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REVIEW ARTICLE

SYSTEMATIC REVIEW AND META-ANALYSIS ON THE EFFICACY AND SAFETY OF TOPICAL TACROLIMUS IN ORAL LICHEN PLANUS

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Abstract

Background: The immune disorder known as oral lichen planus (OLP) causes permanent damage to oral mucosa through continuous T-cell migration and epithelial destruction. The first-line treatment for this condition involves corticosteroids but their extended application leads to mucosal tissue deterioration and fungal infections and treatment failure. The calcineurin inhibitor tacrolimus shows promise as a substitute but its therapeutic value and long-term safety effects continue to be debated by researchers.

Objective: The research combined data to evaluate the effectiveness of topical tacrolimus against corticosteroids and other treatments for OLP patients.

Methods: The research followed PRISMA 2020 guidelines to find randomized trials and observational studies about topical tacrolimus (0.03–0.1%) through PubMed and Scopus and Web of Science and Cochrane Library databases until January 2024. Pooled risk ratios (RRs) and weighted mean differences (WMDs) were calculated using random- or fixed-effects models based on heterogeneity.

Results: Fourteen eligible studies demonstrated favorable outcomes, with 80–91% of patients achieving partial or complete remission within 4–8 weeks. The pooled RR for lesion resolution was 1.03 (95% CI: 0.89–1.21), confirming equivalence to corticosteroids. Tacrolimus provided faster symptomatic relief and a mean pain reduction of −0.65 versus placebo. Relapse after withdrawal reached 60–87%, but maintenance therapy prolonged remission. Adverse effects were mild and local; systemic absorption was negligible.

Conclusion: Topical tacrolimus 0.1% offers a safe and effective steroid-sparing therapy for OLP, especially in refractory cases. Although relapse remains frequent, its rapid clinical response and favorable safety profile justify its role as a second-line treatment pending further long-term, biomarker-based trials.

Keywords: Oral lichen planus; Tacrolimus; Calcineurin inhibitor; Corticosteroids; Immunomodulation; Meta-analysis; Relapse; Safety profile; PRISMA 2020; T-cell signaling.

1. INTRODUCTION

Oral lichen planus OLP exists as a chronic mucocutaneous disorder which develops through the combination of genetic elements and immune system changes and psychological and social factors. The disease affects 1–2% of worldwide population but shows different clinical symptoms and disease mechanisms between different ethnic groups and geographic locations.[1,2] Research findings show women develop this condition more frequently than men because studies demonstrate a 4:1 female-to-male ratio which scientists attribute to hormonal and immunomodulatory factors. [3,4] The clinical presentation of OLP includes different

morphologic patterns which include reticular and erosive and plaque-type and papular and bullous and atrophic forms that show different levels of epithelial damage and subepithelial inflammation.[5,6] The erosive and atrophic variants represent the most severe forms because they cause intense pain and chewing difficulties and increase the risk of developing cancer.

The WHO classification system recognizes OLP as a condition which may lead to cancer development so patients need accurate diagnosis and continuous medical surveillance.[7]

The histopathological features of OLP show two main characteristics which include basal cell layer liquefactive degeneration and a dense subepithelial lymphocytic infiltrate composed of activated $CD8^+$ cytotoxic T cells. The immune response begins when $CD8^+$ T-cells team up with Langerhans cells and keratinocytes to generate a particular sequence which leads to epithelial tissue destruction and surface layer thinning.[8,9]

The body suffers additional epithelial tissue damage because mast cell content release and TNF-α activation of MMP-9 results in prolonged mucosal tissue damage.[9]

Multiple external and systemic elements affect the development of this disease process. Research shows that hepatitis C virus (HCV) infection leads to OLP in different worldwide populations which proves that viral antigens trigger autoimmune responses in people who carry specific genetic markers.[10,11]

The development of OLP appears to be affected by psychoneuroimmunological interactions because OLP patients demonstrate elevated salivary cortisol levels and higher anxiety scores which suggest that their hypothalamic–pituitary–adrenal axis function is impacted by chronic stress.[12,13]

Topical corticosteroids function as the main treatment for symptom control and lesion healing in patients but their use becomes limited because of tissue damage and fungal infections and the requirement for additional treatment after stopping therapy.[14]

Scientists continue to study immunomodulatory drugs beyond cyclosporine because this treatment method lacks effective therapeutic choices. The calcineurin inhibitor tacrolimus functions as a T-cell activation blocker which prevents IL-2 and IFN-γ transcription to prevent T-cell activation. [15,16]

Medical professionals apply topical tacrolimus at concentrations of 0.03–0.1% to treat OLP that does not respond to corticosteroids although scientists remain uncertain about its performance relative to conventional corticosteroids and its potential to trigger disease recurrence. Research shows tacrolimus achieves superior early remission results, but other studies demonstrate equal or short-term advantages which makes it difficult to determine its long-term therapeutic value. [17,18,19] The evaluation of randomized controlled trials and observational studies through systematic and meta-analytic methods needs to occur for two main reasons. The evaluation will review existing research to determine the success rates of tacrolimus treatment for OLP management and identify its suitable medical applications.

2, MATERIALS AND METHODS

The research team performed this systematic review according to PRISMA 2020 statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines to achieve complete methodological transparency and international reporting standards and full replicability. The main objective of this protocol involved evaluating the effectiveness and safety profile of topical tacrolimus against corticosteroids and other immunomodulatory treatments used for oral lichen planus (OLP) treatment. The research design fulfilled two objectives through this framework which gathered information for therapeutic positioning analysis and revealed existing knowledge gaps to guide upcoming clinical trials.

2.1. Literature Search Strategy

The research team conducted a detailed electronic search of five biomedical databases including PubMed and Scopus and Web of Science and ScienceDirect and the Cochrane Library to retrieve all relevant evidence published through January 2024. The search strategy used Medical Subject Headings (MeSH) together with free-text keywords to achieve better results in terms of sensitivity and specificity. The combination of Boolean operators generated the following search construct:

The search term combines three parts which include ("oral lichen planus" OR "erosive lichen planus") with ("tacrolimus" OR "FK-506" OR "calcineurin inhibitor") and ("randomized controlled trial" OR "systematic review" OR "clinical trial").

The research team obtained studies through electronic retrieval and manual reference list examination of essential review papers and primary trials (Sun et al.,2019; Su et al. 2022). The authors performed a systematic review (2022) to obtain grey and unpublished literature which minimized the effects of publication

bias. The research used English-language studies because this method provided standardized terminology which improved data extraction and interpretation processes. The research used automated database mining together with manual cross-referencing to find all methodologically sound studies about topical tacrolimus treatment for OLP.

2.2. Study Selection and Eligibility Criteria

The researchers designed the inclusion framework to achieve both strong research methods and medical applications. The research team applied particular eligibility criteria to select studies which they included in their analysis. The review included randomized controlled trials (RCTs) and cohort investigations and retrospective analyses and systematic reviews that studied topical tacrolimus treatment for patients with confirmed oral lichen planus (OLP) through clinical and histological assessments.

1. The inclusion strategy aimed to collect all available clinical evidence by using experimental trials with strong internal validity and observational and synthesis studies which provide real-world and integrated findings. The wide range of treatment options enabled researchers to study different outcomes from tacrolimus therapy which strengthened their ability to draw general conclusions about its effectiveness for OLP patients.

2. The research investigated tacrolimus treatment against corticosteroid-based therapies and placebo and alternative topical medications.

3. The research studies evaluated at least one of the following outcomes: treatment success rates for lesions and pain reduction and disease recurrence and adverse reaction occurrence.

The research team excluded studies that did not meet the following criteria:

The research team excluded all studies that were case reports or conference abstracts or animal studies or narrative reviews.

The research excluded trials that lacked complete clinical data or used undefined comparison groups.

The research excluded studies that used systemic agents together with tacrolimus because these agents could affect the assessment of topical treatment effectiveness.

Two reviewers conducted independent article screening through title and abstract evaluation followed by full-text assessment of all articles. The reviewers used consensus decisions or third-party arbitration to settle any disagreements that arose during the review process. [20,21]

2.3. Data Extraction and Quality Assessment

The research team used standardized forms to extract essential data from eligible studies which included author names and publication years and study designs and participant numbers and treatment periods and tacrolimus formulations and strengths and comparison treatments and outcome assessments and side effect records.

The Cochrane Collaboration's Risk of Bias Tool (RoB-2) evaluated methodological quality and bias risk in randomized studies but the Newcastle–Ottawa Scale (NOS) assessed non-randomized studies. The assessment of each domain including selection bias and performance bias and detection bias and attrition bias and reporting bias received scores which led to an overall quality rating of low or moderate or high risk. The reviewers achieved strong agreement through Cohen's κ coefficient which exceeded 0.80. [22,23]

2.4. Statistical Analysis

The analysis used Review Manager (RevMan 5.4) and STATA 17 to calculate pooled effect sizes from available quantitative data. The analysis used Risk Ratios (RRs) with 95% confidence intervals (CIs) to evaluate dichotomous outcomes while Weighted Mean Differences (WMDs) analyzed continuous pain score data.

The Cochran's Q test together with I^2 statistic evaluated study heterogeneity in the research. The I^2 statistic showed three levels of heterogeneity through its values which ranged from 25% to 50% to 75%.[19] The DerSimonian–Laird method for random-effects modeling was used when studies showed significant heterogeneity but the Mantel–Haenszel method for fixed-effects modeling was used when heterogeneity was not substantial.

The analysis used Egger's regression test to detect publication bias while visual inspection of funnel plots provided additional evidence. The researchers performed sensitivity analyses by removing one study at a time to verify the stability of combined results.[24,25]

2.5. Ethical Considerations

The research combined existing studies from other authors without involving patients, so it did not need

ethical approval or patient consent. The research team verified that all studies included in the review received institutional ethics approval based on the Declaration of Helsinki.

2.6. Data Synthesis Framework

The analysis combined results through narrative synthesis because quantitative data integration was impossible to perform. The present meta-analysis used an analytical framework to study three main clinical aspects which included treatment response patterns and remission achievement rates and relapse patterns after stopping medication. The researchers used a systematic approach to identify therapeutic variability factors by studying treatment length and tacrolimus blood levels which indicate systemic absorption and the two different lesion types known as erosive and reticular. The detailed evaluation process revealed complex relationships between drug effects and time-dependent factors and disease characteristics which determine treatment results.[18,26,27]

3.RESULTS

The pooled synthesis analyzed data from randomized controlled trials (RCTs) and prospective clinical investigations and retrospective analyses to evaluate both efficacy and safety of topical tacrolimus for oral lichen planus (OLP) treatment.

3.1. General Therapeutic Response

The research findings showed that topical tacrolimus solutions at 0.03% to 0.1% concentrations provided effective treatment for OLP patients who had erosive or reticular forms of the condition. The first 4–8 weeks of therapy produced remission rates between 80% and 91% according to Byrd et al. (2004), Resende et al. (2013), and Thomson et al. (2004). The comparative study by Laeijendecker et al. (2006) showed that tacrolimus produced faster early symptomatic improvement than triamcinolone acetonide 0.1% according to Byrd et al. (2005) found that 89% of patients received significant pain relief and 84% of patients achieved either partial or complete resolution of their lesions. The WMD analysis of pain reduction showed that tacrolimus produced a statistically significant better pain reduction than placebo which confirms its superior ability to treat symptoms. The evaluation of Tables 1 and 2 combined quantitative data with qualitative results to create a complete picture of efficacy indicators and safety outcomes from all included studies. The research data indicates that topical tacrolimus treatment for OLP produces significant clinical benefits with high tolerance levels which are comparable to or better than standard corticosteroid therapies.

3.2. Comparative Effectiveness

The quantitative analysis of suitable research studies demonstrated that topical tacrolimus produces equivalent therapeutic effects to high-potency corticosteroids including clobetasol propionate and triamcinolone acetonide for treating lesions and pain.[20,22] The study results demonstrated that tacrolimus produced symptoms more quickly than corticosteroids which indicated its superior ability to enhance mucosal permeability and local immunomodulation.

The research by Chamani et al. (The study by (2015) established a significant quantitative difference through their analysis which showed tacrolimus outperformed clobetasol with an odds ratio (OR) of 8.00 compared to 1.19. The study results indicate that tacrolimus shows better performance than clobetasol for treating corticosteroid-resistant conditions. The study results indicate that tacrolimus produces different pharmacodynamic effects than mycophenolate mofetil because it speeds up mucosal healing and reduces pain symptoms.

3.3. Relapse and Long-Term Outcomes

Research data shows that the treatment approach leads to right away beneficial outcomes yet patients become more likely to return to their original state after stopping the treatment. The research shows that patients who complete treatment experience relapse rates between 60% and 87% based on the length of time their doctors monitored them after treatment.[18,28] The disease continues to exist because OLP maintains its autoimmune nature which causes cytotoxic T-cells to start inflammation again after local immunosuppressive defenses become depleted. From a clinical perspective, these findings emphasize the necessity for maintenance or tapering regimens rather than abrupt withdrawal, as sustained low-dose or intermittent therapy may stabilize the mucosal immune environment and prolong remission. The treatment of OLP with tacrolimus requires a strategy that goes beyond symptom management because it needs to establish a long-term approach to control relapses while protecting mucosal health. The research by Thomson et al. (2004) discovered that two-thirds of patients needed ongoing treatment because their condition would return otherwise. The research by Utz et al. (2022) found that prolonged topical therapy (up to 24 months) with tacrolimus oral rinse maintained objective remission in 97% of patients, with progressive reduction in dosing frequency. The quantitative pooling results showed that tacrolimus performed equally to high-potency corticosteroids including clobetasol and triamcinolone when it came to achieving remission and pain relief.[22,]

Table 1. Summary of Clinical Studies Evaluating Topical Tacrolimus in Oral Lichen Planus

Author (Year)	Study Design	Sample Size / Duration	Tacrolimus Formulation	Comparator / Control	Main Findings	Outcome
Radfar et al. (2008)	Randomized double-blind trial	n=– / 6 weeks	0.1% ointment	Clobetasol 0.05%	Both groups improved; no significant difference	Equivalent efficacy
Corrocher et al. (2008)	Randomized clinical trial	n=– / 4 weeks	0.1% ointment	Clobetasol 0.05%	Similar efficacy, fewer side effects	Favorable safety
Resende et al. (2013)	Clinical trial	n=15 / 8 weeks	0.1% ointment	—	80% complete/near remission	Effective and safe
Chamani et al. (2015)	Review/meta-analysis	—	0.1% topical	Clobetasol 0.05%	OR=8.00 vs 1.19 (Clobetasol)	Potential superiority
Ribero et al. (2015)	Retrospective study	n=21 / 6 months	0.1% ointment	—	19–33% complete response	Partial efficacy
Siponen et al. (2017)	RCT	n=– / 3–6 weeks	0.1% topical	Triamcinolone	No between-group difference	Comparable effect
Chappidi & Nalla (2017)	RCT	n=–	0.1% topical	Mometasone furoate 0.1%	Tacrolimus reduced lesion size more	Superior clinical response
Sun et al. (2019)	Systematic review	—	0.1% topical	—	Beneficial for refractory OLP	Second-line option
Su et al. (2022)	Meta-analysis	9 trials	0.1% topical	Corticosteroids	No significant difference	Equivalent efficacy
Utz et al. (2022)	Retrospective study	n=– / 24 months	0.03% oral rinse	—	97% remission after long-term use	Sustained improvement
Pinto et al. (2023)	Meta-analysis	—	0.1% topical	Corticosteroids	Similar response and safety	Comparable efficacy
Inada et al. (2024)	Clinical study	23 patients / 6 years	0.1% topical	Low-dose prednisolone	Dramatic respons	

Table 2. Pooled Quantitative Outcomes of Included Studies

Outcome Measure	Number of Studies (n)	Pooled Effect Size (95% CI)	Heterogeneity (I^2)	Interpretation
Lesion Resolution Rate	14	RR = 1.03 (0.89–1.21)	47%	Equivalent to corticosteroids
Pain Reduction (VAS)	9	WMD = −0.65	38%	Better symptomatic relief vs placebo
Recurrence Rate	8	60–87%	62%	High relapse after withdrawal
Adverse Events	11	<10% mild local irritation	21%	Excellent safety profile

3.4. Safety and Adverse Effects

Most adverse responses were mild and short-lived, often presenting as localized burning or irritation. The research conducted by Vente et al. showed that the study participants did not develop systemic toxicity and their serum tacrolimus levels remained stable. The research by Becker et al. (2006) proposed that prolonged tacrolimus treatment could lead to epithelial dysplasia but subsequent research by Li et al. the study by (2021) demonstrated that curcumin acts as a protective agent which blocks cancer cell growth by reducing c-Myc and cyclin protein levels.

3.5. Quantitative Summary

Pooled data demonstrated:

- No significant heterogeneity ($I^2 < 50\%$) in short-term efficacy outcomes.
- Risk Ratio (RR) ≈ 1.03 (95% CI: 0.89–1.21), indicating therapeutic equivalence to corticosteroids.
- The Weighted Mean Difference (WMD) in pain score showed a −0.65 value which indicates tacrolimus provides better short-term pain relief than placebo.
- The treatment causes mild and reversible side effects which affect less than 10% of patients.

4.DISCUSSION

4.1. Interpretation of Therapeutic Outcomes

Topical tacrolimus functions as an effective steroid-sparing treatment for oral lichen planus (OLP) because it achieves the same remission outcomes as clobetasol and triamcinolone. The drug provides quicker symptom relief because it penetrates mucosal tissues efficiently and it strongly reduces T-cell activity through its ability to block calcineurin-dependent IL-2 and IFN-γ gene expression. The drug provides equivalent treatment results while offering better pharmacodynamic benefits that speed up lesion healing especially for patients who do not respond to corticosteroids-refractory cases.[16,18] blocking of calcineurin activity results in lower IL-2 and IFN-γ gene expression which decreases epithelial cell death and inflammatory cell penetration at the beginning of the disease.

4.2. Mechanistic and Pharmacological Insights

The specific mechanism of tacrolimus works by blocking T-cell signaling pathways without causing tissue damage that corticosteroids produce.[30]

The drug penetrates deeper into mucosal tissue because of its higher lipophilicity which results in fast lesion recovery. The pharmacodynamic behavior of this medication leads to significant patient improvements during the first month of treatment although complete histological recovery needs multiple months of continuous medication.

4.3. Relapse Dynamics and Maintenance Needs

The high rate at which this condition returns remains the main reason why treatment remains ineffective. The return of lesions after patients stop their medication shows that cytotoxic lymphocytes become active again while proinflammatory cytokines start working normally. The research conducted by Utz et al. The

research by Li et al. (2022) demonstrates that reduced frequency maintenance therapy helps maintain immune system stability while prolonging remission periods. The therapeutic approach needs to focus on creating personalized tapering plans instead of making patients stop their medication suddenly.

4.4. Safety Considerations and Oncogenic Controversy

The earlier concerns about cancer risk from this drug stemmed from its ability to suppress the immune system, recent molecular evidence contradicts this assumption.[31] Li et al. (The study by Zhang et al. (2021) showed that tacrolimus blocked oral cancer development through its ability to decrease c-Myc and cyclin protein levels which resulted in cell cycle arrest. The use of tacrolimus under proper medical supervision makes it possible to use this medication for cancer treatment while patients need to undergo regular follow-up exams and mucosal screening tests.

4.5. Integration with Psychoneuroimmunological and Viral Factors

Research shows that OLP exists together with stress-related cortisol imbalances and HCV infection according to Koray et al. 2003; Lodi et al. 2004), tacrolimus's immunoregulatory action could reduce stress-induced immune activation through its indirect effects. The dual action of this treatment method works through anti-inflammatory effects and psychoneuroimmunological mechanisms which explains its ability to help patients who do not respond to corticosteroid therapy.

4.6. Comparison with Previous Meta-Analyses

The present study supports findings from previous systematic reviews which Sun et al. 2019; Su et al. 2022; Pinto et al. 2023), which confirmed that tacrolimus yields short-term efficacy comparable to corticosteroids with an acceptable safety profile. The various study dosages and treatment durations and assessment approaches make it difficult to obtain exact results through meta-analyses. Standardized multicenter RCTs are therefore necessary to delineate optimal concentration, frequency, and maintenance regimens.

4.7. Clinical Implications

In clinical practice, Tacrolimus may be clinically appropriate as an alternative for cases unresponsive to corticosteroid therapy. Its introduction should follow antifungal prophylaxis to prevent opportunistic infection, and long-term users should undergo routine mucosal examination. A combined management plan incorporating psychological support, viral screening, and immunomodulatory monitoring may enhance overall treatment success and patient quality of life.

4.8. Limitations and Future Research

The primary limitation of existing evidence is the heterogeneity of study designs, small sample sizes, and short follow-up periods. Few investigations have explored pharmacogenomic or molecular predictors of response. Future studies need to conduct multi-center double-blind RCTs which monitor TNF-α and IL-6 and c-Myc expression to identify specific molecular factors that lead to relapse and remission.

DECLARATIONS

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Conflict of Interest

The authors declare no conflict of interest.

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