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REVIEW ARTICLE

Clinical evidence on topical tacrolimus in exfoliative cheilitis: a systematic review

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Abstract:

This systematic review aimed to evaluate the available clinical evidence regarding the efficacy and safety of topical tacrolimus in the treatment of exfoliative cheilitis (EC). A systematic review was conducted in accordance with PRISMA guidelines and registered in PROSPERO (CRD420251043565). Searches were performed through PubMed, Scopus, Web of Science, SciELO, Embase, Cochrane Library, Google Scholar and grey literature. Manual searches for reference lists were conducted. Two independent reviewers selected studies, extracted data and assessed bias. Eligible studies included randomized controlled trials (RCTs), cohort, case-control studies, and case series. Risk of bias was evaluated using RoB 2.0 and JBI checklists. Two studies met inclusion criteria: one RCT and one cross-sectional study, totaling 61 participants. Both evaluated topical tacrolimus for EC, with concentrations of 0.03 and 0.1%. Most patients achieved complete clinical resolution compared to control groups (triamcinolone acetonide and petroleum jelly) during 3–6 months follow-up, demonstrating significantly lower recurrence rates (30.8-38.5% vs. 61.5-100% in controls; $p<0.05$ for both comparisons). The pooled data demonstrated negligible treatment-related adverse effects. While demonstrating safety and efficacy, tacrolimus therapy is associated with recurrence rates surpassing 30% during 3–6-month follow-up. EC is highly prevalent but remains a clinical challenge due to its unclear etiopathogenesis, which hinders the development of evidence-based treatments. Considering its substantial symptomatic and aesthetic impact, our findings highlight the urgent need for high-quality research in this area.

Keywords: Exfoliative cheilitis; Lip diseases; Treatment outcome; Tacrolimus.

INTRODUCTION

Exfoliative cheilitis (EC) is a chronic inflammatory condition of the lips with unknown etiology[1], predominantly affecting young females[1,2]. The management of EC is often challenging and its prevalence varies depending on the studied population. Multiple factors have been suggested as contributors to its development, including vitamin and immune deficiencies, fungal or bacterial infections, psychiatric conditions, seasonal changes, and factitious activities[1]. Common symptoms include lip dryness, persistent production and desquamation of scales, cracking, bleeding, burning sensation, and itching[1]. Treatment options include topical corticosteroids, tacrolimus, *Calendula officinalis* 10% ointment, antibiotics, antidepressants, dupilumab, laser therapy, and phytotherapy[1,3,4]. However, available evidence remains limited, and no definitive management protocol has yet been established[1].

Clinical Significance Statement
This review highlights tacrolimus as a promising treatment for exfoliative cheilitis, offering symptom control despite relapses, and emphasizes the need for interdisciplinary management to optimize therapeutic outcomes.

In addition to its physical manifestations, EC can have a considerable psychosocial impact, often leading to distress, social embarrassment, and reduced quality of life, particularly in young adults[5]. These effects may be further aggravated in patients with psychiatric disorders, such as anxiety, depression, or obsessive-compulsive behaviors, which are frequently reported in association with EC[5]. Immunologically, studies have indicated altered local immune responses and epithelial barrier dysfunctions[6], leading to hypersensitivity and with evidence suggesting a potential

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role of T-cell-mediated, as observed in other chronic inflammatory dermatoses[6]. These findings reinforce the hypothesis that EC may involve complex multifactorial mechanisms that require further investigation, not only to improve therapeutic efficacy but also to minimize recurrence and long-term burden.

Therefore, the aim of this systematic review was to critically assess the available clinical evidence regarding the efficacy and safety of topical tacrolimus in the management of EC.

METHODS

A systematic review was conducted according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, with the aim of identifying the most effective treatment for EC. The following research question was formulated: "What evidence is available regarding the efficacy of topical tacrolimus in the treatment of exfoliative cheilitis?".

The PICOS framework was used to guide the eligibility criteria: P (Population) — patients diagnosed with EC; I (Intervention) — topical tacrolimus; C (Comparison) — no comparison group required; O (Outcome): treatment efficacy and clinical outcomes; S (Study design) — all clinical human studies (observational and experimental). This review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the registration number CRD420251043565.

Search strategy

A comprehensive literature search was conducted across multiple databases, with PubMed serving as the primary source (Table 1). The search encompassed all available records up to July 2025, applying no restrictions on publication date or language. Studies were identified using a combination of keywords and their respective MeSH entry terms, which were used independently and subsequently combined using the Boolean operator AND to refine the results. Additional searches were performed through Embase, Web of Science, Scopus, SciELO, Google Scholar, and the Cochrane Library. A complementary search for grey literature was conducted through IBICT (Instituto Brasileiro de Informação em Ciência e Tecnologia). Furthermore, a manual search of the reference lists of the included articles was carried out to identify any additional studies not captured through the electronic searches. This multi-source strategy aimed to maximize sensitivity and minimize the risk of omitting relevant publications, adhering to PRISMA guidelines for systematic reviews.

Eligibility criteria and risk of bias assessment

Two independent reviewers (M.C.S. and M.K.C.) conducted a comprehensive screening of the articles during the selection process. The inclusion criteria were original clinical studies in humans, including randomized controlled trials (RCTs), prospective and retrospective cohort studies, case series, and case-control studies. The exclusion criteria included: *in vitro* or animal studies; case reports; literature reviews; conference abstracts and proceedings; studies without detailed treatment descriptions; inconclusive diagnosis; and cases with allergen-related (allergic contact cheilitis) or sun exposure-related (actinic cheilitis) etiology. Disagreements between reviewers were resolved through discussion, with unresolved cases adjudicated by a third reviewer (E.S.T.).

The results were combined, and, after duplicate removal (EndNote web software, Clarivate Analytics, Philadelphia, Pennsylvania, USA), the reviewers screened the yielded titles and abstracts. After the evaluation of the full text, the selected articles were submitted to the quality assessment and final review.

The risk of bias was evaluated using the following tools: the Cochrane Risk of Bias (RoB 2.0) tool for RCTs[7,8] (Table 2); the Joanna Briggs Institute (JBI) critical appraisal checklists for case series and cross-sectional studies[9] (Table 3). Studies rated as having a high risk of bias were excluded from the final analysis.

Data extraction

Data extraction was performed using a standardized spreadsheet developed specifically for this review. The process was conducted independently by two reviewers, and discrepancies were resolved by consensus. The following variables were extracted from each included study: number of patients, age, treatment protocol, clinical outcomes, adverse effects, follow-up duration, and time to recurrence.

RESULTS

The results are presented in Figure 1. The databases and manual search yielded 236 potentially relevant references. After duplicate removal, 222 studies underwent title/abstract screening, of which five met eligibility criteria for full-text review. Two studies were excluded due to unavailability of full texts, and another

Table 1. Search strategy and databases.

Database	Keywords
Google scholar	("Exfoliative cheilitis" OR "Desquamative cheilitis" OR "Lip dermatitis") AND ("Topical treatment" OR "Topical corticosteroids" OR "Tacrolimus" OR "Systemic treatment" OR "Oral corticosteroids" OR "Immunosuppression therapy")
Scopus	TITLE-ABS-KEY("Exfoliative cheilitis" OR "Desquamative cheilitis" OR "Cheilitis" OR "Exfoliative lip dermatitis" OR "Chronic cheilitis" OR "Chronic lip inflammation" OR "Lip dermatitis" OR "Idiopathic cheilitis") AND TITLE-ABS-KEY("Topical treatment" OR "Topical corticosteroids" OR "Tacrolimus" OR "Systemic treatment" OR "Oral corticosteroids" OR "Immunosuppression therapy") AND TITLE-ABS-KEY("Efficacy")
SciELO	("Exfoliative cheilitis" OR "Desquamative cheilitis" OR "Lip dermatitis") AND ("Topical treatment" OR "Topical corticosteroids" OR "Tacrolimus" OR "Systemic treatment" OR "Oral corticosteroids" OR "Immunosuppression therapy")
Web of Science	TS=("Exfoliative cheilitis" OR "Desquamative cheilitis" OR "Cheilitis" OR "Exfoliative lip dermatitis" OR "Chronic cheilitis" OR "Chronic lip inflammation" OR "Lip dermatitis" OR "Idiopathic cheilitis") AND TS=("Topical treatment" OR "Topical corticosteroids" OR "Tacrolimus" OR "Systemic treatment" OR "Oral corticosteroids" OR "Immunosuppression therapy") AND TS=("Efficacy")
PubMed	((((((((((Exfoliative cheilitis) OR (Desquamative cheilitis)) OR (Cheilitis)) OR (Actinic cheilosis)) OR (Cheilitides)) OR (Exfoliative lip dermatitis)) OR (Chronic cheilitis)) OR (Chronic lip inflammation)) OR (Lip dermatitis)) OR (Idiopathic cheilitis)) AND ((((((((((((((((((((((((((((((Topical treatment) OR (Topical corticosteroids)) OR (Tacrolimus)) OR (Prograf)) OR (Prograft)) OR (Anhydrous Tacrolimus)) OR (Tacrolimus, Anhydrous)) OR (Tacrolimus Anhydrous)) OR (Anhydrous, Tacrolimus)) OR (FK-506)) OR (FK 506)) OR (FK506)) OR (FR-900506)) OR (FR900506)) OR (FR 900506)) OR (Systemic treatment)) OR (Oral corticosteroids)) OR (Immunosuppression therapy)) OR (Immunosuppression Therapies)) OR (Therapies, Immunosuppression)) OR (Therapy, Immunosuppression)) OR (Antirejection Therapy)) OR (Anti-Rejection Therapy)) OR (Anti-Rejection Therapies)) OR (Anti Rejection Therapy)) OR (Immunosuppressive Therapy)) OR (Immunosuppressive Therapies)) OR (Therapies, Immunosuppressive)) OR (Therapy, Immunosuppressive)) OR (Immunosuppression)) OR (Immunosuppressions)) OR (Therapy, Antirejection)) OR (Antirejection Therapies)) OR (Therapy, Anti-Rejection))) AND (Efficacy)
The Cochrane Library	TS=("Exfoliative cheilitis" OR "Desquamative cheilitis" OR "Cheilitis" OR "Exfoliative lip dermatitis" OR "Chronic cheilitis" OR "Chronic lip inflammation" OR "Lip dermatitis" OR "Idiopathic cheilitis") AND TS=("Topical treatment" OR "Topical corticosteroids" OR "Tacrolimus" OR "Systemic treatment" OR "Oral corticosteroids" OR "Immunosuppression therapy") AND TS=("Efficacy")
Embase	("Exfoliative cheilitis"/exp OR "Desquamative cheilitis":ti,ab OR "Cheilitis"/exp OR "Exfoliative lip dermatitis":ti,ab OR "Chronic cheilitis":ti,ab OR "Chronic lip inflammation":ti,ab OR "Lip dermatitis":ti,ab OR "Idiopathic cheilitis":ti,ab) AND ("Topical treatment":ti,ab OR "Topical corticosteroids"/exp OR "Tacrolimus"/exp OR "Systemic treatment":ti,ab OR "Oral corticosteroids"/exp OR "Immunosuppression therapy"/exp) AND ("Efficacy":ti,ab OR "Effectiveness"/exp)
IBICT (Brazilian Grey Literature)	(Todos os campos:Exfoliative cheilitis OU Todos os campos:Desquamative cheilitis OU Todos os campos:Cheilitis OU Todos os campos:Cheilitides OU Todos os campos:Exfoliative lip dermatitis OU Todos os campos:Chronic cheilitis OU Todos os campos:Chronic lip inflammation OU Todos os campos:Lip dermatitis OU Todos os campos:Idiopathic cheilitis) E (Todos os campos:Topical treatment OU Todos os campos:Topical corticosteroids OU Todos os campos:Tacrolimus OU Todos os campos:Prograf OU Todos os campos:Prograft OU Todos os campos:Anhydrous Tacrolimus OU Todos os campos:Tacrolimus, Anhydrous OU Todos os campos:Tacrolimus Anhydrous OU Todos os campos:Anhydrous, Tacrolimus OU Todos os campos:FK-506 OU Todos os campos:FK 506 OU Todos os campos:FK506 OU Todos os campos:FR-900506 OU Todos os campos:FR900506 OU Todos os campos:FR 900506 OU Todos os campos:Systemic treatment OU Todos os campos:Oral corticosteroids OU Todos os campos:Immunosuppression therapy OU Todos os campos:Immunosuppression Therapies OU Todos os campos:Therapies, Immunosuppression OU Todos os campos:Therapy, Immunosuppression OU Todos os campos:Antirejection Therapy OU Todos os campos:Anti-Rejection Therapy OU Todos os campos:Anti-Rejection Therapies OU Todos os campos:Anti Rejection Therapy OU Todos os campos:Immunosuppressive Therapy OU Todos os campos:Immunosuppressive Therapies OU Todos os campos:Therapies, Immunosuppressive OU Todos os campos:Therapy, Immunosuppressive OU Todos os campos:Immunosuppression OU Todos os campos:Immunosuppressions OU Todos os campos:Therapy, Antirejection OU Todos os campos:Antirejection Therapies OU Todos os campos:Therapy, Anti-Rejection) E (Todos os campos:Efficacy)

IBICT: *Instituto Brasileiro de Informação em Ciência e Tecnologia.*

was eliminated based on high risk of bias. The final analysis included two articles: one RCT[10] and one cross-sectional study[11].

The data extracted from the included studies are presented in Table 4. The sample sizes of the studies ranged from 26[11] to 35[10] participants, totaling 61 patients. The two included studies both examined topical tacrolimus, with Kothari et al.[11] investigating 0.1% concentration (*vs.* petroleum jelly control) in cases of EC induced by isotretinoin use, and Liu et al.[10] evaluating

Table 2. Risk of bias assessment – ROB 2.0[1,10]

Domain	Liu et al.,[10] Judgment	Liu et al.,[10] Justification	Zhang et al.,[1] Judgment	Zhang et al.,[1] Justification
D1 – Bias arising from the randomization process	Low risk	Randomization by computer-generated code, opaque envelopes, odd=experimental, even=control.	Low risk	Randomization was reported; however, no detailed information on sequence generation or allocation concealment was provided.
D2 – Bias due to deviations from intended interventions	Low risk	Double-blind; participants and evaluators blinded.	High risk (no blinding)	Despite being described as double-blind, inconsistencies were noted regarding participant and personnel blinding.
D3 – Bias due to missing outcome data	Some concerns	One dropout related to adverse outcome; handling of this case was not clearly described.	Low risk	No losses or exclusions; all participants completed the study.
D4 – Bias in measurement of the outcome	Low risk	Blinded evaluators, well-defined outcomes.	High risk (no blinding, subjective outcomes)	Subjective outcomes (e.g., pain, desquamation, erythema, fissure) with insufficient assurance of assessor blinding.
D5 – Bias in selection of the reported result	Low risk	All prespecified outcomes were reported.	Low risk	All outcomes listed in the objectives were reported with no evidence of selective reporting.
Overall risk of bias	Low risk	Minor concern regarding missing data handling, but does not compromise overall validity.	High risk	Overall bias judged as high due to unclear randomization details and high risk in outcome measurement.

Table 3. Risk of bias assessment[11].

Inclusion criteria clearly described	Subjects and setting described in detail	Reliable measurement of exposure	Valid and reliable measurement of condition	Confounding factors identified	Strategies to deal with confounding	Valid and reliable outcome measurement	Appropriate statistical analysis
Yes	Yes	Yes	Yes	Partially	No	Yes	Yes

Overall Judgment: Low risk of bias, with limitation regarding confounding factors.

0.03% concentration (*vs.* triamcinolone acetonide 0.1% cream) in cases of idiopathic EC.

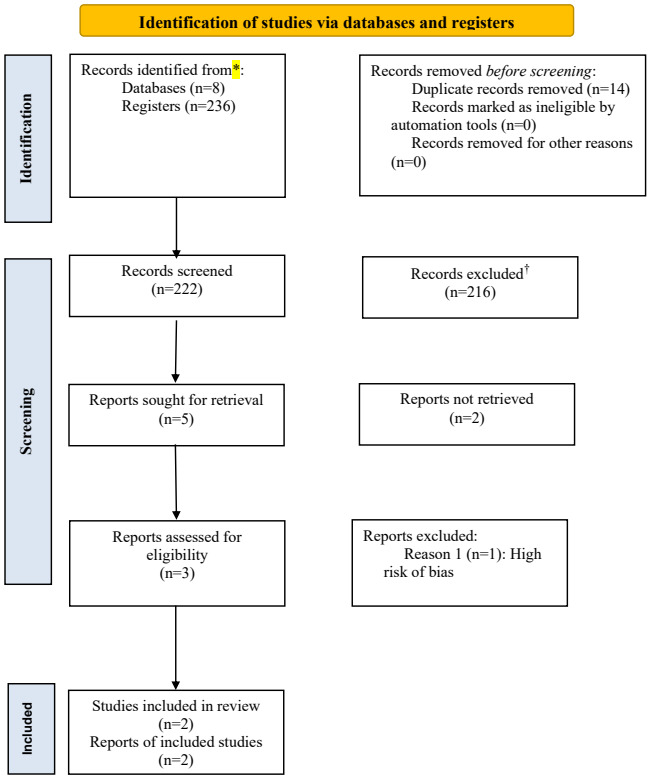
Pooled analysis of 31 patients receiving tacrolimus revealed significantly better therapeutic responses compared with controls. The 0.03% concentration[10] showed favorable safety parameters in the absence of systemic absorption or serious adverse effects, whereas 0.1% tacrolimus[11] promoted faster resolution of isotretinoin-associated lesions. For patients who received treatment with triamcinolone acetonide 0.1% (n=17), only 5 (29.4%) showed complete resolution, in comparison with 72.2% in the group which received tacrolimus[10].

Liu et al.[10] employed a 3-week treatment protocol and the patients with complete healing were followed up for 3 months to evaluate recurrence. Recurrence occurred in 8 cases (100% of controls *vs.* 30.8% of tacrolimus-treated patients; p=0.029), with symptom severity during recurrence episodes being 75% milder in patients who had received 0.03% tacrolimus. Similarly, Kothari et al.[11] implemented a 6-month observation period with intervention during active symptoms, demonstrating significantly lower recurrence rates in the 0.1% tacrolimus group (38.5% *vs.* 61.5% in controls; p=0.047).

DISCUSSION

EC is a chronic inflammatory condition affecting the lips, causing both painful discomfort and aesthetic concerns[4,12,13]. It lacks standardized treatments due to its poorly understood etiology[3-5,12,14-16]. The prevalence of EC varies according to studied populations. Among HIV-positive individuals, a prevalence of 28.5% has been documented, potentially linked to concurrent *Candida* infections[17]. Similarly, epidemiological data from Russia indicate that EC represents 31.58% of all diagnosed lip disorders[18].

Although some therapeutic modalities have already been reported, such as topical corticosteroids and antibiotics, laser and phytotherapy, monoclonal antibodies and antidepressants[1,3,4], both studies included in



*indicates the sources from which the studies were retrieved. In the present review, these sources correspond to the electronic databases described in the Methods section, including PubMed (primary database), Embase, Web of Science, Scopus, SciELO, Google Scholar, and the Cochrane Library. In addition, grey literature was searched through the *Instituto Brasileiro de Informação em Ciência e Tecnologia* (IBICT), and a manual search of the reference lists of the included studies was performed to identify potentially relevant publications not captured through the electronic searches; † indicates the sources from which the studies were retrieved. In the present review, these sources correspond to the electronic databases described in the Methods section, including PubMed (primary database), Embase, Web of Science, Scopus, SciELO, Google Scholar, and the Cochrane Library. In addition, grey literature was searched through the *Instituto Brasileiro de Informação em Ciência e Tecnologia* (IBICT), and a manual search of the reference lists of the included studies was performed to identify potentially relevant publications not captured through the electronic searches.

Figure 1. PRISMA flowchart of the studies selection.

this review addressed the topical use of tacrolimus[10,11]. The inclusion of only two studies in this systematic review reflects the substantial heterogeneity and methodological limitations prevalent in the existing literature on this topic. While numerous case reports and case series are available, their variability in intervention protocols and outcome measures precluded meaningful synthesis. In contrast, the selected studies demonstrated methodologically robust designs, including comprehensive documentation of participant flow, adverse event monitoring, and short-term recurrence assessment. Although the small sample size limits the strength of conclusions, these studies provide preliminary evidence supporting the therapeutic potential of topical tacrolimus for EC management, with significant clinical improvement compared to their respective control groups.

Tacrolimus is an immunomodulator[19] that exerts its therapeutic effect in EC through calcineurin inhibition[20]. The complex formed between tacrolimus and the FK506-binding protein competitively binds to calcineurin, thereby blocking T-cell signal transduction and suppressing the production of several pro-inflammatory cytokines, including interleukin-2 (IL-2), interferon-gamma, and tumor necrosis factor-alpha[20,21]. In addition to its immunomodulatory effect, this mechanism contributes to the restoration of tissue integrity by promoting angiogenesis and stimulating collagen deposition[22]. These properties distinguish tacrolimus from topical corticosteroids, such as triamcinolone acetonide, whose mechanism is primarily based on vasoconstriction and alterations in vascular permeability[22], which, in the long term, may impair the healing process.

Liu et al.[10] conducted a comparative clinical study evaluating the therapeutic efficacy of 0.03% tacrolimus versus triamcinolone acetonide over a 3-week treatment period. The tacrolimus group demonstrated significantly superior outcomes, with 72.2% of patients achieving complete lesion resolution compared to only 29.4% in the control group (p=0.018). Quantitative intergroup analysis revealed tacrolimus's marked superiority across multiple clinical parameters, particularly in reducing epithelial desquamation (p=0.003), pain severity (p=0.012), and fissure formation (p=0.008).

Kothari et al.[11] evaluated patients with EC induced by isotretinoin use for acne treatment. The study compared topical 0.1% tacrolimus (twice daily application) versus petroleum jelly (control) with equivalent application frequency. The results demonstrated significantly faster resolution in the tacrolimus group, with clinical improvement observed after just two applications and complete healing achieved within one week. In contrast, the petroleum jelly control group showed a slower therapeutic response, with initial signs of improvement appearing only by the third day of treatment. While some control patients eventually achieved similar outcomes after prolonged treatment, others showed no resolution even after four weeks of follow-up.

The pilot study by Zhang et al.[1] also evaluated the efficacy of 0.1% tacrolimus ointment, differentiating groups based on the frequency of application — once or twice daily — for a period of two weeks. Both groups showed significant clinical improvement in objective signs such as desquamation, dryness, and fissures by

Table 4. Characteristics of included studies.

Author	Study design	N	Treatment modality	Duration	Primary outcome	Primary results (p-value)	Secondary outcomes	Secondary results (p-value)	Follow-up/ recurrence
Liu et al.[10]	RCT	35	Tacrolimus 0.03% ointment (n=18) vs triamcinolone acetonide 0.1% cream (n=17), 3/2/1 daily doses over 3 weeks	3 weeks	Complete cure rate after 3 weeks	72.22% (test) vs 29.41% (control) p=0.018	Improvement in signs and symptoms Recurrence rate	Dryness (p=0.001), Fissures (p=0.012), Edema (p=0.045), Roughness (p=0.028), Pruritus (p=0.020) Recurrence: 30.77% (p=0.029)	3 months Recurrence: 4/13 (test), 4/4 (control)
Kothari et al.[11]	Cross-sectional	26	Tacrolimus 0.1% vs petrolatum jelly (both 2x/day)	1 week	Time to complete resolution of lesions	Tacrolimus: 4.38 days Control: 10.27 days p=0.0006	Recurrence rate	5 recurrences (test) vs 8 (control) p=0.047	6 months Recurrence: 5 (test), 8 (control)

RCT: randomized controlled trials.

the end of treatment. The total efficacy in alleviating objective signs was 50% in both groups, reaching 100% specifically for the desquamation variable. No statistically significant difference was observed between the different application frequencies, indicating comparable efficacy. Despite employing a clearly described methodology with appropriate reporting of outcomes and dropouts, the study was rated as having a high risk of bias in domains 2 and 4 of the ROB 2.0 tool, related to the blinding of participants and outcome assessors. This limitation precluded its inclusion in the present systematic review.

Regarding follow-up, Liu et al.[10] monitored 17 patients (13 in the experimental group and 4 in the control group) for three months after treatment completion. Of these, eight experienced recurrence — four in each group — with the difference in recurrence rates being statistically significant (p=0.029). Similarly, in the cross-sectional study by Kothari et al.[11], the recurrence rate was significantly lower in the tacrolimus-treated group (p=0.047), with five patients experiencing recurrence compared to eight in the control group.

Both included studies reported that adverse events associated with topical tacrolimus were mostly mild and self-limiting. The most frequently observed reactions were pruritus, burning sensation, mild edema, and localized numbness, in line with previously published data[23]. In the study by Liu et al.[10], only one patient discontinued treatment due to more intense adverse effects. Additionally, this study measured serum tacrolimus concentrations, reporting a mean level of 0.87 ng/mL, which is considered clinically insignificant from a systemic perspective[24]. These findings are consistent with current literature demonstrating negligible systemic absorption of topical tacrolimus[20]. However, the long-term safety profile, particularly concerning potential cumulative effects, remains an important consideration warranting further investigation in future studies.

The reviewed studies consistently showed tacrolimus's clinical superiority in treating EC; however, observed recurrence rates of 30.8–38.5% suggest its limitations in achieving sustained therapeutic effects despite outperforming control treatments. This therapy does not appear to be fully effective for sustained long-term disease control. Consequently, these findings must be interpreted with caution. This systematic review highlights the critical need for well-designed RCTs to overcome existing evidence limitations in EC management.

Future studies should prioritize:

1. Rigorous case selection criteria, particularly given the primarily clinical nature of EC diagnosis;
2. Standardized drug concentrations and treatment protocols;
3. Extended follow-up periods with recurrence assessment; and
4. Comparative evaluation of alternative topical and systemic therapies, which currently lack robust evidence.

The establishment of definitive treatment guidelines for this clinically challenging entity ultimately depends on addressing these fundamental research gaps through rigorously controlled investigations.

CONCLUSION

Tacrolimus currently stands as a clinically validated EC treatment, offering documented safety and efficacy despite ≥30% recurrence rates at 3-6 months. This persistent limitation underscores the necessity for both optimized tacrolimus delivery protocols and the development of novel targeted therapies to address EC refractory behavior.

AUTHORS' CONTRIBUTIONS

MCS: Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. MKC: Conceptualization, Formal analysis, Funding acquisition, Writing – original draft, Writing – review & editing. GCS: Formal analysis, Supervision, Writing – review & editing. EST: Conceptualization, Data curation, Formal analysis, Resources, Writing – original draft, Writing – review & editing.

CONFLICT OF INTEREST STATEMENT

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Competing interests: The authors have no relevant financial or non-financial interests to disclose.

Ethics approval: Approval from a Research Ethics Committee involving human subjects was not required for this study.

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