Dermatology Practical & Conceptual

Topical Tacrolimus for Lichen Sclerosus: Systematic Review of Efficacy and Safety

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ABSTRACT

Introduction: Lichen sclerosus (LS) is a chronic inflammatory dermatosis affecting both genital and extragenital sites, with a prevalence of approximately 3% among females in the United Kingdom, particularly in the post-menopausal population. Although its etiology remains incompletely understood, LS can significantly impair quality of life through pain, pruritus, and scarring [1]. Current guidelines recommend potent topical corticosteroids, most commonly clobetasol, as first-line therapy [2]; however, long-term use is limited by adverse effects such as skin atrophy [3].

Objectives: This systematic review evaluates the efficacy and safety of topical tacrolimus in the management of lichen sclerosus.

Methods: A comprehensive literature search was conducted in accordance with PRISMA guidelines [4]. Fourteen randomized controlled trials comprising 335 patients with lichen sclerosus were included.

Results: Of the included patients, 2% (N=6) presented with extragenital disease and 98% (N=331) with anogenital involvement. Most patients (81%, N=272) were treated with topical tacrolimus 0.1% twice daily, while 19% (N=63) received clobetasol as a comparator. Clinical improvement, ranging from partial symptom relief to complete remission, was observed in 90% (N=244) of tacrolimus-treated patients. Severe adverse events requiring discontinuation were rare (1%, N=3). Compared with corticosteroids, tacrolimus was associated with superior patient-reported outcomes, clinician-reported improvement, and histological response.

Conclusion: Topical tacrolimus appears to be a safe and effective therapeutic option for lichen sclerosus, demonstrating favorable clinical and histological outcomes with minimal adverse effects. Further long-term prospective trials are needed to confirm its comparative efficacy, safety, and role in future treatment guidelines.

Introduction

Lichen sclerosus (LS) is a chronic inflammatory dermatosis that predominantly affects the anogenital region, though extragenital involvement can also occur. Clinically, LS is characterized by depigmented or hypopigmented, erythematous, and atrophic patches or plaques. It affects approximately 3% of females in the United Kingdom, particularly those in the post-menopausal demographic. Whilst the etiology is not fully understood, the impact on quality of life due to pain, itching, and scarring can be significant; however, patients may be asymptomatic. Chronic anogenital involvement can lead to scarring and carries an increased risk of squamous cell carcinoma (SCC) when not adequately treated [1].

The mainstay of therapy for anogenital LS is topical immunosuppression with high-potency corticosteroids [2]. Although many cases of anogenital LS respond well to high-potency topical corticosteroids, the second-line therapy is tacrolimus, which is often better tolerated than steroid-related side effects that can limit use of topical steroids [3]. Herein, we performed a systematic review to evaluate the efficacy and safety of using topical tacrolimus in lichen sclerosus.

Objectives

The primary objective of this systematic review was to evaluate the efficacy and safety of topical tacrolimus in the management of lichen sclerosus, with particular focus on clinical, patient-reported, and histological outcomes. Secondary objectives were to assess rates of treatment response, relapse, and adverse effects, and to compare outcomes with those reported for potent topical corticosteroids, which remain the current first-line therapy according to UK national guidelines [2]. Given ongoing concerns regarding corticosteroid-associated skin atrophy [3] and limited long-term data on topical calcineurin inhibitors, this review aimed to clarify the therapeutic role of tacrolimus, particularly in patients with steroid-refractory disease or disease affecting sensitive anatomical sites [6,15,17]. Additionally, this review sought to highlight methodological heterogeneity and gaps in outcome reporting to inform the design of future prospective studies in lichen sclerosus [4].

Methods

This systematic review was performed in line with a registered protocol and reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [4]. The review was also registered on PROSPERO Centre for Reviews and Dissemination.

A literature search was performed in August 2025 using MEDLINE (via PubMed), EMBASE (via OVID), and Cochrane database using MeSH terms in all combinations: 'tacrolimus' or 'tacrolimus ointment' or 'topical tacrolimus' or 'pimecrolimus' or 'topical pimecrolimus' and 'lichen sclerosus' or 'lichen sclerosus et atrophicus' and 'symptom control' or 'efficacy' and 'adult' or 'middle-aged' and 'human'. Two reviewers completed full-text reviews. Studies identified were reviewed for duplicates.

The exact search strategy is detailed below in Figure 1:

The inclusion and exclusion criteria were established before commencing the literature search. The inclusion criteria are as follows:

i. randomized controlled trials (RCT), prospective or retrospective cohort studies, case (control) studies, cross-sectional studies
ii. patients had established lichen sclerosus
iii. there were reported outcomes after a course of tacrolimus given as intervention
iv. original, full publications published in the English language

The following parameters were measured: patient age, site of disease, reported outcome, tacrolimus dosage/intervention, time that intervention was applied, relapse, interventions previously tried and reported, adverse effects, side effects of intervention. As there are no standardized, widely accepted scales to measure clinical improvement in patients with LS, we considered cases to have improved if there was any reported improvement as assessed by patient- or clinician-reported improvement, improvement in symptomatology, improvement in physical exam findings, or histological improvement. Patients who demonstrated relapse in the follow-up window were still considered to have improved with therapy if there was a period of improvement before relapse.

Results

The initial literature search identified 32 studies for screening. After removal of duplicates (N=4), 28 studies remained. Of these, 12 were excluded as they did not meet eligibility criteria (ongoing clinical trials or incomplete data), leaving 16 studies for full-text review. Ultimately, 14 primary studies, comprising a total of 335 patients, were included in this systematic review. Systematic reviews and meta-analyses were examined separately. The included studies consisted of 10 cohort studies, two retrospective studies, and two case reports. Publication dates ranged from 2003 to 2014. Evidence is summarized in Table 1.

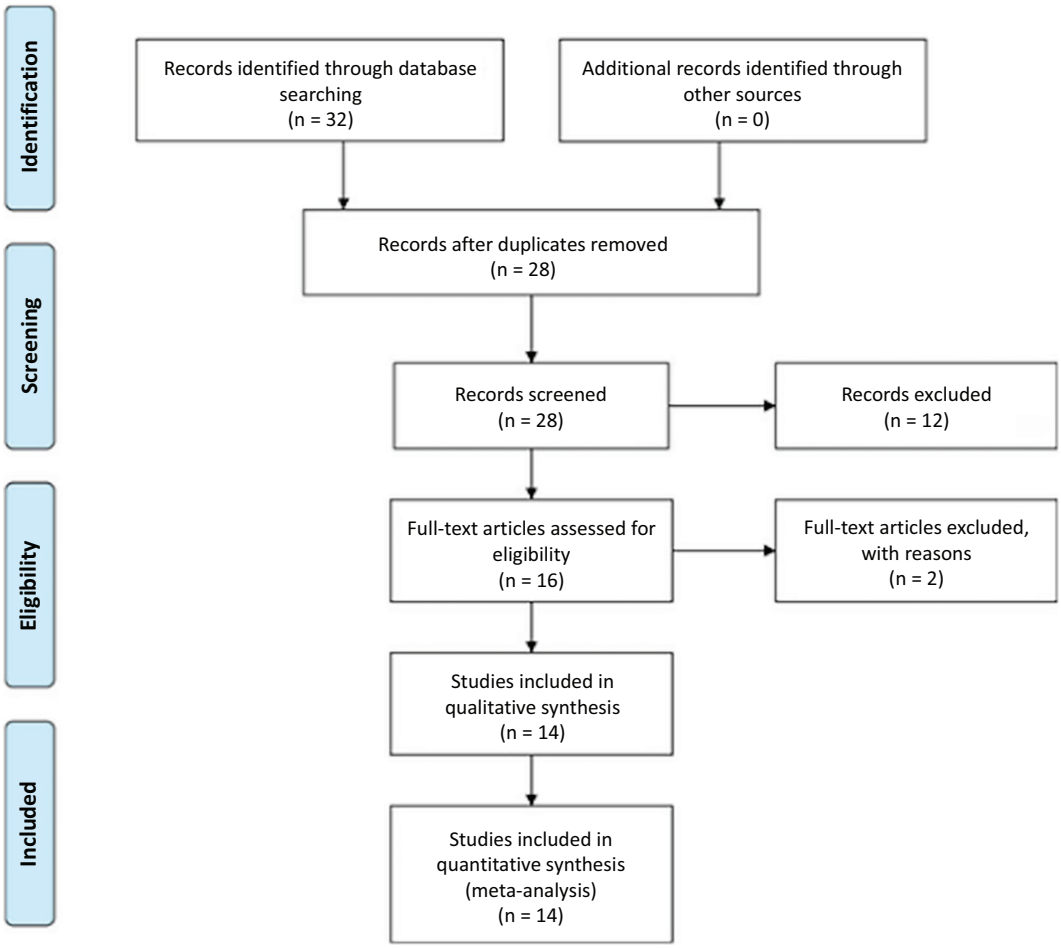

Figure 1. Search strategy in accordance with PRISMA.

Patient Characteristics and Treatment Regimens

Among the included cohort, 81% (N=272) of patients were treated with topical tacrolimus 0.1% twice daily, while 19% (N=63) received clobetasol, either as a comparator or control arm [15-17]. The vast majority of patients (98%, N=331) had anogenital LS, while only 2% (N=6) had extragenital disease [8]. Patient ages ranged from 4 to 85 years; however, age data were not reported for 31% (N=105) of patients. Follow-up periods varied from four weeks to 12 months. One third of patients (33%, N=112) had previously failed treatment with corticosteroids, emollients, or topical estrogens before commencing tacrolimus [9-15].

Efficacy Outcomes

Of the 272 patients treated with tacrolimus, 90% (N=244) demonstrated improvement ranging from partial symptomatic relief to complete remission. A subset of 10% (N=28) failed to respond to therapy [9,16,12,13,17,15]. Relapse was reported in 11 patients, of whom five had anogenital LS and six had an unspecified site of disease. Relapses were commonly associated with shorter treatment durations or discontinuation of tacrolimus; in several cases, remission was re-established upon restarting treatment [13,17,8].

To visually summarize treatment responses across included studies, a forest plot was generated. This demonstrates that most cohorts reported moderate-to-high rates of clinical improvement with topical calcineurin inhibitors, with a pooled estimate indicating benefit in the majority of patients (Figure 2).

Diagnostic Confirmation and Outcome Measures

The majority of patients had biopsy-proven LS prior to treatment initiation, although 11% (N=36) were diagnosed clinically without histological confirmation. Outcomes were assessed through a range of subjective and objective measures. The most common approach was symptom monitoring, including changes in pruritus, erythema, atrophy, and hypopigmentation. Visual analogue scales (VAS) for burning /pain and pruritus were used in 37% (N=124) [10,11,15], providing a quantitative assessment of symptom severity. The Female Sexual Distress Scale (FSDS) was used in 11% (N=36) to evaluate impact on sexual function [6]. Objective assessments included pre- and posttreatment biopsies in 19% (N=65), which demonstrated improvements in histological parameters such as increased type I and type III procollagen synthesis, reduced inflammatory infiltrates, downregulation

Table 1. Evidence summary table – topical calcineurin inhibitors in lichen sclerosus.

Study (Ref)	N (patients)	Age (range/ mean)	Location	Prior treatment	Intervention (dose)	Follow-up	Diagnosis	Outcome	Adverse effects	Relapse
Kauppila et al. [5]	25	41–85 (mean 66.5)	Anogenital	Corticosteroid	Pimecrolimus 1% BD	2 mo	Biopsy proven LS	Histological improvement in 20/25	n/a	n/a
Böhm et al. [6]	6	5–62 (mean 27)	Anogenital	Multiple (emollients, antifungal, etc.)	Tacrolimus 1% BD	1.5–10 mo	Biopsy proven LS	Complete symptom resolution in 6/6	n/a	n/a
Kim et al. [8]	16	8–67 (mean 36)	10 Anogenital, 6 Extra	8 had corticosteroids (no benefit)	Tacrolimus 0.1% BD	6–24 wks (genital), 4–12 wks (extra)	Biopsy proven LS	9/10 improved (genital), 1/6 improved (extra-genital)	n/a	6
Goldstein et al. [7]	36	Not listed	Anogenital	n/a	19 Clobetasol OD, 17 Pimecrolimus BD	12 wks	Biopsy proven LS	18/19 clobetasol improved; 9/17 pimecrolimus improved	n/a	n/a
Burrows et al. [6]	36	≥18 (not listed)	Anogenital	n/a	19 Pimecrolimus BD, 17 Clobetasol OD	12 wks	Biopsy proven LS	Histological + FSDS improvement in 36/36	n/a	n/a
Hengge et al. [17]	70	5–85 (mean 59)	Anogenital	n/a	Tacrolimus 1% BD	16 wks	Biopsy proven LS	54/70 improved	1 withdrawal	3
Nissi et al. [13]	26	42–79 (mean 61)	Anogenital	19/26 systemic/ topical oestrogen	Pimecrolimus 1% BD	2 & 6 mo	16/26 biopsy	23/26 improved, 1/26 no response	2 withdrawals	2
Goldstein et al. [18]	4	8–62 (mean 37)	Anogenital	n/a	Pimecrolimus 1% BD	3 mo	n/a	4/4 improved; 3/4 remission; 2/4 histological improvement	n/a	n/a

Study (Ref)	N (patients)	Age (range/ mean)	Location	Prior treatment	Intervention (dose)	Follow-up	Diagnosis	Outcome	Adverse effects	Relapse
Virgili et al. [12]	11	32–80 (mean 54)	Anogenital	Potent corticosteroids	Tacrolimus 1% BD	3.5 mo	2/11 biopsy	4 remission; 4 good; 2 slight; 1 no response; 2 histological improvement	n/a	n/a
Patsatsi et al. [11]	13	Mean 59	Anogenital	Methylprednisolone aceponate (8 wks)	Tacrolimus OD	12 wks	n/a	VAS score improvement in 13/13	n/a	n/a
Ozer Arican et al. [16]	1	74	Anogenital	n/a	Tacrolimus BD	16 wks	Biopsy proven LS	No improvement	n/a	n/a
Kyriakou et al. [10]	20	≥18	Anogenital	Methylprednisolone aceponate (8 wks)	Tacrolimus 0.1%	12 wks	Biopsy proven LS	VAS score improvement in 20/20	n/a	n/a
Luesley & Downey [9]	16	31–79 (median 48)	Anogenital	Fluorinated steroids + emollients	Tacrolimus 0.1% BD	12 mo	Biopsy proven LS	2 complete; 8 partial; 6 no response	5 (no withdrawal)	n/a
Funaro et al. [15]	55	4–73 (mean 47)	Anogenital	n/a	28 Tacrolimus, 27 Clobetasol	4 mo	Biopsy proven LS	Symptom + VAS reduction in both groups (55/55)	n/a	n/a

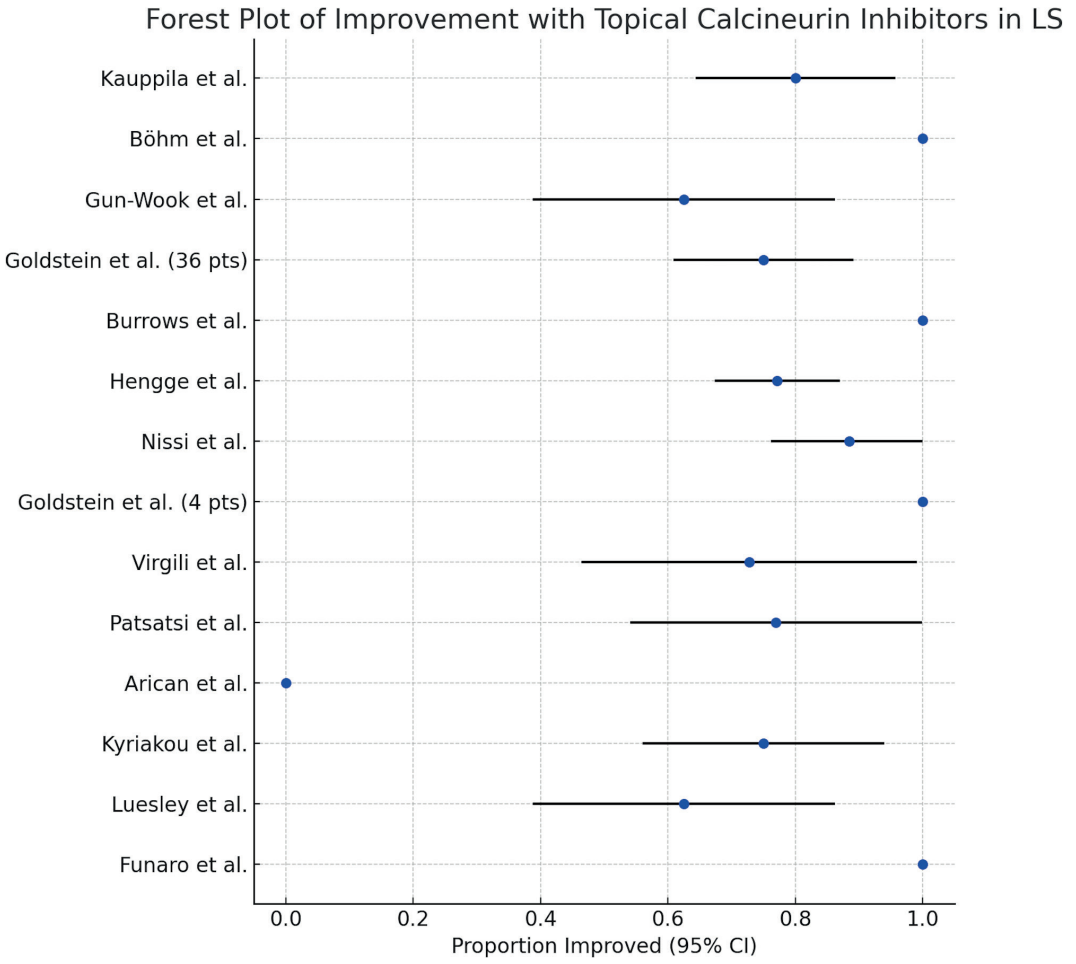

Figure 2. Forest plot of improvement with topical calcineurin inhibitors in LS.

of CD3 and CD8 T cells, CD57+ natural killer cells, and decreased CD68+ macrophage staining [12,18,6,5].

Safety Outcomes

The most frequently reported adverse effects associated with tacrolimus were transient stinging or itching at the site of application, which typically resolved within a few days of continued use. Severe adverse effects requiring discontinuation of treatment were rare, occurring in only 1% (N=3) of patients [17,13].

Discussion

According to the *British Association for Sexual Health and HIV* in the *2014 UK National Guideline on the management of vulval conditions*, the first-line management of vulval lichen sclerosus is clobetasol propionate [2]. The adverse reactions related to topical steroids are correlated with skin atrophy, and particularly in the context of lichen sclerosus, can exacerbate the symptoms associated with disease [3]. With the prevalence of anogenital lichen sclerosus, topical steroids would be used in an already sensitive area with thin skin. This analysis has indicated the role of tacrolimus after failed topical steroid treatment. Making tacrolimus first line could avoid the use of steroids in this particularly sensitive area and have the added benefit of increasing collagen stimulation in an otherwise atrophic disease [6].

Cost needs to be considered, with clobetasol being GBP 1.86 drug tariff price versus GBP 25.92 for tacrolimus [19]. This raises the question of whether clinical management should prioritise initial use of a lower-cost therapy with recognised adverse effects, or instead favour a more expensive option that offers superior efficacy and a more favourable, transient side-effect profile.

There are concerns surrounding the link between the use of systemic tacrolimus and developing cancer, particularly squamous cell carcinoma. A study conducted in rats demonstrated that the CD4:CD8 ratio was significantly reduced and there was an effect on Erk and p53 cancer signaling pathways, highlighting its carcinogenic potential [20]. However, a systematic review in humans showed that pimecrolimus had little-to-no association with cancer when compared to the control and was deemed safe in atopic dermatitis [21]. The data need to be further investigated to allow confidence in changing tacrolimus to first line.

Furthermore, the etiology of lichen sclerosus is still unknown. It is primarily treated by gynecology specialists, as seen in the UK national guideline, with only one of the consultants having a dermatology background [2]. By treating lichen sclerosus in a multidisciplinary manner and utilizing the relevant expertise, patients can be better treated for this debilitating disease.

The limitations of this study include its retrospective nature and the variation in outcomes measured in each study, which ranged from observing subjective symptom control, a visual analog scale, and biopsy of skin lesions with histology. This can be difficult to interpret; however, the variance contributes to heterogeneity. This could be combatted by using a validated scoring system to quantify lichen sclerosus symptoms, which would help in standardizing outcomes and improving record keeping.

Further prospective studies could include the long-term implications of topical tacrolimus use. In addition, creating and trialing a standardized symptom scale for lichen sclerosus can measure outcomes more uniformly.

Conclusion

This systematic review demonstrates that topical tacrolimus is a safe and effective therapeutic option for patients with lichen sclerosus, particularly in cases where corticosteroids are poorly tolerated or have failed to provide adequate control. Across the included studies, tacrolimus consistently improved symptoms, clinical signs, and histological markers of disease activity, with relapse often responsive to re-initiation of therapy [13,17,8]. Adverse effects were infrequent, mild, and typically self-limiting [17,13].

While current guidelines continue to recommend potent corticosteroids as first-line treatment [2], these findings highlight the potential role of tacrolimus as an alternative or adjunctive therapy, especially in sensitive anatomical sites where steroid-related atrophy poses significant concerns. However, heterogeneity in outcome measures and a lack of long-term prospective trials limit definitive conclusions regarding tacrolimus's comparative efficacy and long-term safety.

Future research should focus on large, prospective, randomized trials incorporating standardized and validated outcome measures as well as on cost-effectiveness analyses to better define the place of topical tacrolimus in the management algorithm for lichen sclerosus.

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