolimus or tacrolimus for the treatment of anogenital lichen sclerosis, genital lichen planus, vulvar lichen simplex chronicus or related pruritic vulvar dermatoses (chronic vulvar pruritus and ACD-V). The case reports, series of cases and studies were grouped by type of vulvar dermatosis and reviewed independently by each author. For each TCI, data concerning the treatment regimen, patients' characteristics, response to other therapies, treatment outcome and tolerability were collected from each case report or study, discussed in relation to the clinical characteristics of each vulvar dermatosis and summarized in tabular form. Because of the nature of the available literature, it

was impossible to perform a meta-analysis of the data or an authentic systematic review.

3. Case report and study description by type of vulvar dermatosis

3.1. Anogenital lichen sclerosis

Lichen sclerosis is a chronic inflammatory skin disease that predominantly involves the anogenital area (Fig. 1), particularly the vulva [8]. The disease runs a chronic course and is often characterized by severe pruritus, dysuria, painful defecation and dyspareunia [8]. Typical lesions of lichen sclerosis are porcelain-white papules and plaques [9]. The skin commonly appears thinned, whitened and crinkling ("cigarette paper" appearance) [9] (Fig. 1). Significant disability may result from destruction and fusion of the labia minora, narrowing of the introitus, and scarring of the clitoris [8,9].

The first case reports of vulvar lichen sclerosis successfully treated with pimecrolimus cream 1% were small case series [13–15]. Two of these reports [13,14] involved premenarchal girls whose disease had not been adequately controlled with other therapies, including TCSs (Table 1). In the third report [15], 4 patients with histologically-proven vulvar lichen sclerosis were treated with pimecrolimus cream 1% twice daily for 3 months (Table 1). Three patients reported complete resolution of vulvar itching and burning. Two of these patients had repeated vulvar skin biopsies, and the histological examination showed reversal of the characteristic histopathologic changes of lichen sclerosis. One woman had to reduce the use of topical pimecrolimus because of application site burning and stinging but still experienced significant improvement of symptoms. In 3 out of 4 patients, treatment with pimecrolimus cream 1% was well tolerated.

A more recent pilot study [16] evaluated the safety and efficacy of pimecrolimus cream 1%, applied twice daily for up to 6 months, in 29 women with severe lichen sclerosis previously unsatisfactorily treated with TCSs (Table 1). Of the 26 patients who completed the follow-up period, 24 showed improvement and 11 (42%) experienced remission. In 9 patients (35%), remission was achieved within 2 months from treatment start. Biopsy specimens from 16 patients demonstrated increased collagen synthesis after 2 months of pimecrolimus treatment in comparison with baseline. Three patients withdrew from the study during the first week of treatment because of intense pruritus and/or no satisfactory response. Fifty percent of the patients who continued treatment reported application site burning and itching, lasting 3–14 days. Blood concentrations of pimecrolimus were measured in 10 patients at the 2-month visit and were undetectable in all cases.

The efficacy of pimecrolimus cream 1% in postmenopausal women with histologically-proven vulvar lichen sclerosis was specifically evaluated in a prospective study [25], involving 16 patients aged 46–75 years (Table 1). Eleven women had previously demonstrated an unsatisfactory response to the recommended treatment with clobetasol propionate [8,9]. All patients were treated with pimecrolimus cream 1% twice daily for 3 months and thereafter as required if disease recurred during a follow-up period of 12 months. After 3 months of treatment, complete disease remission was observed in 11 patients (69%) and partial remission in 4 (25%). Seven of the 11 patients who had been successfully treated with pimecrolimus cream 1% experienced a complete remission for up to 1 year. Eight of these patients had repeated vulvar skin biopsies and the histological examination confirmed that the typical features of lichen sclerosis had disappeared. The other 4 patients suffered from a relapse between 3 and 6 months after treatment discontinuation but active lesions responded to topical pimecrolimus, when therapy was resumed. Only one

Table 1
Summary of case reports and initial studies with pimecrolimus cream 1%.

Report/study	Treatment	Patients	Response to other therapies	Outcome	Tolerability
Anogenital lichen sclerosis					
Case report by Goldstein et al. [13]	Applications twice daily for 3 months and every other day for the next 6 months	Premenarchal girl with vulvar involvement	Temporary remission of the disease and superimposed infection with clobetasol ointment 0.05% daily for 3 months (two courses)	Remission within 6 weeks	Less application site burning than with topical corticosteroids
Case report by Boms et al. [14]	Twice-daily applications for 4 months	4 prepubertal girls (vulvar involvement and additional perianal involvement in 3 patients)	Partial response to various therapies: emollients, topical antifungal agents and cryotherapy plus TCSs (products not specified)	Substantial improvement within 6 weeks and almost complete remission in all patients at the end of the treatment period. No relapse during the following 3 months in 2 patients who returned for follow-up.	Transitory, mild application site burning at the beginning of the treatment period in all patients
Case report by Goldstein et al. [15]	Twice-daily applications for 3 months	One 8-year-old girl and 3 women (aged 28, 48 and 62 years) with vulvar involvement	No previous treatment	Complete resolution of symptoms in 3 patients and histologically-proven reversal of the skin lesions in 2 patients; 50% symptom improvement in the 62-year-old patient (reduced medication use because of side effects)	Application site burning and stinging, leading to a reduced medication use, in the 62-year-old woman
Pilot study by Nissi et al. [16]	Twice-daily applications for 6 months	29 women aged 42–79 years: 22 patients with the erosive form (histologically-confirmed diagnosis of lichen sclerosis)	No remission on previous treatment with mild (38% of patients) or potent (55% of patients) TCSs: products not specified	Disease improvement in 24 of 26 patients who completed the study, with clinical resolution in 11 patients; increased collagen synthesis after 2 months of pimecrolimus treatment in comparison with baseline	3 discontinuations due to intense pruritus and/or poor response to treatment; transient application site burning and itching in 50% of the patients who completed the study
Prospective open-label study by Oskay et al. [25]	Twice-daily application for 3 months and on as-required basis thereafter (in case of disease relapse)	16 postmenopausal women, aged 46–75 years, with histologically-proven vulvar lichen sclerosis	Previous treatment with clobetasol propionate in 11 patients with unsatisfactory response	Complete remission within 3 months in 11 patients (69%), partial remission in 4 patients (25%) and no response in 1 patient (6%). Seven patients with complete remission at 3 months had no relapses over 12 months of follow-up	Transient application site burning during the first week of treatment in 6 patients (37.5%)
Genital lichen planus					
Series of cases by Lonsdale-Eccles and Velangi [21]	Twice-daily applications until resolution	11 women aged 60–83 years: 10 patients with the erosive form	Poor response to TCSs (products not specified) ($n = 10$); TCS-related side effects ($n = 3$); intolerant of tacrolimus ointment ($n = 4$); occurrence of herpes virus infection on topical tacrolimus ($n = 1$)	Disease improvement within 4–6 weeks of treatment in 82% of patients and no residual activity of the disease after 10 months in 55% of patients.	Mild application site reactions in 6 patients during the first days of treatment. Persistent itching and local irritation in 2 patients
Vulvar lichen simplex chronicus and related pruritic dermatoses					
Open-label prospective study by Goldstein et al. [22]	Twice-daily applications for 12 weeks	12 women aged 25–53 years with histologically-confirmed lichen simplex chronicus	Not reported	Decrease in median VAS-PR score from 6 cm at baseline to 0 cm at week 12. Complete resolution of pruritus by week 4 in 7 patients. Decrease in median IGA score from 2.5 at baseline to 0 at week 12.	No side effects reported; pimecrolimus blood concentrations below the limit of quantification in all samples
Open-label, prospective study by Sarifakioglu and Gumus [24]	Twice-daily applications for 4 weeks	15 women aged 30–60 years with chronic vulvar pruritus but no histopathologic changes	Not reported	Complete resolution of pruritus in 10 patients; improvement of pruritus in 3 additional patients; 2 patients lost to follow-up	Transient and slight application site burning in 3 patients
Case report by Black [23]	Applications twice daily for the first month, every other day for the second month, and twice weekly for the third month	67-years-old woman with ACD-V	No response to aclometasone dipropionate and clobetasol propionate after previous prolonged use of these products for the treatment of stasis dermatitis	Clearance of ACD-V at the end of the treatment period and no relapse over the next 9 months	No side effects mentioned in the report

ACD-V: allergic contact dermatitis of the vulva, TCS: topical corticosteroid.

Table 2
Summary of case reports and initial studies with tacrolimus ointment 0.1%.

Report/study	Treatment	Patients	Response to other therapies	Outcome	Tolerability
Anogenital lichen sclerosis					
Case report by Assmann et al. [10]	Twice-daily applications for 6 weeks	71-year-old woman (vulvar involvement)	Unresponsive to mometasone furoate and clobetasol propionate	Resolution of skin lesions	Initial, slight application site burning
Case report by Kunstfeld et al. [11]	Twice-daily applications for 6 months	19-year-old woman (vulvar involvement)	Moderately responsive to diflucortolon-21-valerate twice daily for 2 months, with prompt relapse upon discontinuation	Complete resolution without relapse during the 12-month follow-up period	Transient application site burning
Case report by Böhm et al. [12]	Once-daily application for up to 10 months	3 prepubertal girls and 3 adults (anogenital involvement)	Unsuccessful response to various therapies, including potent TCSs (products not specified)	Complete resolution in all patients without relapses for up to 1 year	Transient application site burning in the girls
Pilot study by Luesley and Downey [18]	Twice-daily application for 3 months, followed by twice-daily application of ointment 0.03% for up to 12 months	16 women aged 26–79 years (vulvar involvement)	Incomplete response to fluorinated topical corticosteroids (products not specified) ($n = 10$) or no compliance with treatment (concerns regarding side effects) ($n = 5$)	Complete response in 12.5% of patients (persisting until the end of the study); symptom improvement in a further 50% of patients	Mild burning sensation for ≤ 30 min following ointment application in 5 patients
Pilot study by Virgili et al. [19]	Applications twice daily for 6 weeks, once daily for the next 2 weeks and twice weekly for the last 4 weeks	11 women aged 32–80 years (vulvar involvement)	Unresponsive or poorly responsive to potent and superpotent TCSs (products not specified)	Symptom remission or improvement: $n = 10$; disease resolution or good improvement by objective parameters: $n = 2$; slight disease improvement by objective parameters: $n = 6$; no recurrences on follow-up	Transient application site itching and burning in 3 patients; brown pigmentation on the labia majora in 3 patients
Phase II, open-label trial by Hengge et al. [17]	Twice-daily applications for 24 weeks	49 women, 32 men and 3 girls aged 5–85 years (long-standing disease with predominant anogenital involvement)	Long-standing disease despite prior treatments, including treatment with TCSs (products not specified), in 90% of patients	Clearance of active lesions in 43% of patients and partial resolution in 34% of patients. Recurrence rate $< 10\%$ in the 18-month follow-up period	Incidence rate of relevant adverse events: application site burning (25%); herpes virus infection (2%); vulvovaginal candidiasis (2%)
Genital lichen planus					
Retrospective series of cases by Byrd et al. [20]	Twice-daily applications for 3 months, then reduced or discontinued	16 women with recalcitrant erosive vulvar disease	Poor response to other treatments, including TCSs in 13 patients and oral corticosteroids in 5 patients (products not specified)	Improvement of signs and symptoms in 94% of patients. Less severe, tacrolimus-responsive recurrence in 10 patients within 6 months	Application site reactions in 6 patients (38%)

TCS: topical corticosteroid.

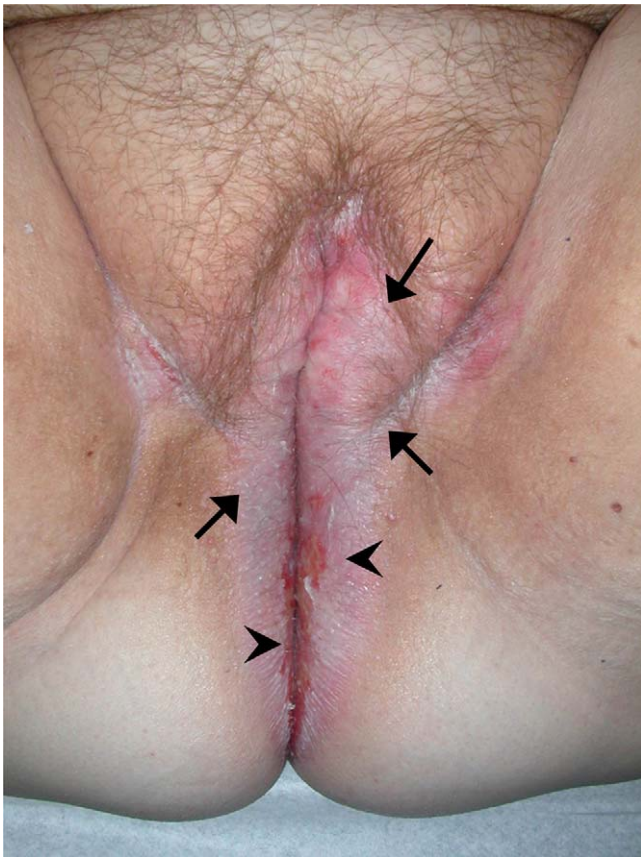


Fig. 1. Anogenital lichen sclerosus with the characteristic “cigarette paper” wrinkling (arrows) and erosions (arrowheads).

patient did not show an appreciable improvement during the study. The only adverse event reported was a burning sensation at the application site during the first week of treatment (6 patients). The application site reactions were transient and mild or moderate in severity.

The data from three case reports [10–12], two pilot studies [18,19], and one multi-centre, phase II, open-label trial [17] (Table 2) suggest that tacrolimus ointment 0.1% may also be effective and well tolerated in the treatment of anogenital lichen sclerosus, both in adults and in prepubertal girls. The main findings of the three case reports [9–11] are summarized in Table 2. In the first pilot study [18], 16 women with histologically-proven vulvar lichen sclerosus, who had previously demonstrated an incomplete response to topical fluorinated steroids (10 patients) or poor compliance with TCS treatment (5 patients), were initially treated with tacrolimus ointment 0.1% twice daily for 3 months (Table 2). In responders, treatment was continued with twice-daily application of tacrolimus ointment 0.03% for up to 12 months. A complete response was observed in 12.5% of patients and remission was maintained at 12 months. Symptom improvement was reported by a further 50% of patients. Six women (37.5%) did not show any improvement by the end of the first 3 months of treatment and were switched to other therapies. Treatment was well tolerated. Only 5 women reported side effects, consisting in mild burning sensation for 30 min or less following ointment application. In the second pilot study [19], 11 women with vulvar lichen sclerosus unresponsive or poorly responsive to TCSs were treated with tacrolimus ointment 0.1% twice daily for 6 weeks (Table 2). Treatment was then tapered over the next 6 weeks. Remission or improvement of symptoms was observed in 4 and 6 patients, respectively. Three patients reported transient application site reactions and 3 hyperpigmentation of the skin.

Finally, in the multi-centre, phase II, open-label trial mentioned above [17], 49 women, 32 men and 3 girls (aged between 5 and 85 years) with long-standing anogenital lichen sclerosus, involving also extra-genital areas in 5 patients, were treated with tacrolimus ointment 0.1% twice daily for 16–24 weeks (Table 2). Clearance of the active lesions was observed in 43% of patients at 24 weeks of treatment. Partial resolution was reached in 34% of patients. The maximal therapeutic response occurred between 10 and 24 weeks of continuous treatment. The recurrence rate during the entire follow-up period of 18 months was less than 10%, with 3 patients (9%) experiencing a relapse during the first 3 months after discontinuation of treatment. Burning and itching at the application site were the most frequently reported adverse events (25% and 20% of patients, respectively). These transient reactions usually disappeared within 2–3 weeks. However, itching and pain caused treatment interruption in 2 patients and led to premature discontinuation from the study in another patient. Genital herpes virus infection and vulvovaginal candidiasis were the most common infections, but were infrequently observed, each occurring in 2% of patients. None of the patients showed treatment-related skin atrophy.

Reactivation of the papilloma virus may occur after treatment of anogenital lichen sclerosus with topical corticosteroids and a similar event has been reported following treatment of this disease with topical tacrolimus [26]. The safety data currently available for the two TCIs in atopic dermatitis indicate no consistent increase in the risk of cutaneous infections, which is however comparable to that associated with TCS treatment [2,27,28].

Lichen sclerosus predisposes to the occurrence of malignancies (squamous cell carcinoma) in the lesional areas, even in the natural course of the disease [8]. It is therefore important to consider that the safety of a continuous use of TCIs in the long-term is not known [27]. Although a causal relationship has not been established, rare cases of skin malignancies and lymphoma have been reported in patients treated with these agents [27]. However, there is no evidence of systemic immune suppression or increased risk of malignancies in patients treated intermittently with topical pimecrolimus or tacrolimus in clinical trials for up to 4 years, and the observed incidence of malignancies in post-marketing surveillance is lower than that detected in the general population [2,27,28]. None of the case reports and initial studies mentioned above has described the occurrence of skin malignancies or lymphomas in patients with anogenital lichen sclerosus treated continuously with pimecrolimus cream 1% or tacrolimus ointment for long periods of time, but these preliminary data need to be confirmed by controlled long-term trials.

3.2. Genital lichen planus

Genital lichen planus is a debilitating inflammatory disease that tends to run a chronic or relapsing course, resistant to treatment. It predominantly affects women between 30 and 60 years of age [8]. Patients with the erosive form of lichen planus (Fig. 2) complain of severe vulvovaginal symptoms, including pain, burning, dyspareunia and post-coital bleeding [8]. Scarring and destruction of the normal vulvar architecture and obliteration of the vaginal lumen can be observed [8].

In a series of cases [21], genital lichen planus was treated with twice-daily application of pimecrolimus cream 1% for 2–10 months in 11 women (Table 1). Ten of 11 patients had the erosive form of lichen planus. The eleventh patient had classical lichen planus affecting the perianal area. Nine patients had histologically-proven disease. In the other 2 patients, a biopsy was not performed because they showed typical clinical features of lichen planus. The mean disease duration was 9 years. Despite appropriate use of TCSs, the disease had been poorly controlled, both clinically and



Fig. 2. Genital lichen planus, demonstrating severe erosions in the vulvar vestibule (arrowheads) and scarring of the vulva (arrow).

symptomatically, in the 10 patients with the erosive form of lichen planus. Two of these patients suffered from corticosteroid-related side effects in the adjacent, unaffected skin, such as periorificial dermatitis and atrophy. The patient with classical lichen planus had demonstrated good response to treatment with potent TCSs, but she showed atrophy of the surrounding, unaffected skin. Five of the 10 women with corticosteroid-resistant disease had already tried topical tacrolimus. Four had not tolerated this treatment because it had been associated with persistent burning, stinging and pain. The fifth patient had responded to tacrolimus ointment but had discontinued treatment because of herpes simplex virus infection. Nine (82%) of the 11 patients treated with pimecrolimus cream 1% twice daily tolerated it well, including 3 of the 4 patients who had been previously intolerant of topical tacrolimus. All 9 patients experienced disease improvement within 4–6 weeks of treatment: 2 of them showed no visible activity of the disease and 7 had a partial response, with reduction in erythema, erosions and overall extent of the disease. With longer treatment periods (up to 10 months), 6 (55%) of the 9 patients who tolerated well treatment with pimecrolimus cream 1%, showed no residual activity of the disease and 3 (27%) had a partial response. Two of these partial responders still showed residual glazed erythema after 5 months of topical pimecrolimus. Overall, the response rate to pimecrolimus cream 1% was impressive because most patients apparently had a corticosteroid-resistant disease. Six of the 9 patients who tolerated well treatment with pimecrolimus cream 1%, only experienced mild warmth, stinging, burning tingling or itch on applying the cream during the first 2–3 days of the treatment period. Three patients had no symptoms at all after the application of pimecrolimus cream 1%. The 2 patients who were unable to tolerate pimecrolimus cream 1%, reported persistent itching and

local irritation after the cream application. The 3 patients who showed corticosteroid-induced skin atrophy, had complete response to treatment with pimecrolimus cream 1% and a substantial improvement of the atrophic changes. The patient who had developed herpes simplex virus infection during treatment with topical tacrolimus did not have any recurrence of the infection while using pimecrolimus cream 1%.

In a retrospective series of cases [20], effective treatment of recalcitrant vulvar lichen planus with tacrolimus ointment 0.1% twice daily was reported in 16 women (mean disease duration: 4.5 years) (Table 2). Fifteen patients (94%) experienced improvement of symptoms within 3 months, with at least partial resolution of the vulvar lesions. Of the 16 patients, 13 were followed after treatment cessation for 15.7 months, on the average. Lichen planus recurred in 10 patients within 6 months, but these relapses were less severe than those that had occurred in the past. Furthermore, the active lesions responded to topical tacrolimus, when therapy was resumed. Local application site reactions, such as burning and tingling, were reported in 6 patients.

Like genital lichen sclerosus, vulvar lichen planus is associated with an increased risk of squamous cell carcinoma [8]. Therefore, the considerations regarding the safety of continuous long-term treatment with TCIs [27] also apply to the use of these agents in patients with genital lichen planus.

3.3. Vulvar lichen simplex chronicus and related pruritic dermatoses

3.3.1. Vulvar lichen simplex chronicus

Any pruritic dermatosis of the vulva can lead to a self-perpetuating cycle of itch-scratch, which eventually results in the changes of the skin known as lichen simplex chronicus [8]. The vulvar skin is thickened, dry and rugose, scaly and hypo- or hyperpigmented (Fig. 3). Recent scratching may make the involved area red and swollen, with visible excoriation. The aim of treatment is to break the itch-scratch cycle [8].

In an open-label, exploratory study [22], 12 women (aged 25–53 years) with histologically-proven lichen simplex chronicus were treated with pimecrolimus cream 1% twice daily for 12 weeks (Table 1). The primary efficacy variable was the change in pruritus severity from baseline, as assessed by patients using a 10-cm Visual Analog Scale for Pruritus Relief (VAS-PR). Overall disease severity was evaluated by the investigators using the Investigator's Global Assessment (IGA) scoring system. The median VAS-PR score decreased from 6 cm (range 4.9–9.0 cm) at baseline to 0 cm (range 0–2.1 cm) at the end of the study. Seven patients (58%) reported complete resolution of pruritus by week 4 and showed no recurrence thereafter. IGA scores decreased from a moderate-to-severe median baseline score of 2.5 (range 2–3) to 0 (range 0–2) at study end. Erythema and lichenification improved in all patients. Pimecrolimus blood concentrations remained below the limit of quantification of the assays throughout the study and no adverse event was reported. To the best of our knowledge, there is no available study on the effectiveness of topical tacrolimus in the treatment of vulvar lichen simplex chronicus.

3.3.2. Chronic vulvar pruritus

Chronic vulvar pruritus may result in lichen simplex chronicus if left untreated [8]. In a recent open-label prospective study [24], 15 women with chronic vulvar pruritus of unknown cause were treated with pimecrolimus cream 1% twice daily for up to 4 weeks (Table 1). Thirteen patients showed an improvement and 10 of these had complete remission of pruritus, which persisted until completion of the 3-month follow-up period after treatment discontinuation. Three patients reported slight and transient application site burning, disappearing after the first 2–3 days of treatment in most cases.

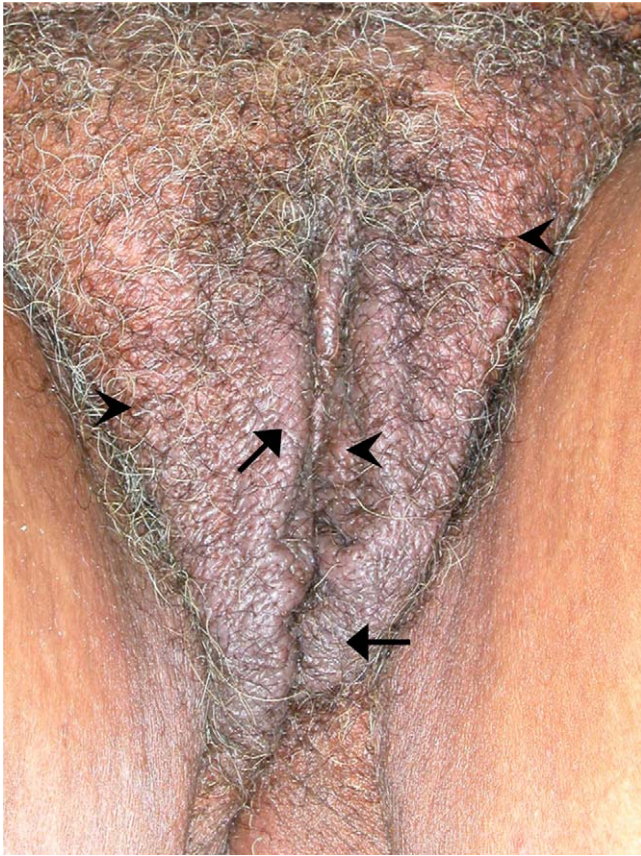


Fig. 3. Vulvar lichen simplex chronicus with severe lichenification (arrows) and evidence of excoriation of the labia majora (arrowheads).

3.3.3. Allergic contact dermatitis of the vulva (ACD-V)

ACD-V is caused by the application of substances that elicit a delayed type IV hypersensitivity reaction in predisposed individuals. Following sensitization to a given allergen, which may take place over years, patients will experience an inflammatory reaction, with itching and burning, within 48–72 h after re-exposure to that allergen. The inflammatory reaction persists for days and becomes chronic if the causative agent is not identified (often requiring patch testing) and avoided. The findings on physical examination may vary from mild erythema to erosions and fissures [8]. Scratching and chronic rubbing may lead to lichenification of the vulvar skin [8]. Several substances can cause these delayed hypersensitivity reactions [8,29,30], including the active ingredients of topical antibiotics and TCSs plus excipients, antiseptics, preservatives, fragrances, and spermicides. In up to 5% of cases, the dermatitis is due to sensitization to propolis, an excipient sometimes present in ointment medications [29,30].

In a case report [23], treatment with pimecrolimus cream 1% was effective at improving ACD-V in a 67-year-old woman with a 16-year history of chronic venous insufficiency, recurrent varicose ulcers and stasis dermatitis (Table 1). The patient had previously received long-term treatment with topical preparations for her stasis dermatitis and her ACD-V developed as a consequence of sensitization to propolis, as confirmed by the results of a patch test, presumably due to the long-term use of propolis-containing ointment formulations. Because tacrolimus ointment was erroneously thought to contain propolis [31], the patient was treated with pimecrolimus cream 1% twice daily for 1 month, on alternate days for the following month, and then twice per week for the third month. Her ACD-V cleared by the end of the treatment period and

there was no relapse over the following 9 months. The treatment was tolerated well.

4. Comment

The case reports, series of cases and open-label prospective studies discussed above suggest that TCI may represent a valuable second-line therapeutic option for anogenital lichen sclerosis, vulvar lichen planus, lichen simplex chronicus and related pruritic dermatoses in patients who are intolerant of, or resistant to TCSs. Local irritation may limit the use of these agents in some individuals, but pimecrolimus cream 1% may be better tolerated than topical tacrolimus as it has been successfully used in tacrolimus-intolerant patients [21]. Controlled clinical trials and comparative studies are warranted to substantiate the promising findings reviewed in this article.

Conflicts of interest

Andrew Goldstein has received funding for research from Novartis. Diamant Thaçi has received research grants and consulting honoraria from Astellas, Novartis, Schering-Plough, Sanofi-Aventis and Leo-Pharmaceutical Products, and has served as member of the speakers' bureau for the same companies. Thomas Luger has received research grants and consulting honoraria from Novartis, Abbott, Schering Plough, Serono, Wyeth, Hermal, Symrise, CERES, Danone, Leo Pharma and Shire, and has served as member of the speakers' bureau for the same companies. Avail GmbH (Basel, Switzerland) provided editorial support through funds from Novartis.

References

- [1] Grassberger M, Steinhoff M, Schneider D, Luger TA. Pimecrolimus—an anti-inflammatory drug targeting the skin. *Exp Dermatol* 2004;13:721–30.
- [2] Hultsch T, Kapp A, Spergel J. Immunomodulation and safety of topical calcineurin inhibitors for the treatment of atopic dermatitis. *Dermatology* 2005;211:174–87.
- [3] Alomar A, Berth-Jones J, Bos JD, et al. The role of topical calcineurin inhibitors in atopic dermatitis. *Br J Dermatol* 2004;151(70):3–27.
- [4] Hoetzenecker W, Ecker R, Kopp T, Stuetz A, Stingl G, Elbe-Bürger A. Pimecrolimus leads to an apoptosis-induced depletion of T cells but not Langerhans cells in patients with atopic dermatitis. *J Allergy Clin Immunol* 2005;115:1276–83.
- [5] Simon D, Vassina E, Yousefi S, Braathen LR, Simon HU. Inflammatory cell numbers and cytokine expression in atopic dermatitis after topical pimecrolimus treatment. *Allergy* 2005;60:944–51.
- [6] Büchau AS, Schaubert J, Hultsch T, Stuetz A, Gallo RL. Pimecrolimus enhances TLR2/6-induced expression of antimicrobial peptides in keratinocytes. *J Invest Dermatol* 2008;128:2646–54.
- [7] Hengge UR, Ruzicka T, Schwartz RA, Cork MJ. Adverse effects of topical glucocorticoids. *J Am Acad Dermatol* 2006;54:1–15.
- [8] Salim A, Wojnarowska F. Skin diseases affecting the vulva. *Curr Obstet Gynaecol* 2005;15:97–107.
- [9] ACOG Practice Bulletin No. 93. Diagnosis and management of vulvar skin disorders. *Obstet Gynecol* 2008;111:1243–53.
- [10] Assmann T, Becker-Wegerich P, Grewe M, Megahed M, Ruzicka T. Tacrolimus ointment for the treatment of vulvar lichen sclerosis. *J Am Acad Dermatol* 2003;48:935–7.
- [11] Kunstfeld R, Kirnbauer R, Stingl G, Karlhofer FM. Successful treatment of vulvar lichen sclerosis with topical tacrolimus. *Arch Dermatol* 2003;139:850–2.
- [12] Böhm M, Frieling U, Luger TA, Bonsmann G. Successful treatment of anogenital lichen sclerosis with topical tacrolimus. *Arch Dermatol* 2003;139:922–4.
- [13] Goldstein AT, Marinoff SC, Christopher K. Pimecrolimus for the treatment of vulvar lichen sclerosis in a premenarchal girl. *J Pediatr Adolesc Gynecol* 2004;17:35–7.
- [14] Boms S, Gambichler T, Freitag M, Altmeyer P, Kreuter A. Pimecrolimus 1% cream for anogenital lichen sclerosis in childhood. *BMC Dermatol* 2004;4:14. doi: 10.1186/1471-5945-4-14.
- [15] Goldstein AT, Marinoff SC, Christopher K. Pimecrolimus for the treatment of vulvar lichen sclerosis: a report of 4 cases. *J Reprod Med* 2004;49:778–80.
- [16] Nissi R, Eriksen H, Risteli J, Niemimaa M. Pimecrolimus cream 1% in the treatment of lichen sclerosis. *Gynecol Obstet Invest* 2007;127:808–16.
- [17] Hengge UR, Krause W, Hofmann H, et al. Multicentre, phase II trial on the safety and efficacy of topical tacrolimus ointment for the treatment of lichen sclerosis. *Br J Dermatol* 2006;155:1021–8.
- [18] Luesley DM, Downey GP. Topical tacrolimus in the management of lichen sclerosis. *BJOG* 2006;113:832–4.

- [19] Virgili A, Lauriola MM, Mantovani L, Corazza M. Vulvar lichen sclerosis: 11 women treated with tacrolimus 0.1% ointment. *Acta Derm Venereol* 2007;87:69–72.
- [20] Byrd JA, Davis MD, Rogers RS. Recalcitrant symptomatic vulvar lichen planus. *Arch Dermatol* 2004;140:715–20.
- [21] Lonsdale-Eccles AA, Velangi S. Topical pimecrolimus in the treatment of genital lichen planus: a prospective case series. *Br J Dermatol* 2005;153:390–4.
- [22] Goldstein AT, Parneix-Spax A, McCormick CL, Burrows LJ. Pimecrolimus cream 1% for treatment of vulvar lichen simplex chronicus: an open label, preliminary trial. *Gynecol Obstet Invest* 2007;64:180–6.
- [23] Black RJ. Vulval eczema associated with propolis sensitization from topical therapies treated successfully with pimecrolimus cream. *Clin Exp Dermatol* 2005;30:91–2.
- [24] Sarifakioglu E, Gumus II. Efficacy of topical pimecrolimus in the treatment of chronic vulvar pruritus: a prospective case series—a non-controlled, open-label study. *J Dermatol Treat* 2006;17:276–8.
- [25] Oskay T, Sezer HK, Genç C, Kutlay L. Pimecrolimus 1% cream in the treatment of vulvar lichen sclerosis in postmenopausal women. *Int J Dermatol* 2007;46:527–32.
- [26] Bilenchi R, Poggiali S, De Padova LA, Pisani C, De Paola M, Fimiani M. Human papillomavirus reactivation following topical tacrolimus therapy of anogenital lichen sclerosis. *Br J Dermatol* 2007;156:405–6.
- [27] Spergel JM, Leung DY. Safety of topical calcineurin inhibitors in atopic dermatitis: evaluation of the evidence. *Curr Allergy Asthma Rep* 2006;6:270–4.
- [28] Langley RGB, Luger TA, Cork MJ, Schneider D, Paul C. An update on the safety and tolerability of pimecrolimus cream 1%: evidence from clinical trials and post-marketing surveillance. *Dermatology* 2007;215(1):27–44.
- [29] Gallenkemper G, Rabe E, Bauer R. Contact sensitization in chronic venous insufficiency: modern wound dressings. *Contact Dermatitis* 1998;38:274–8.
- [30] Bauer A, Geier J, Elsner P. Allergic contact dermatitis in patients with anogenital complaints. *J Reprod Med* 2000;45:649–65.
- [31] Lübke J, Sanchez-Politta S. Propolis, beeswax, and the sensitization potential of topical calcineurin inhibitors. *Clin Exp Dermatol* 2006;31:147–8.