Systematic Review/Meta-analysis

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Efficacy and safety of calcineurin inhibitors in cutaneous lupus: a systematic review and brief meta-analysis of recommended concentration, type, and outcomes

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Background: Establishing effective treatment for cutaneous lupus erythematosus (CLE) is of major importance given lack of approved medications for this autoimmune condition. Topical calcineurin inhibitors have been used to treat all types of CLE, yet there is currently no robust study that evaluated the efficacy of calcineurin inhibitors in this patient population. Our aim is to study the efficacy of topical calcineurin inhibitors for treating patients with CLE and assess the side effects associated with the use of this class of medications.

Materials and methods: A systematic review was conducted following the AMSTAR guidelines. A systematic search for articles published between 2003 and 2024 in PubMed, MEDLINE, the Cochrane library (Cochrane Databases of Systematic Reviews), and the Cochrane Register of Controlled Trials for relevant studies that assessed the efficacy of calcineurin inhibitors in patients with CLE.

Results: Twenty-five studies met the criteria, and we reviewed and collectively included. Based on the Quality assessment, some concerns are raised in the quality assessment of RCTs studies. However, Observational studies have high methodological quality.

Conclusion: In conclusion, our systematic review analyzed 25 studies to evaluate the efficacy and safety of topical calcineurin inhibitors in treating CLE. Our systematic review findings support the effectiveness of these inhibitors, namely pimecrolimus cream and tacrolimus ointment in improving clinical manifestations and disease activity in various forms of CLE, such as discoid lupus and subacute CLE. However, the result from RCTs metanalysis showed no significant difference between calcineurin inhibitors and other treatments. While calcineurin inhibitors are generally safe, the most common side effect was skin burning sensation at application site in the first few days of treatment. Further research is needed to prove the effectiveness of these drugs, explore the comparative effectiveness between different calcineurin inhibitors and comparing their types and their concentration.

Keywords: calcineurin inhibitors, cutaneous lupus erythematosus, discoid lupus, pimecrolimus, subacute LE, tacrolimus

Introduction

Cutaneous lupus erythematosus (CLE) is an inflammatory autoimmune disease and can be in the form of chronic cutaneous lupus erythematosus (CCLE), acute CLE (ACLE), subacute CLE (SCLE) Other rare forms include chilblain LE, LE panniculitis and LE tumidus (LET)[1]. Systemic therapeutic treatments in CLE include corticosteroids, hydroxychloroquine, methotrexate, cyclosporine, quinacrine, mycophenolate mofetil and thalidomide. Topical treatments, such as topical calcineurin inhibitor, topical steroids and sunscreen protection are also helpful to treat symptoms associated with CLE[2]. Topical calcineurin inhibitors (pimecrolimus and tacrolimus) are of considerable utility in the treatment of localized CLE through anti-inflammatory and immunomodulatory actions by inhibiting T-cell activation and interleukin-2 (IL-2, IL-3, IL-4, tumor necrosis factor (TNF-α), granulocyte/macrophage colony-stimulating factor and interferon-γ production[3,4].

HIGHLIGHTS

- Systematic review of topical calcineurin inhibitors (TCIs) for cutaneous lupus erythematosus (CLE) was conducted.
- TCIs, particularly tacrolimus, are effective in improving CLE symptoms.
- TCIs are generally safe, with the most common side effect being skin burning.
- Tacrolimus higher concentration (0.1%) shows better results than lower concentration (0.03%).
- Studies included in the review were of moderate quality.

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Calcineurin inhibitors have similar efficacy compared to topical steroids with fewer side effects.[5-10] Many studies showed improvement of cutaneous lupus with calcineurin inhibitors; eight were review studies.[1-27][28-32] Two reviews by Wollina *et al* and Rosen *et al* showed that the efficacy of topical calcineurin inhibitors depend on the chronicity of lesions with limited efficacy as in the case of hypertrophic chronic while better results can be seen with acute and subacute CLE[4,6]. Moreover, a review conducted on topical calcineurin inhibitors revealed a good response to all types of CLE except discoid lupus[8,9]. A review of treatment of discoid lupus showed topical calcineurin inhibitors to be effective as adjuvant therapy and not sufficient to be monotherapy[11]. Relapses can occur after stopping treatment. Adverse effects including application site burning or pruritus have been observed with these topicals[12]. A study revealed that topical calcineurin inhibitors use for sustaining remissions particularly in facial lesions but found lacking to control flares of the disease[13].

The optimal efficacy of topical calcineurin inhibitors is not clearly established. Which leads us to the following guiding question: are topical calcineurin inhibitors effective on treating all types of CLE? Our systematic review aims to test and compare the efficacy of topical calcineurin inhibitors on treating CLE and assess the possible side effects of calcineurin inhibitors.

Methods

Search strategy

In this review, electronic databases independently and systematically searched by four authors (A.H. Alshathri, R.A. Abdellatif, A.H. Alshathri, L.F. Alharbi) including: PubMed, MEDLINE, The Cochrane Library (Cochrane Databases of Systematic Reviews), Cochrane Register of Controlled Trials.

A three-step search strategy used as follows: Firstly, a predetermined list of keywords searched in Cochrane and MEDLINE databases followed by identifying additional text words in the title and abstract as well as index terms of the resulting articles. Secondly, all documented text words and index terms searched thoroughly across all databases. This step also includes registered ongoing and complete trials. Lastly, the reference list of all retrieved studies is carefully reviewed to ensure including missed articles.

Studies published in English language were included. The initial terms (and synonyms) to be used in the first step are:"Calcinurin inhibitors" AND "Cutaneous lupus erythematosus OR AND "Pimecrolimus" AND "Tacrolimus."

Eligibility criteria

Titles and abstracts of retrieved articles were screened for eligibility. Relevant articles were read in full and those fulfilling inclusion criteria had their data extracted. Four authors performed all the literature selection steps individually and then discussed the differences with two other authors.

Studies were included in this systematic review if they met all the following eligibility criteria: Adult age 18, both genders (males and females), all races and nationalities, individuals with or without comorbidities with the diagnosis of CLE, Non-English studies, case reports, case series, non-human studies, studies assessing calcineurin inhibitors efficacy on other CLE were excluded.

Data extraction and bias assessment

Four authors independently reviewed the included articles to extract data, such as algorithm or technique used, and evaluation results into a data abstraction spreadsheet. We resolved disagreements through consensus with two authors.

Study record and selection process

The data selection process was done by four authors (A.H. Alshathri, R.A. Abdellatif, A.H. Alshathri, L.F. Alharbi), then independently reviewed by two authors (R.A. Allehyani, M.A. Alawaji). We manage the record on data by using Mendeley to remove duplication and data were recorded by using endnote. We select the studies after screening according to the eligibility criteria.

Quality assessment

The quality assessment has been done using the most recent available tools. Randomized controlled trials have been evaluated using ROB II tool. Additionally, the Newcastle Ottawa Scale (NOS) is used for cohort studies. The risk of bias in the study was avoided with careful quality assessment of the individual studies by using the AMSTAR tool.

Result

Study selection

Demonstrates the results of the literature search. Our search resulted in a total of 810 articles. Two independent reviewers screened the articles. At first, the title and abstract were screened thoroughly, and 588 articles remained for further screening. Full text screening was carried out by the reviewer and 50 articles were left for eligibility. After application of inclusion and exclusion criteria, 32 articles were included in the final report. The inclusion and exclusion procedure has been visualized (Fig. 1).

Characteristics of included study

The summary characteristics of the included studies was tabulated (Table 1), the studies comprise of 19 review article, 4 Randomized control trial and 2 Cohort studies. The total number of patients included are 1006 patients. The research was published in Japan (3 studies), Germany (6 studies), Greece (2 studies), USA (6 studies), UK (3 studies), Australia 91 study), China (2 study), Iran, Turkey and Bangladesh 1 study each.

Results synthesis

Quality assessment

Based on the Quality assessment, some concerns are raised in the quality assessment of RCTs studies (Fig. 6). However, Observational studies have high methodological quality (Table 2).

Summary of findings

Calcineurin inhibitors efficacy

Seven reviews revealed that topical calcineurin inhibitors like tacrolimus 0.1% and pimecrolimus 0.3% match the efficacy of topical steroids in many types of SLE with varied efficacy definitions. They're ideal for children and facial lesions, avoiding

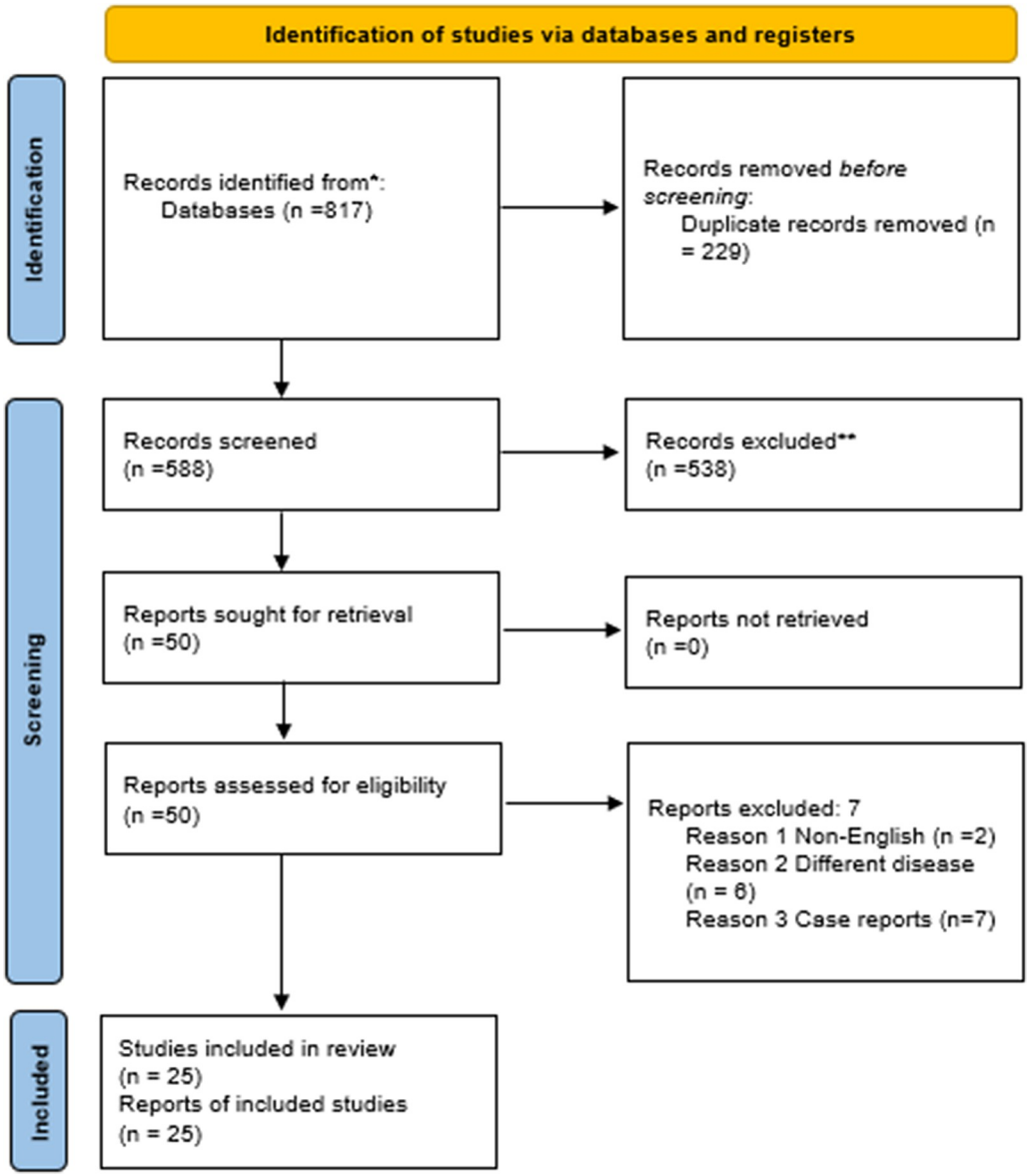

Figure 1. Flowchart of included studies.

side effects like telangiectasias and atrophy seen with corticosteroids.[8,16,17,22] Avgerinou G. *et al* conducted a retrospective, non-randomized, non-blinded study that investigated the efficacy of tacrolimus and pimecrolimus in patients with CLE (DLE, SCLE, LET) using improvement in their erythema, desquamation, and edema as efficacy measurement tools. 18 patients in all received topical tacrolimus therapy, with 14 receiving it in combination with hydroxychloroquine and 4 receiving it as monotherapy. 20 patients in total received topical pimecrolimus therapy, 16 of them in combination with

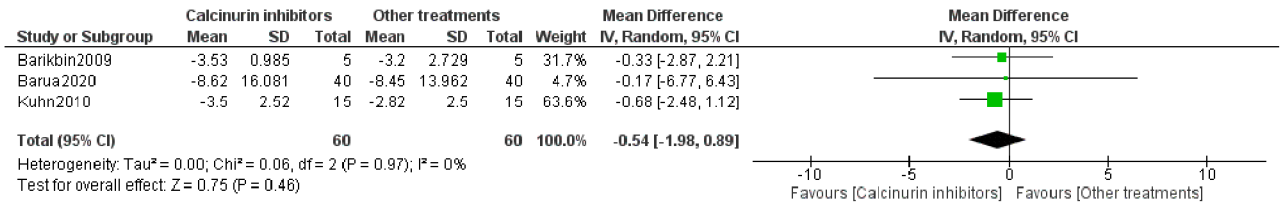

Figure 2. Comparison of clinical severity scores between calcineurin inhibitors and other treatments.

Table 1

The characteristics of the studies included, and the patients recruited

Author	Study design	Country	Number of patients	Type of CLE	Type of calcineurin inhibitors	Strobe score
Tzellos TG *et al* 2007[3]	Review article	Greece	60 patients	DLE, SCLE, LET	• Tacrolimus ointment (0.1%) • Pimecrolimus cream (1%)	17/22
Wollina U. *et al* 2008[4]	Review article	Germany	90 patients	SCLE, CCLE, DLE, LET	• Tacrolimus ointment (0.1%) • Pimecrolimus cream (1%)	17/22
Barikbin B. *et al* 2009[17]	Randomized double-blind pilot study	Iran	10 patients	DLE	• Pimecrolimus ointment (1%) • Betamethasone valerate ointment (0.1%)	18/22
Madan V. *et al* 2009[14]	Retrospective cohort study	UK	13 patients	DLE, SCLE	• Tacrolimus 0.3% in clobetasol propionate 0.05% ointment	16/22
Christos ELampropoulos *et al* 2010[16]	Review article	UK	103 patients	DLE, LET, SCLE	• Tacrolimus ointment (0.1%) • Tacrolimus 0.03% in clobetasol propionate 0.05% • Pimecrolimus cream (1%)	17/22
Haydee M. Knott *et al* 2010[22]	Review	USA	12 patients	DLE, SCLE	• Pimecrolimus 1% cream • Tacrolimus ointment (0.1%)	17/22
Aileen Y. Chang *et al* 2011[23]	Review	USA	4 studies	DLE, LET, SCLE, ACLE	• Tacrolimus ointment (0.1%) • Pimecrolimus cream (1%)	17/22
Michael Sticherling *et al* 2011[15]	Review article	Germany	144 patients	DLE, SCLE, LET	• Tacrolimus ointment (0.1%) • Tacrolimus ointment (0.3%) • Tacrolimus ointment (0.03%) • Pimecrolimus cream (1%) • 0.05% clobetasole propionate and 0.3% tacrolimus	18/22
Annegret Kuhn *et al* 2011[21]	Randomized control trial	Germany	30 patients	DLE, LET, SCLE, ACLE	• Tacrolimus ointment (0.1%)	18/22
Avgerinou G *et al* 2012[2]	Retrospective cohort study	Greece	38 patients	DLE, SCLE, LET	• Tacrolimus ointment (0.1%) • Pimecrolimus cream 1%	17/22
Wang *et al* 2015[28]	Randomized controlled clinical trial	China	41 patients	DLE	• Tacrolimus ointment (0.03%)	19/22
Anna Cristina Garza-Mayers *et al* 2016[11]	Review article	USA	3 studies 51 patients	SCLE, DLE	• Tacrolimus lotion (0.03%) in an alcohol base, in conjunction with oral antimalarial therapy • Tacrolimus ointment (0.1%) • Pimecrolimus cream (1%)	19/22
Joshua chang *et al* 2016[5]	Review article	USA	4 studies 62 patients	DLE, LET, Resistant DLE	• Tacrolimus ointment (0.1%) • Pimecrolimus • Tacrolimus lotion (0.3%)	18/22
Fnu Nutan *et al* 2017[29]	Review article	USA	1 study	ACLE, CCLE, SCLE, LET	• Tacrolimus ointment(0.1%) • Pimecrolimus ointment (0.3%)	20/22
Jessop S *et al* 2017[10]	Systematic review	South Africa	2 studies 24 patients	DLE	• Pimecrolimus cream (1%) • Tacrolimus ointment (0.1%)	18/22
Annegret Kuhn *et al* 2017[1]	Guidelines	Germany	3 studies 51 patients	SCLE, DLE, LET	• Tacrolimus ointment (0.1%) • Pimecrolimus cream (1%)	21/22
J.L. Fairleya *et al* 2019[30]	Systematic review	Australia	30 studies 250 patients	DLE, LET, ACLE, SCLE	• Tacrolimus Ointment (0.1%) • Tacrolimus ointment (0.03%) • Pimecrolimus cream (1%)	20/22
Rosen *et al* 2019[6]	Review article	USA	3 studies	CLE	• Tacrolimus Ointment (0.1%) • Tacrolimus ointment (0.03%) • Pimecrolimus cream (1%)	19/22
Lyn Guenther1 *et al* 2019[8]	Review article	UK	169 patients	CLE	• Tacrolimus ointment (0.1%) • Pimecrolimus cream (1%)	19/22
Stephanie Clare Blake *et al* 2019[9]	Review of literature	Australia	38	CLE, resistant CLE	• Tacrolimus ointment (0.1%) • Tacrolimus with clobetasol propionate	19/22
François *et al* 2019[31]	Review article	France	3 RCT, 1 case series (3 patients)	DLE, LET	• Pimecrolimus cream (1%) • tacrolimus ointment (0.1%) • Tacrolimus lotion (0.3%)	20/22
Deva Pratim Barua *et al* 2020[32]	Randomized control trial	Bangladesh	40 patients	DLE	• Tacrolimus ointment (0.1%)	19/22
Cora W Hannon *et al* 2021[12]	Intervention review	NA	22 studies	ACLE, SCLE, CCLE, lupus-non-specific lesions	• Tacrolimus 0.1% ointment • Tacrolimus 0.03% ointment • Pimecrolimus 1% cream	19/22

(*Continued*)

Table 1

(Continued).

Author	Study design	Country	Number of patients	Type of CLE	Type of calcineurin inhibitors	Strobe score
Qianjin Lu *et al* 2021[33]	Review article	China	6 studies 110 patients	ACLE, SCLE, CCLE, LET, DLE, Verrucous LE, Profundus LE, Chilblain LE	• Tacrolimus ointment (0.1%) • Tacrolimus ointment (0.03%) • Pimecrolimus cream (1%)	19/22
Dennis Niebe *et al* 2023[18]	Review article	Germany	NA	ACLE, ACLE, CCLE	• Tacrolimus ointment (0.1%) • Pimecrolimus cream (1%)	20/22

hydroxychloroquine and 4 as monotherapy. All patients receiving tacrolimus or pimecrolimus as monotherapy experienced clinical improvement in their erythema, desquamation, and edema. Patients receiving tacrolimus or pimecrolimus in combination with hydroxychloroquine experienced statistically significant improvement in erythema, desquamation, and edema. Comparing combination treatment to topical monotherapy, 100% of patients receiving combination treatment demonstrated clinical edema improvement, as opposed to 75% of patients receiving monotherapy[2].

Calcineurin inhibitors efficacy in cutaneous lupus erythematosus (CLE)

A systematic review conducted by Rosen *et al* showed that topical calcineurin inhibitors were effective as adjuvant therapy in CLE. Furthermore, when compared pimecrolimus and tacrolimus to clobetasol no significant difference in efficacy was shown[6].

Lampropoulos *et al* published a systematic review including 15 studies showing significant improvement in most patients who have skin lesions in SLE, but the response of treatment is partial in patients with discoid lupus or SCLE, they may need prolonged therapy. However, topical calcineurin inhibitors are considered safe and attractive alternative treatment for resistant cutaneous lesions in lupus erythematosus[4]. A study showed a statistically significant improvement in the change in clinical parameters of erythema, desquamation, and edema when using topical calcineurin inhibitors as monotherapy or in combination with hydroxychloroquine for a period of 60 days[2]. A study compared the efficacy of formulated preparation of topical tacrolimus 0.3% in combination with clobetasol propionate 0.05% ointment (TCPO) and 0.1% tacrolimus ointment alone in the treatment of therapy-resistant CLE including 11 discoid LE, 1 systemic LE, and 1 subacute cutaneous LE and the result showed that TCPO is more effective than either 0.1% tacrolimus or clobetasol propionate 0.05% ointment alone in treating therapy-resistant CLE. The study used. Two patients showed telangiectasia and acne in this study[14].

Calcineurin inhibitors efficacy in discoid lupus erythematosus (CLE)

According to a review article published by Sticherling *et al* revealed that patients with resistant DLE responded well to treatment with a 0.05% and 0.3% tacrolimus combination given twice daily. The facial manifestation had nearly completely disappeared after 6 and 8 weeks, respectively. There were no side effects noted. Additionally, individuals 'skin lesions significantly regressed after daily use daily dose of topical 0.1% tacrolimus. Patients who applied 1% pimecrolimus cream twice daily saw improvements in their lesions' infiltration, scaling, and diameter compared to before treatment[15]. While, a review study about discoid lupus management revealed that 0.1% tacrolimus ointment applied twice daily for 3 months showed a significant improvement, in addition use of 0.3% tacrolimus ointment in conjunction with oral antimalarial therapy for hair regrowth in three individuals with scarring alopecia secondary to discoid lupus[11]. According to a review article by Lampropoulos *et al* Tacrolimus 0.1% ointment once daily for 4 weeks in SLE and DLE patients with face rash improved all SLE patients except for one with discoid lesions. While one patient with discoid lupus was successfully treated with pimecrolimus cream 1%, other patients with discoid lupus exhibited considerable improvement with tacrolimus ointment 0.03% with 0.05% clobetasol propionate cream. Another study demonstrated the successful treatment of 10 individuals with discoid lupus for 8 weeks with pimecrolimus[16]. Furthermore, Stephanie *et al* review article, tacrolimus 0.1% proves helpful in treating CLE patients. Unfortunately, DLE may be resistant to calcineurin inhibitors given the thick and scaly nature of these lesions. Tacrolimus with clobetasol propionate was shown to be effective in achieving good or excellent improvement of lesions in previously treatment-resistant CLE, and it also decreased the incidence of telangiectasia[9]. While randomized double-blind pilot study comparing pimecrolimus 1% and betamethasone valerate 0.1% showed no significant difference between the two groups in terms of therapeutic efficacy in treating patients with severe to moderate discoid lupus[17]. A review article conducted by Niebe *et al* showed that topical calcineurin inhibitors (pimecrolimus, tacrolimus) may be utilized (off-label) for maintaining

Table 2

Quality assessment for observational studies (Newcastle-Ottawa Scale)

Study ID	Selection	Comparability	Outcome	Total score
Madan2009	★★★		★★★	6(high Quality)
G. Avgerinou2012	★★★		★★★	6(high Quality)

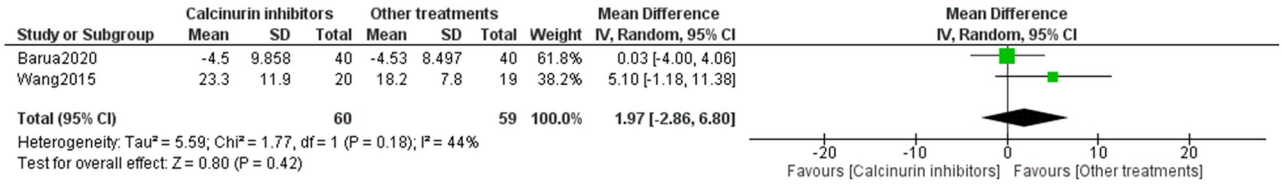

Figure 3. Analysis of erythema score changes in discoid lupus patients across treatment groups.

remissions, particularly in facial lesions, they frequently fall short of controlling disease flare-ups[18]. The European dermatology forum established a new guideline for CLE and considered topical calcineurin inhibitors as alternative options to topical corticosteroids, as well as topical treatment considered first line along with antimalarials[1].

Calcineurin inhibitors efficacy in lupus erythematosus tumidus (LET)

A review study showed Tacrolimus (0.1%) effective in treating drug-induced subacute lupus erythematosus triggered by bupropion and monocyclic antidepressants also two other cases of LE tumidus on the face and arms showed marked improvement in 3 weeks with topical pimecrolimus 1.0% cream. Topical calcineurin inhibitors at concentrations of 0.1%, 0.3%, and 1% were utilized to treat chronic manifestations as steroid alternatives[4]. Moreover, a clinical trial study compared tacrolimus 0.1% to vehicle twice daily for 12 weeks associated CLE edema responded rapidly to tacrolimus 0.1% ointment and the effect was significant in comparison to treatment with vehicle after 28 days. Moreover, patients with lupus erythematosus tumidus respond with the highest degree of improvement to tacrolimus 0.1% but desquamation, hypertrophy, and subjective symptoms like dysesthesia did not change[1].

Brief meta-analysis comparing calcineurin inhibitors versus other treatments in SLE

A brief meta-analysis comparing between the calcineurin inhibitors and other treatments (betamethasone 17-valerate 0.1% cream, topical halobetasol propionate 0.05%, vehicle and triamcinolone acetonide 0.1% cream) was done in four randomized controlled trials in order to evaluate the efficacy and safety. Regarding the efficacy outcomes, there was no significant statistical difference between calcineurin inhibitors and other treatments group in the main change in clinical severity scores outcome [MD=-0.54 [-1.98, 0.89] 95% CI, P= 0.97] and our result was homogenous (I2= 0%, P= 0.97) (Fig. 2). Additionally, the analysis of two included studies of discoid lupus patients reveled no significant difference between both groups in the main change in erythema scores outcome [MD=1.97 [-2.86, 6.80] 95% CI, P= 0.18] (Fig. 3). However, the result showed moderate heterogeneity and the sensitivity test was not applicable (I2= 44%, P= 0.18). Similarly, no significant difference between both groups with discoid lupus disorder was visible in the adverse effects outcome [MD=0.04 [-0.11, 0.19] 95% CI, P= 0.12]. Nevertheless, the result showed high heterogeneity and the sensitivity test was not applicable (I2= 59%, P= 0.12) (Fig. 4). In Wang et al 2015 the adverse effects in calcineurin group were burning, irritation and mild itching sensation at coating sites which subsided after a week. Comparably, the drug was tolerated in Barua et al. 2020 and adverse effects mainly consisted of burning sensation and telangiectasia that stopped after termination of the treatment. Finally, the analysis of recurrence outcome exhibited no significant difference between calcineurin inhibitors and other treatments [MD=-0.05 [-0.28, 0.18] 95% CI, P= 0.58] and homogenous results (I2= 0%, P= 0.58) (Fig. 5).

Calcineurin inhibitors safety in SLE patients

Many studies have shown that topical calcineurin inhibitors are safe for chronic inflammatory skin diseases. The majority of adverse effects are mild and transient side effects like irritation and burning. Additionally, there is a lower risk of systemic effects because of the drugs low penetration in inflamed skin. Moreover, there is a less possibility of steroids adverse effects such as skin atrophy and other long-term complications even in sensitive areas and during infancy[4]. Although there are some limitations in using these drugs in patients with pre-existing infections, no significant reports of local infections are available. In 2005, some concerns from the FDA about the risk of cancer associated with tacrolimus were relieved according to some animal studies and squamous cell carcinoma reports in some patients. Nevertheless, no additional reviews have linked topical calcineurin inhibitors to risk of cancer in adults and children since then. While some studies showed a small increase in lymphoma risk, this is similar to topical steroids risks. Finally, there are no large clinical studies with findings of increased cancer risk by these agents are existing[16].

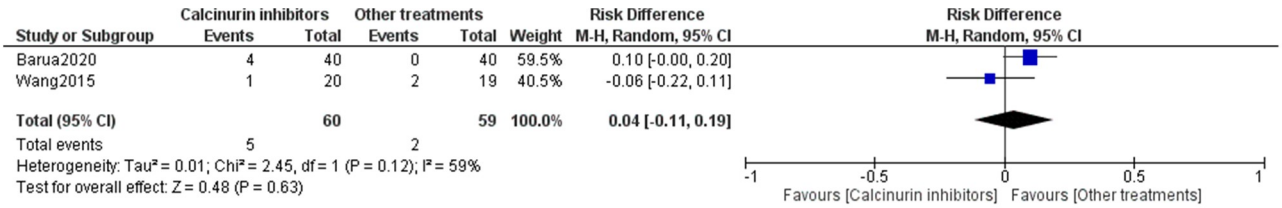

Figure 4. Overview of adverse effects associated with calcineurin inhibitors versus other treatments in discoid lupus patients.

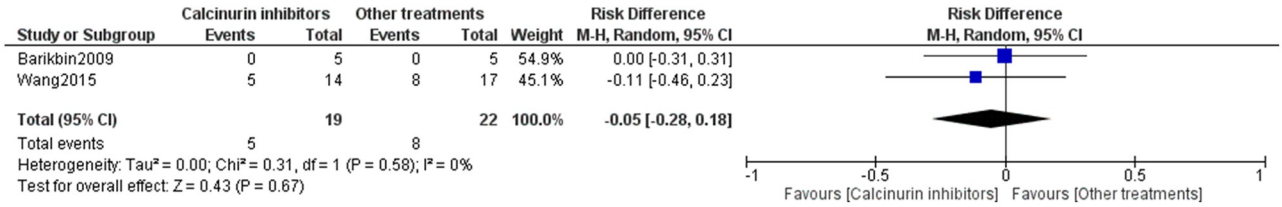

Figure 5. Examination of recurrence outcomes among patients treated with calcineurin inhibitors compared to alternative therapies.

Tacrolimus versus pimecrolimus and recommended concentration

In terms of comparing tacrolimus and pimecrolimus efficacy, only two studies compared the efficacy. Systematic review conducted on eight studies utilized topical tacrolimus (0.03 or 0.1%), four studies used topical pimecrolimus (1%) and one study combined tacrolimus and pimecrolimus, in patients with DLE, LET, and ACLE, tacrolimus shown a significant improvement in treating these patients[19]. Another systematic review revealed that tacrolimus demonstrated a slightly higher response rate when compared to pimecrolimus[3]. However, no studies compared the efficacy between tacrolimus and pimecrolimus directly; both studies were systemic reviews. While other studies recommended combining of calcineurin inhibitors with other agents to increase efficacy. A study showed significant improvement in three clinical parameters of erythema, desquamation, and edema in DLE patients, combination calcineurin inhibitors with hydroxychloroquine treatment resulted in improvement of edema in 100% of patients, while monotherapy did so in 75% of patients[2].

Discussion

This systematic review study aimed to establish the efficacy of calcineurin inhibitors on different types of CLE, safety of topical calcineurin inhibitors.

In terms of safety our systematic review revealed that calcineurin inhibitors are safe and used as alternatives to topical steroids. This is consistent with a Japanese study that showed the safety of using tacrolimus during pregnancy on controlling lupus activity[20]. However, some other studies reported risk of cancer associated with these medications. Further, a study revealed that 0.1% tacrolimus ointment has some side effects including burning or itching while pimecrolimus 1% cream have no side effects reported when applied twice daily for 3 months in DLE patients[21]. Moreover, no enough cost-effective studies of these medications are available. This raises the question of whether the potential benefits outweigh the financial implications for patients, especially in cases where conventional corticosteroid therapy may be more cost-effective.

In terms of efficacy our study revealed that calcineurin inhibitors are effective as solitary treatment in different conditions of CLE (subacute cutaneous LE, discoid lupus, tumidus lupus, and chilblain lupus). This is supported by different study[22]. However, a study by Madan *et al* revealed that topical tacrolimus 0.3% combined clobetasol propionate 0.05% ointment to increase the efficacy[14]. Furthermore, a study showed the most efficient alleviators of pruritus among lupus patients are calcineurin inhibitors when compared to systemic treatment antimalarials, corticosteroids, antihistamines, and other antipruritic agents[23]. However, our meta-analysis result showed no difference between calcineurin inhibitors and other treatment.

In terms of comparing efficacy of tacrolimus and pimecrolimus our result showed that the tacrolimus has higher response rate compared to pimecrolimus among patients with CLE. A review consistent with our finding showed that tacrolimus has higher efficacy and better tolerance than pimecrolimus, but the study was applied on patients with atopic dermatitis[24].

Limitations

Our study has a lot of limitations. First, the variation in the definition of calcineurin inhibitors efficacy limit the results generalization. Second, no enough studies were available in order to evaluate the cost-effectiveness of the calcineurin inhibitors for SLE patients. Additionally, the small RCTs sample size limits the

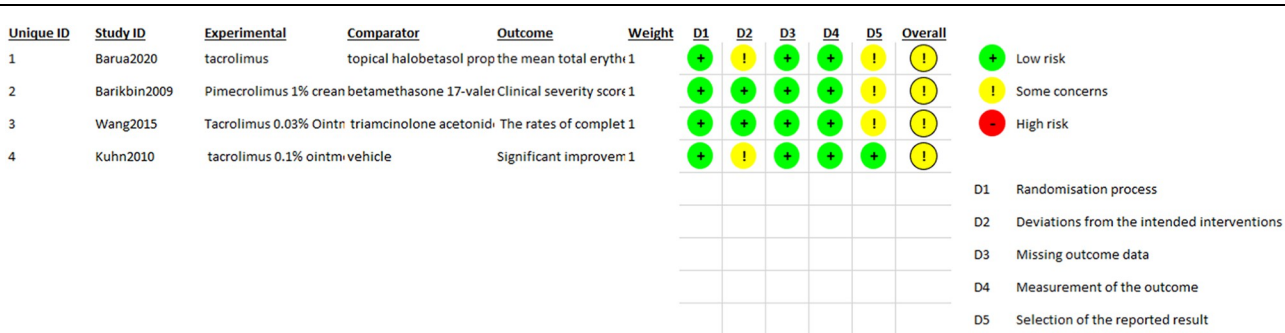

Figure 6. Quality assessment for RCTs studies (ROB II tool).

validity of our study. More studies are needed in order to strengthen our result. Additionally, more studies should investigate the cost-effectiveness of these drugs because of their high prices.

Conclusion

In conclusion, our systematic review analyzed 25 studies to evaluate the efficacy and safety of topical calcineurin inhibitors in treating CLE. Our systematic review findings support the effectiveness of these inhibitors, namely pimecrolimus cream and tacrolimus ointment in improving clinical manifestations and disease activity in various forms of CLE, such as discoid lupus and subacute CLE. However, the result from RCTs meta-analysis showed no significant difference between calcineurin inhibitors and other treatments. While calcineurin inhibitors are generally safe, the most common side effect was skin burning sensation at application site in the first few days of treatment. Further research is needed in order to strengthen our result, explore the comparative effectiveness between different calcineurin inhibitors and comparing their types and their concentration.

Ethical approval

None.

Consent

None.

Sources of funding

None.

Author's contribution

A.A.: conceptualization, methodology, writing – original draft, visualization, writing – review & editing. A.H.A.: supervision, data collection, formal analysis, writing – original draft, methodology. A.H.A.: data collection, writing – original draft, visualization, conceptualization. L.F.A.: literature review, data interpretation, writing – review & editing. R.A.A.: data collection, methodology, writing – review & editing. R.A.A.: project administration, data analysis, writing – review & editing. M.A. A.: investigation, data curation.

Conflicts of interest disclosure

The authors declare they have no conflicts of interest.

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Guarantor

Almaha H. Alshathri.

Provenance and peer review

None.

Data availability statement

The datasets are available upon reasonable request.

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