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TOPICAL USE OF CALCINEURIN INHIBITORS FOR DISCOID LUPUS ERYTHEMATOSUS-A SYSTEMATIC REVIEW

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ABSTRACT

Background: *Discoid lupus erythematosus is a persistent skin condition marked by inflammatory plaques. Without timely diagnosis and intervention, it can result in scarring and skin atrophy, potentially causing disfigurement. The primary treatment for DLE involves the use of topical steroids i.e. calcineurin inhibitors.*

Objectives: *The objective of this review is to assess the topical use of calcineurin inhibitors for Discoid Lupus Erythematosus.*

Methodology: *The included studies fell into various categories, including published peer-reviewed articles, clinical trials, observational studies, case-control studies, and case reports. After comprehensive review, eleven articles met the inclusion criteria and included in this review.*

Results: *Mostly patients with DLE have lesions on face and scalp. Majority of studies used topical tacrolimus with different concentrations while other used pimecrolimus.*

Conclusion: *Calcineurin inhibitors have a suitable effect for treating DLE. They are used as a maintenance therapy to treat chronic or recurring DLE lesions, aiding in the long-term control of the condition.*

Keywords: *Discoid lupus erythematosus, topical agents, calcineurin inhibitors.*

INTRODUCTION

The incidence of systemic lupus erythematosus (SLE) varies in the general population based on factors such as age, sex, race, ethnicity, and national origin. Discoid lupus erythematosus (DLE) is a persistent skin condition marked by inflammatory plaques. Without timely diagnosis and intervention, it can result in scarring and skin atrophy, potentially causing disfigurement (1). DLE is the most prevalent type of chronic CLE, manifesting as a localized form (80%) with lesions on the face, ears, and scalp or a disseminated form (20%) with lesions both above and below the neck. The disseminated form, particularly when involving the

trunk, is linked to an elevated risk of progressing to SLE (2). The initial morphological sign of DLE is a well-defined, coin-shaped (discoid) erythematous patch of varying size, followed by adherent follicular hyperkeratosis, creating a "carpet tack sign" when scales are removed. These lesions slowly expand with active inflammation and hyperpigmentation at the periphery, resulting in central atrophy and scarring, telangiectasia, and hypopigmentation. DLE lesions primarily occur in UV-exposed areas such as the scalp, face, ears, neck, and arms but can also manifest at palmoplantar sites and rarely in inguinal folds. In the scalp, DLE can progress to irreversible scarring alopecia. Inflammation in DLE, typically involving the bulge area of the follicles, raises the possibility of stem cell damage contributing to permanent hair loss (3).
DLE diagnosis, involves a comprehensive history, physical examination, and standard laboratory tests, including a complete blood cell count, renal function tests, and urinalysis. Hematologic and serologic abnormalities may be present, with an elevated sedimentation rate observed in some cases. Rheumatoid factor positivity and decreased complement levels may also occur. Approximately 20% of DLE patients may exhibit a positive antinuclear antibody. Early and effective intervention during the initial stages of DLE can lead to the complete resolution of skin lesions. Treatment failure, however, may result in permanent scarring, particularly disfiguring for individuals with darker skin tones. Unsuccessful treatment can manifest as depressed scars, hair loss, and pigmentary alterations (1). The primary treatment for DLE involves the use of topical steroids, starting with potent ones applied twice daily and transitioning to lower-potency steroids when possible. Intralesional steroids are beneficial for chronic and hyperkeratotic lesions or those inadequately responding to topical treatment (4).

Materials & methodology

The included studies fell into various categories, including published peer-reviewed articles, clinical trials, observational studies, case-control studies, and case reports. This diversity in study types contributed to a comprehensive understanding of the topic. The participants under investigation were required to be humans diagnosed with DLE, regardless of age, gender, or ethnic background, ensuring a broad and inclusive representation of the population.
The intervention of interest was the topical application of calcineurin inhibitors, either as a primary treatment method or as an adjunctive therapy for DLE. This specificity in the intervention allowed for a focused exploration of its effectiveness. Outcome measures considered in the analysis encompassed a spectrum of factors, including efficacy outcomes such as lesion improvement and disease activity reduction, as well as safety outcomes involving adverse events and local skin reactions. Additionally, the review assessed the impact on quality of life, patient-reported outcomes, and recurrence rates.
Finally, to ensure the feasibility of analysis and synthesis, studies had to be published in English. This criterion was set to alleviate potential language limitations that could impede the comprehensive evaluation of the available evidence. Together, these inclusion criteria provided a structured framework for the systematic review, ensuring a careful analysis of the relevant literature on the topic.

Results

Seven hundred fifty papers were found using the search technique, which involved manual, searches of the original research articles and reviews reference lists. Three hundred and eighty titles and abstracts were eventually found through the conducted searches. Forty were left out as they were not written in English. A total of 340 articles underwent comprehensive screening to prepare them for further processing. At this point, 125 items have been excluded since they were written before the year 2000. Two hundred and fifteen papers made it through the quality evaluation process, while two hundred and four were deemed ineligible for inclusion in the current review. Finally eleven articles met the inclusion criteria and included in the review (Figure 1).

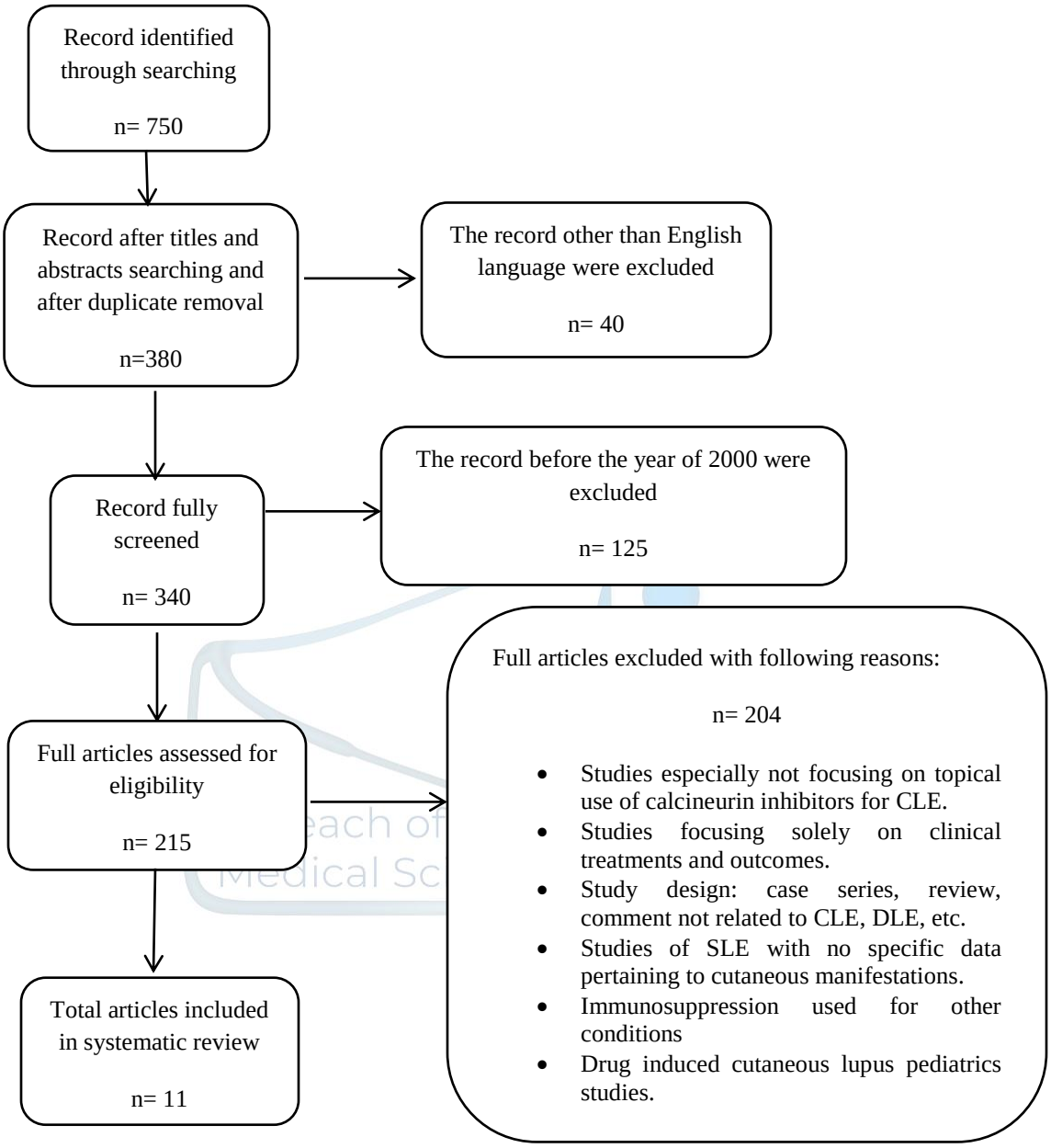

Figure 1: PRISMA flow diagram showing selection process of included articles

The studies range from the oldest that was published in 2004 to the recent, which was published in 2015. All studies mainly focused on the topical use of calcineurin inhibitors for DLE. The studies were conducted in different countries. The exact duration of studies were mentioned in some studies. In all studies, both male and female were included. The ages of study participants were varying in range from 18-79 years.

Table 1: Characteristics of the included studies

Publication Year	Place of study	Study period	Age of study participants (Years)	No. of study participants	Gender	Reference
2015	China	03 years	18 to 60	32	Males and females	(5)
2012	Thailand	02 years	18 to 60	31	Males and females	(6)
2011	Germany	03 months	18 or above	30	Males and females	(7)
2009	Iran	04 months	20 to 53	10	Males and females	(8)
2007	Taiwan	02 months	37 to 79	20	Males and females	(9)
2005	Mexico	03 months	5 to 56	10	Males and females	(10)
2004	London	02 months	22 to 72	12	Males and females	(11)
2012	Greece	01 year	Median age 53	38	Males and females	(12)
2010	United Kingdom	12 months	19 to 76	18	Males and females	(13)
2005	United states of America	03 months	Not mentioned	05	Not mentioned	(14)
2004	United Kingdom	01 month	11 to 76	11	Males and females	(15)

From all included studies, five were randomized control trial, two were non-controlled clinical trial, three were case series, and one was observational study. All studies mainly used medical history performa for data collection. In each study, the topics for which questions were posed and the outcomes of the study were clearly defined. All the included studies used different enrolment criteria's. The confirmation of DLE was done through biopsy. Form total, six studies have confirmed all patients from biopsy, one study only confirmed selected patients through biopsy, and three studies did not mentioned any record of hitopathological examination of patients.

Table 2: Materials and methodology of the included studies

Study design	Enrolment criteria	Data collection instrument	Status of Biopsy	Reference
Randomized control trial	Odd numbers: Experimental group Even numbers: Control group	Medical history performa	Proven-All patients	(5)
Randomized control trial	Head coin: 0.1% topical tacrolimus ointment Tail coin: 0.05% clobetasol propionate ointment	Medical history performa with global assessment score for patient efficacy evaluation	Proven-All patients	(6)
Randomized control trial	Group 1 (tube A vehicle and tube B tacrolimus 0.1%) Group 2 (tube B vehicle and tube A	Medical history performa	Proven-All patients	(7)

	tacrolimus 0.1%)			
Randomized control trial	Odd numbers: Group 1 (pimecrolimus 1% cream) Even numbers: Group 2 (0.1% betamethasone valerate)	Medical history performa	Proven-All patients	(8)
Randomized control trial	Random selection form patients	Medical history performa with global assessment score for patient efficacy evaluation	Not recorded	(9)
Non-controlled clinical trial	Diagnosed patients of DLE	Medical history performa	Proven-All patients	(10)
Non-controlled clinical trial	Diagnosed patients of DLE	Medical history performa	Not recorded	(11)
Observational Study	Those patients of DLE who did not respond to hydroxychloroquine treatment	Medical history performa	Selected patients	(12)
Case series	Those patients of DLE who did not respond to f tacrolimus 0.3% in clobetasol propionate 0.05% ointment and 0.1% tacrolimus ointment alone	Medical history performa	Not recorded	(13)
Case series	Diagnosed patients of DLE through histological examination	Medical history performa with 5-point scale grading system	Proven-All patients	(14)
Case series	Diagnosed patients of DLE	Medical history performa	Proven-All patients	(15)

Mostly patients with DLE have lesions on face and scalp. Detailed site of infections are given in table 3. Majority of studies used topical tacrolimus with different concentrations while other used topical Pimecrolimus. The five randomized control trial used different comparator against different intervention while one study used placebo (vehicle ointment). The other studies with different study design did not use any comparator against interventions. The duration of intervention was different in different studies which range from three weeks to three months.

Table 3: Clinical data of the included DLE studies

Site involved	Intervention	Duration of intervention	Comparator	Reference
Face	Tacrolimus 0.03%	3 weeks	Triamcinolone acetonide 0.1%	(5)
Right and left side of the body	Tacrolimus 0.1%	One side of the body for 6 weeks	0.05% clobetasol propionate on contralateral side of the body	(6)
Face and other areas	Tacrolimus 0.1%	3 months	Placebo	(7)

Face	Pimecrolimus 1%	Twice daily for 8 weeks	Betamethasone valerate 0.1%	(8)
Face	Tacrolimus 0.1% on one side of face	8 weeks	Clobetasol 0.05% propionate on contralateral side of face	(9)
Face and scalp	Pimecrolimus 1%	8 weeks	None	(10)
Face, arms, legs, neck and scalp with alopecia	Tacrolimus 0.1%	6 weeks	None	(11)
Face	Tacrolimus or Pimecrolimus	Not mentioned	None	(12)
Face and scalp	Tacrolimus 0.1%	3 months	Tacrolimus 0.1% ointment combined with clobetasol propionate 0.05%	(13)
Face	Tacrolimus 0.1%	12 weeks	None	(14)
Face	Pimecrolimus 1%	3 weeks	None	(15)

Topical calcineurin inhibitor treatment was shown to enhance outcomes in all investigations, but generally to a minor degree (5, 6, 8, 9, 13). The benefit was comparable to that of topical corticosteroid treatment. Wang et al., 2015 reported that the tacrolimus and triamcinolone do not differ in the rate of healing. Erosion, erythema, and reticulation decreased in both groups after therapy, with no group differences. The randomized control trial of Pothinamthong & Janjumratsang, 2012 showed the significant decrease in the severity index activity score and area of cutaneous lupus erythematosus disease with tacrolimus-only therapy. Patient satisfaction scores significantly decreased, and this trend persisted for four weeks after therapy. The area and severity index activity score of cutaneous lupus erythematosus disease significantly decreased after therapy, however, the cutaneous lupus erythematosus disease area and severity index damage score did not significantly rise while using clobetasol. In 2011, Kuhn et al., reported much higher oedema improvement in the tacrolimus group. Tacrolimus significantly improves DLE patient outcomes. Topical tacrolimus showed higher results for lesions that persisted for longer than six months. The randomized control trials of Barikbin et al., 2009 and Tzung et al., 2007 observed significant drop in clinical severity scores from pre- to post-treatment levels in both groups.

The non-controlled clinical trial of Tlacuilo-Parra et al., 2005 reported the notable decline in clinical severity ratings reduced infiltration, corneal plugging, and hyperkeratosis while the other non-controlled clinical trial by Lampropoulos et al., 2004 showed that the only two patients were marked better after treatment. One patient show mild improvement while two patients did not show any improvement. In 2012, Avgerinou et al., conducted an observational study and reported decrease in erythema, desquamation, and oedema both before and after therapy was significant. The case study of Madan et al., 2010 included 13 patients for combination therapy. From total, 06 patients shows excellent response, 05 patients shows good response, 01 patient show slight improvement while 01 patient did not show any improvement. They also included 05 patients for mono-therapy. Form total 5 patients, 01 patient show good response while 02 patients show slight response. The Heffernan et al., 2005 observed total 03 patients, 01 patient shows mild improvement, 01 shows moderate response, and 01 shows marked response. Kreuter et al., 2004 observed significantly lower clinical score at the end of therapy than at baseline.

Abruptly stopping therapy carried a risk of recurrence (5, 15). Tacrolimus significantly improved one patient's condition that had DLE (7). Similar benefits in DLE with malar rash were seen in a randomized control trial (9). While erythema and oedema in DLE improved equally in one observational study,

improvements across subtypes were equivalent in one non-controlled trial (12). If any side effects were reported, they were mild; some studies reported pruritis, discomfort, or burning (6, 10, 12, 13, 15).

Table 4: Reported outcomes and adverse effects of the included studies

Reported outcomes	Adverse effects	Reference
Tacrolimus and triamcinolone do not differ in the rate of healing. Erosion, erythema, and reticulation decreased in both groups after therapy, with no group differences. Relapse in both groups after stopping therapy.	None	(5)
The significant decrease in the severity index activity score and area of cutaneous lupus erythematosus disease with tacrolimus-only therapy. Patient satisfaction scores significantly decreased, and this trend persisted for four weeks after therapy.	Pruritis and burning	(6)
Much higher oedema improvement in the tacrolimus group. Tacrolimus significantly improves DLE patient outcomes. Lesions on the face showed more recovery at day 28 than lesions on other body parts. Topical tacrolimus showed higher results for lesions that persisted for longer than six months.	None	(7)
Significant drop in clinical severity scores from pre- to post-treatment levels in both groups.	None	(8)
Tacrolimus and clobetasol significantly decreased from baseline to week eight.	None	(9)
Notable decline in clinical severity ratings. Reduced infiltration, corneal plugging, and hyperkeratosis.	Pruritis and erythema	(10)
Two patients were marked better after treatment. One patient show mild improvement while two patients did not show any improvement.	Burning	(11)
Decrease in erythema, desquamation, and oedema both before and after therapy was significant.	Skin irritation or pruritis	(12)
Combination therapy From total 13 patients, six patients shows excellent response, five patients shows good response, one patient show slight improvement while one patient did not show any improvement. **Mono-therapy** Form total 5 patients, one patient show good response while two patients show slight response.	Minor only Mainly in combined group; telangiectasia, acne, greasiness, irritation	(13)
From total three patients, one patient shows mild improvement, one shows moderate response, and one shows marked response.	None	(14)
Significantly lower clinical score at the end of therapy (2.73 + 1.00) than at baseline (6.45 + 0.80). Recurrence was observed in two out of eleven patients.	Minor	(15)

Discussion

Calcineurin inhibitors like tacrolimus and pimecrolimus are immunomodulatory medications known for their ability to modulate the immune response by inhibiting calcineurin, a protein that plays a role in T-cell activation (16). While their primary use is in conditions like atopic dermatitis (eczema), and their role in

DLE is not as extensively studied or established. That's why this topic was selected to review the topical use of calcineurin inhibitors for DLE. Calcineurin inhibitors offer a targeted approach by acting directly on the affected skin areas without affecting the entire immune system, potentially reducing the risk of systemic side effects associated with systemic immunosuppressive medications. Responses to these medications can vary among individuals. Some patients may experience improvement in DLE lesions with the use of calcineurin inhibitors, while others may not respond as well (17).

The topical use of calcineurin inhibitors for DLE was the subject of 11 researches that were found during this study. The research designs, procedures, therapies, and treatment outcome measures of the included studies varied greatly. Topical corticosteroids are commonly utilized in practice as systemic drug combination treatment in cases of more severe and extensive illness, or as first line mono-therapy in moderate localized DLE. For DLE, however, topical calcineurin inhibitor therapy has been well investigated and might be a promising first-line topical steroid-sparing treatment. The results of this search point to moderately consistent evidence in favor of topical calcineurin inhibitor treatment as a means of reducing reliance on topical steroids.

Tacrolimus 0.03% is a topical immunosuppressant used in treating various inflammatory skin conditions, including DLE lesions. Tacrolimus 0.01% is another formulation of the same medication, albeit at a lower concentration than tacrolimus 0.03%. This review reported that the 07 studies used topical Tacrolimus 0.01% (6, 7, 9, 11-14) while one study used topical Tacrolimus 0.03% (5) for DLE lesion on face, scalp and other infected parts of body. While it's not considered a primary treatment for DLE, it can sometimes be used as an alternative or adjunct therapy. Tacrolimus works by inhibiting certain immune cells that contribute to inflammation. By reducing inflammation, it may help alleviate some symptoms associated with DLE lesions, such as redness, scaling, and itching. It's applied topically directly to the affected areas, allowing for targeted treatment without affecting the entire body's immune system.

The outcomes of the use of topical tacrolimus 0.01% and 0.03% in DLE lesions are much better than the other topical calcineurin inhibitors. According to Wang et al., 2015 and Kuhn et al., 2011 topical tacrolimus do not differ in the rate of healing as compared to other topical calcineurin inhibitors. Erosion, erythema, and reticulation were decreased in both groups after therapy with no group differences. The studies of Pothinamthong & Janjumratsang, 2012 and Tlacuilo-Parra et al., 2005, shows significant decrease in the severity index activity score with tacrolimus-only therapy. Patient satisfaction scores significantly decreased, and this trend persisted after therapy. Lampropoulos et al., 2004, Avgerinou et al., 2012, and Madan et al., 2010 studies showed marked improvement in DLE patients with topical tacrolimus therapy. But they also observed poor response of topical tacrolimus therapy in some patients. The relapse was also observed by Wang et al., 2015 after stopping therapy.

In some cases, tacrolimus can be used as an alternative to topical corticosteroids, especially in situations where long-term corticosteroid use is not advisable due to side effects. It might be used as a maintenance therapy to manage chronic or recurring DLE lesions, helping to control the condition over time. It's important to note that while tacrolimus has shown promise in certain cases, the evidence supporting its use specifically for DLE lesions is limited (4, 18). Research into its effectiveness for this particular condition is ongoing. Tacrolimus may have side effects, including skin irritation, burning, or itching at the application site. In this review, four studies (6, 11-13) show side effects of topical tacrolimus 0.01% and tacrolimus 0.03% in DLE patients. Long-term safety of topical tacrolimus is still under evaluation (19).

Pimecrolimus is another immunosuppressive medication used topically in the treatment of certain inflammatory skin conditions, particularly eczema and DLE. It belongs to the class of drugs known as calcineurin inhibitors, similar to tacrolimus. Mostly pimecrolimus 1% is used to treat skin infections (20). Like tacrolimus, pimecrolimus works by inhibiting certain immune cells, specifically T-cells, which are involved in the inflammatory response. By dampening the activity of these immune cells, it helps to reduce inflammation and relieve symptoms. It provides a targeted treatment approach, specifically addressing the affected areas of the skin without affecting the entire body's immune system (21). Pimecrolimus 1% is primarily used in the treatment of mild to moderate infections in both adults and children who are at least 2

years old (22). According to present review, four studies (8, 10, 12, 15) used pimecrolimus 1% to treat DLE lesions.

The outcomes of the use of topical pimecrolimus 1% were also better when compared with other topical calcineurin inhibitors. According to Barikbin et al., 2009, significant drop in clinical severity scores from pre- to post-treatment levels was observed. Notable decline in clinical severity ratings with reduced infiltration, corneal plugging, and hyperkeratosis were also observed by Tlacuilo-Parra et al., 2005. The Avgerinou et al., 2012 and Kreuter et al., 2004 also observed significantly lower clinical scores at the end of therapy than at baseline. The recurrence was also observed by Kreuter et al., 2004 in two out of eleven patients after stopping pimecrolimus 1% therapy.

Pimecrolimus 1% helps to reduce redness, itching, and inflammation associated with eczema, thereby providing relief from symptoms. Generally, pimecrolimus is considered safe for short-term and intermittent long-term use. However, there is a possibility of side effects, including a burning sensation at the application site or temporary skin irritation. Long-term safety is still under evaluation (22, 23). The minor side effects of pimecrolimus 1% were also reported by four included studies (8, 10, 12, 15).

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