Clinical Medicine Insights: Dermatology

REVIEW

Topical Calcineurin Inhibitors: An Update on Their Use in Cutaneous Lupus Erythematosus

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Abstract: Lupus erythematosus is a multisystem disorder which frequently manifests in the skin. Acute, sub-acute and chronic cutaneous lupus erythematosus represent distinctive patterns of clinical and histological presentation with varying degrees of association with systemic disease. Skin involvement in lupus erythematosus can cause significant morbidity creating a source of considerable distress to patients. A variety of therapeutic agents including topical corticosteroids and systemic immunosuppression have been used in cutaneous lupus, but many lesions are treatment-resistant and prolonged use may be limited by side-effects. The topical calcineurin inhibitors, tacrolimus and pimecrolimus, inhibit T-cell activation limiting inflammation and offer a treatment option for patients with cutaneous lupus erythematosus. This article reviews existing literature documenting their use in this population. Although there is a lack of randomised control trial data, successful treatment of patients with varying patterns of cutaneous lupus erythematosus is described. Treatment is generally well-tolerated and can be combined with traditional treatment regimens.

Keywords: tacrolimus, pimecrolimus, cutaneous lupus erythematosus

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Introduction

Lupus erythematous (LE) is an autoimmune condition producing a spectrum of disease ranging from solely cutaneous involvement to life-threatening multi-organ dysfunction.[1] A range of skin manifestations exist in both the purely cutaneous form and in systemic disease representing a considerable source of morbidity and distress to patients.[2]

In the UK topical calcineurin inhibitors, tacrolimus and pimecrolimus are licensed for use in moderate to severe and mild to moderate atopic eczema respectively, however they have been used off-label for a variety of conditions including cutaneous lesions in LE.[3] These drugs represent a possible treatment option for patients with cutaneous LE, potentially improving outcomes and reducing exposure to long-term topical steroids and/or systemic medications.

We sought to review the evidence for the use of calcineurin inhibitors in cutaneous LE by systematic review of the available literature. The Medline database was searched using the terms; tacrolimus, pimecrolimus, topical calcineurin inhibitor and cutaneous LE. All publications involving clinical trials (open-label, randomised control and cohort) were included and reference is made to numerous individual case reports/series. To place the evidence in context we begin with a discussion of the classification of cutaneous LE and the mechanism and safety profile of calcineurin inhibitors.

Cutaneous Lupus Erythematosus (LE)

Cutaneous LE is broadly divided into specific- and non-specific types.[4] Non-specific cutaneous LE includes features resulting from leucotocytoclastic vasculitis, purpura, urticaria-like lesions, palmar erythema, diffuse non-scarring alopecia and livedo reticularis. While these skin findings can be seen a variety of other autoimmune conditions, in LE they are commonly associated with systemic involvement and may reflect disease activity.[5]

Cutaneous LE is divided into three main categories; acute (ACLE), sub-acute (SCLE) and chronic (CLE).

Acute cutaneous lupus erythematosus (ACLE)

ACLE occurs most commonly in a localised form presenting with bilateral malar erythema extending over the nasal bridge (the 'butterfly rash'). The eruption may involve the anterior neck and forehead and is accompanied by varying amounts of dermal oedema. In severe cases blistering can occur. Photosensitivity is a prominent feature. The eruption is transient and usually heals without scarring although significant post-inflammatory dyschromia may result. The generalised form of ACLE presents as a more widespread, photosensitive eruption including erythema and oedema of the hands, classically sparing the knuckles.[1] ACLE can occur in isolation, but has the highest association with systemic disease.[6] The 'butterfly rash' of localised ACLE is present at diagnosis in 40%–52% of patients with systemic lupus erythematosus (SLE).[6,7]

Sub-acute cutaneous lupus erythematosus (SCLE)

SCLE is strongly associated with postive anti-Ro antibodies (60%–100%),[8] photosensitivity[9] and may be drug induced.[10] SCLE presents on sun-exposed areas predominantly the upper limbs, neck and back with relative sparing of the midface. Lesions typically appear as individual scaly annular areas which may become confluent or as a papulosquamous eruption. Healing is without scarring, but as with ACLE significant post-inflammatory hypo- or hyperpigmentation may occur. Although approximately half of patients with SCLE meet the American College of Rheumatology criteria[11] for SLE only 10%–15% will develop significant systemic dysfunction.[12]

Chronic cutaneous lupus erythematosus (CLE)

The most common form of CLE is discoid lupus erythematosus (DLE). Rarer subsets incude; lupus panniculitis, mucosal lupus and chillblain lupus. DLE is most common on the head, ears, neck and scalp and presents with inflammatory macules or plaques. A substantial proportion of patients (>50%) develop scarring at the site of previous lesions which may be severe and disfiguring.[13] Patients with CLE are least likely to develop systemic involvement with approximately 5%–10% developing SLE.[14,15] Originally categorised as a form of CLE,[16] lupus tumidus (LET) is recognised as intermittent cutaneous LE[17] characterised by marked photosensitivity[18] and a more benign clinical course.[17]

Histological analysis correlated to clinical findings can be helpful in differentiating forms of cutaneous LE.

Lymphohistiocytic infiltrates are common in ACLE, SCLE and DLE with varying degrees of intensity and depth. In ACLE and SCLE the infiltrate is predominantly in the superficial dermis with SCLE commonly showing an interface reaction. In DLE there is active inflammation of the dermis, epidermis and adnexal structures. The intense nature of the inflammation in DLE correlates to the increased incidence of scarring and the resistant nature of the lesions.[19]

Treatment Options for Cutaneous Lupus Erythematosus

Where relevant, the management of cutaneous LE includes instruction regarding sun-protection[20] and cessation of possible causative medications such as hydralazine, antiepileptic medications or sulphonamide antibiotics.[21] Topical (with or without occlusion) and intralesional corticosteroids have been used for all types of cutaneous LE. Long-term use is limited by the well-documented side effects of topical corticosteroids such as skin atrophy and telangectasia. Short courses of oral corticosteroids have been used for flares of cutaneous disease, but are not recommended for maintenance given the risk of systemic side—effects such as osteoporosis.

A variety of steroid sparing systemic therapies including anti-malarials, mepacrine, immunosuppressants (methotrexate, azathioprine, mycophenolate mofetil), dapsone, thalidomide, oral retinoids, gold and efalizumab have been used for the skin manifestations of LE.[1] The use of systemic medication is accompanied by a variety of associated risks making the prospect of calcineurin inhibitors as alternative topical agents an attractive proposition to patients and clinicians.

Treatment of Cutaneous Lupus Erythematosus with Topical Calcineurin Inhibitors

Background

Calcineurin inhibitors prevent T-lymphocyte activation by preventing calcineurin from dephosphorylating the cytoplasmic subunit of the nuclear factor of activated T cells. In unopposed inflammation the phosphorylated subunit translocates to the nucleus of the T cell stimulating the production of inflammatory cytokines including interleukin (IL)2, IL-3, IL-4, tumour necrosis factor alpha (TNF-α) and granulocyte macrophage stimulating factor. By binding to the FK506 binding protein tacrolimus and pimecrolimus specifically prevent this process.[22] In addition to inhibiting T-cell activation, calcineurin inhibitors interfere with mast cell degranulation thereby preventing the release of additional inflammatory mediators including histamine and tryptase.[23]

Commercially available formulations of topical calcineurin inhibitors include; tacrolimus 0.1% and 0.03% (Protopic®) and pimecrolimus 1% (Elidel®). Tacrolimus is a more potent immunosuppressive agent than pimecrolimus which is more lipophilic ensuring lower permeation even in very inflamed skin and/or under occlusion.[24–26] Systemic absorption of topically applied 0.1% tacrolimus equivalent to oral administration has been documented during treatment of ulcerated pyoderma gangrenosum,[27] but has been deemed negligible during treatment of conditions with an intact epidermis including atopic dermatitis.[28,29]

Unlike topical corticosteroids, skin atrophy does not develop even after prolonged use since neither tacrolimus nor pimecrolimus effect fibroblasts or endothelial cells. This is of particular benefit when treating sites at high risk of steroid side-effects including genital, facial and flexural skin.[30] Conversely, penetration into hyperkeratotic skin lesions may be limited and increased efficacy has been reported with descaling treatments such as salicylic acid[31] or microdermabrasion.[32]

Safety and tolerance

Dysaesthesia ('burning' or 'stinging' sensations) at the site of application is the most common side-effect. It usually improves with continued use, but in some cases may limit patient tolerance of therapy.[33] Cases of contact dermatitis[34] and local infection have been reported. Application of calcineurin inhibitors is contraindicated in the presence of active viral or bacterial infection, but overall incidence has not been found to be significantly increased compared to patients using corticosteroids.[35]

In 2005 the Food and Drug Administration (FDA) issued a 'black box' warning regarding potential risk of malignancy associated with the use of tacrolimus based on effects in animal studies and isolated case reports of cutaneous malignancy or lymphoma

in patients using the drug.[36] Several subsequent systematic reviews have failed to find any significantly increased risk of malignancy in patients utilising topical calcineurin inhibitors compared with patients using topical corticosteroids.[37–39] Animal studies failed to confirm concerns regarding increased risk of ultra violet (UV)-induced skin malignancy.[40,41] Further, it has been suggested that in comparison to use in atopic dermatitis, application to limited areas for relatively short periods could help minimise any theoretical risk in the CLE population.[42]

Topical calcineurin inhibitors have been successfully used as monotherapy and in combination with phototherapy in the treatment of vitiligo[43] with minimal side effects.[44] However, Mikhail et al[45] reported a case of rapid enlargement of a malignant melanoma in a child after use of tacrolimus with vitiligo. While they did not feel that the drug had induced malignant conversion they noted that tacrolimus induces tissue changes which could inhibit the antimelanocytic immune response and promote tumour progression.[45]

While the current evidence suggests that topical calcineurin inhibitors are safe, well tolerated treatments, long-term data is still being generated. Specific sun-protection measures are not generally advocated for patients using topical calcineurin inhibitors. However, patients with CLE should be advised to avoid excessive sun exposure and encouraged to adopt sun-protection measures given the photosensitive native of the condition.

Case reports, case series and open-label studies

In 2002 Yoshimasu et al,[46] Zabawski[47] and Walker et al[48] described the first experiences of topical calcineurin inhibitors for cutaneous LE. Yoshimasu et al described a case series of eleven patients with cutaneous LE (3ACLE, 4DLE) or dermatomyositis (4 DM) who applied tacrolimus 0.1% once a day for four weeks. Of these, three patients with ACLE, one with DLE and two with DM were deemed by the clinicians to show marked regression of their skin lesions while the other participants did not improve.[46] Zabawski described a patient with DLE who improved with pimecrolimus[47] while Walker et al described two case of DLE who improved with a combined preparation of tacrolimus 0.3% in clobetasol 0.05%.[48]

Following these first experiences, a number of case reports/series have documented successful use of topical calcineurin inhibitors in ACLE[49,50] SCLE[50–52] and DLE[51,53–56] as well as LET,[57] drug-induced SCLE[58] and DLE-lichen planus overlap syndrome[59] (see Table 1).

Trial data consists mainly of open-label uncontrolled studies. Tlacuilo-Parra et al[60] reported a series of ten patients with 'moderate' DLE who were treated for eight weeks with twice daily pimecrolimus 1% cream as monotherapy. Patients with co-existing systemic involvement were excluded from the study. None of the participants had previously been exposed to topical calcineurin inhibitors though two had failed to respond to systemic therapy in the past. Response was assessed through clinical severity scores, quality of life scores and patient self-assessment. Based on clinical severity scoring roughly half of patients (52%) showed a significant improvement though a degree of clinical effectiveness was found in all cases. All participants felt there had been subjective improvement in their skin condition and there was a statistically significant improvement in quality of life scores ($P = 0.008$). Treatment was generally well tolerated with transient erythema and pruritus being the only reported side effects.[60]

Kreuter et al reported positive results in an open-label uncontrolled study of eleven patients (4DLE, 3SLE, 2SCLE, 2LET) treated with pimecrolimus 1% cream under semi-occlusive conditions twice daily for 3 weeks.[61] Six patients had coexisting SLE. No other topical treatments were used by participants during the study period, but three remained on concomitant systemic immunosupression. A clinical score was assigned before and after treatment with all patients showing some improvement after treatment ($P < 0.001$). One patient reported transient dysaesthesia which resolved without interventions and all participants completed the study.[61]

Two open label studies were published discussing the use of tacrolimus in cutaneous LE. The first published in 2003 by Kanekura et al[62] contained three patients with ACLE who participated in a side-to-side comparison study. All patients had pre-diagnosed SLE with disease duration between 1–7 years duration of skin lesions ranged from 9 months to 2 years. Tacrolimus 0.1% ointment was applied twice daily to one side of the face together with sunscreen for three

Table 1. The response of cutaneous LE to treatment with topical calcineurin inhibitors—a summary of the medical literature to date.

Year	Ref	Author	Type of series	Patients	Treatment	Duration	Successful treatment
2002	46	Yoshimasu T, et al	Open label study	4DLE, 3SLE, 3DM	Tacrolimus 0.1%	4 weeks	3SLE, DLE, 2DM
2002	48	Walker SL, et al	Case series	2DLE	Tacrolimus 0.3% in clobetasol proprionate 0.05%	6 months and 8 weeks	2DLE
2002	47	Ed Zabawski DO	Case report	1DLE	Pimecrolimus 1%	Not available	1DLE
2003	57	Bacman D, et al	Case report	1 LET	Tacrolimus 0.1%	4 weeks	1LET
2003	49	Böhm M, et al	Case series	1ACLE, 2SCLE,	Tacrolimus 0.1%	8 weeks	1ACLE, 2SCLE
2003	62	Kanekura T, et al	Open-label bilateral comparison study	3ACLE	Tacrolimus 0.1%	3 weeks	3ACLE
2004	51	Drüke A, et al	Case report	1SCLE	Tacrolimus 0.1%	>3months	1SCLE
2004	53	De la Rosa, Carrillo D, et al	Case report	1DLE	Tacrolimus 0.1%	7.5 weeks	1DLE
2004	63	Lampropoulos CE, et al	Open label uncontrolled study	6DLE, 4SLCE, 2SLE	Tacrolimus 0.1%	≥6 weeks	2SCLE, 2DLE, 2SLE
2004	61	Kreuter A, et al	Open-label uncontrolled study	4DLE, 3SLE, 2SCLE, 2LET	Pimecrolimus 1%	3 week	4DLE, 3SLE, 2SCLE, 2LET
2005	60	Tlacuilo-Parra A, et al	Open-label uncontrolled study	10DLE	Pimecrolimus 1%	8 weeks	10DLE
2005	52	Meller S, et al	Case report	1ACLE	Tacrolimus 0.1%	3 weeks	1ACLE
2005	54	Heffernan MP, et al	Case series	5DLE	Tacrolimus 0.1%	12 weeks	5DLE
2005	58	Cassis TB, et al	Case report	1SCLE (drug induced)	Tacrolimus 0.1%	4 weeks	1SCLE
2006	55	Sugano M, et al	Case series	4DLE	Tacrolimus 0.1%	4–8 weeks	4DLE
2006	50	Von Pelchrzim, et al	Case series	3DLE, 1ACLE	Tacrolimus 0.1%	4 weeks	3DLE
2006	59	Nago K, et al	Case report	1DLE-lichen planus overlap	Tacrolimus 0.1%	Not available	1DLE-lichen planus overlap
2007	64	Tzung TY, et al	Randomised double-blind bilateral comparison study	13ACLE, 4DLE, 1SCLE	Tacrolimus 0.1%	4 weeks	13ACLE, 4DLE, 1SCLE
2009	61	Barikbin, et al	Randomised double-blind pilot study	10DLE (5 each group)	Pimecrolimus 1% versus betamethasome 17-valerate 0.1%	8 weeks	10DLE (comparable efficacy)
2009	66	Madan V, et al	Retrospective cohort study	11DLE, 1ACLE, 1SCLE	Tacrolimus 0.3% in clobetasol proprionate 0.05%	Various (1month- 4 years)	10DLE, 1ACLE, 1SCLE
				3DLE, 2ACLE	Tacrolimus 0.1%		3DLE
2010	56	Han YW, et al	Case series	4DLE	Tacrolimus 0.1% or pimecrolimus 1%	Various	4DLE

weeks compared to sunscreen only on the remaining side. All patients showed better clinical improvement on the tacrolimus treated side compared to sunscreen alone. There were no reports of adverse effects.[62]

The second open label trial involving tacrolimus was published in 2004 by Lampropoulos et al.[63] Twelve patients with cutaneous LE (6DLE, 4SLCE, 2SLE) were treated with twice daily tacrolimus 0.1% for varying periods (minimum 6 weeks). Response was assessed subjectively by patients and by the treating clinician. Six patients (2SCLE, 2DLE, 2SLE) showed significant improvement while one further patient with DLE had minor improvement. One patient discontinued treatment due to discomfort from dysaesthesia.[63]

Randomised-control studies

To date the only double-blind randomised control trial comparing topical corticosteroids with tacrolimus was reported by Tzung et al in 2007.[64] Eighteen patients with treatment resistant cutaneous LE of at least six months duration (13SLE, 4DLE, 1SCLE) completed the study applying twice daily tacrolimus 0.1% to one randomly assigned side of the face and clobetasol 0.05% to the other for four weeks. The authors were concerned that the relatively large size of the tacrolimus molecule (822.05 Da) could limit penetration into hyperkeratotic skin lesions and in addition to topical treatments once weekly microbrasion was performed. Response was assessed weekly and one month after completion of treatment using a 7-point rating scale to compare paired lesions. The presence of telangectasia was also graded and side effects recorded. Both treatments were found to be effective treatments and all patients showed improvement in erythema, desquamation and induration from baseline. There was no significant difference in efficacy, but lesions treated with clobetasol 0.05% showed a higher incidence of telangectasia ($P < 0.05$).[64]

Barikbin et al[65] reported a double-blind randomised pilot study with ten patients with DLE randomised to eight weeks of treatment with either pimecrolimus 1% cream or betamethasone 17-valerate 0.1% twice daily. Patients with evidence of SLE were excluded from the study. All other systemic and topical treatments were discontinued at least four weeks prior to the commencement of the trial. Both groups showed significant improvement in erythema, infiltration and scale and the authors concluded that both treatments showed equal efficacy. Neither group experienced any side-effects.

Special formulations

In trying to overcome the limited penetration of commercially available preparations some authors have used specially formulated, more concentrated preparations. Madan et al[66] reported a retrospective cohort study comparing fourteen patient (11DLE, 1ACLE, 1SCLE) who used specially formulated tacrolimus 0.3% in clobetasol propionate 0.05% ointment (TCPO) with five patients (2DLE, 3SLE) who used tacrolimus 0.1%. All patients had cutaneous LE of at least three months duration (range 3 months to 25 years). Response was classified by retrospective review of the clinical case notes as 'poor', 'slight', 'good' or 'excellent'. In the TCPO group six patients (5DLE, 1SCLE) showed an 'excellent' response, five patients (5DLE, 1ACLE) had a 'good' response, one discontinued therapy (DLE) and one showed a 'slight' response. Mean treatment duration in this group was 20.2 months and two patients reported side-effects (acne and telangectasia respectively). In comparison, patients using tacrolimus 0.1% only one showed a 'good' response (DLE), two a 'slight' response (2DLE) and one responded 'poorly'. One patient in this group reported local irritation and subsequently discontinued treatment.[66]

Discussion

Topical calcineurin inhibitors as monotherapy or in combination with topical corticosteroids and/or systemic medication represent a potential treatment option for various forms of cutaneous LE. Reports to date discuss eight years of clinical experience with demonstrable success in a variety of presentations of cutaneous LE. However, evaluation of efficacy is limited by the lack of a unified system for evaluating treatment impact, lack of standardised treatment protocols and a dearth of randomised control trial data.

The best results have been seen in ACLE and SCLE and may be related to the relative degree of skin in duration/thickening. Treatment of hyperkeratotic lesions, such as those typically seen in DLE, may be restricted by the limited penetration of topical calcineurin inhibitors. Penetration, and thereby efficacy,

has been enhanced by descaling of lesions with salicylic acid, occlusion, microbrasion, or specially formulated preparations containing higher concentrations of topical calcineurin inhibitors. The practicality of these adjuncts would need to be assessed on a case-by-case basis depending on local facilities.

It is difficult to comment on whether concomitant systemic involvement or use of immunosuppressants influences likelihood of success when treating cutaneous LE as a relatively small number of published cases are available. Of note many authors have reported on patient(s) with severe, chronic, recalcitrant disease where previous treatment modalities have failed. It may be that less pronounced, acute eruptions are more amenable to treatment, but are chiefly resolved with first-line agents such as topical corticosteroids.

In patients with cutaneous LE topical tacrolimus and pimecrolimus are well-tolerated treatments with only a small number of patients needing to discontinue therapy. Where this occurred, the main complaint was of local dysaesthesia. The risk of local immunosuppression with topical calcineurin inhibitors is well recognised and cases of transient localised infection have been reported in the cutaneous LE population.[67] Combined preparations of topical calcineurin inhibitors with corticosteroids have been used with success and may represent a more potent treatment option than with treatment alone. Use of combined treatment may carry increased risk of infection although this has not been reported in the available series to date.

In the publications reviewed no significant adverse events were reported and there was no evidence of significant systemic absorption. Safety reports from larger cohorts of patients with atopic dermatitis is encouraging, however, as long-term safety data remains limited, it may be sensible to restrict exposure in patients with cutaneous LE. Patients should be aware of the need for adequate sun-protection as an adjunct to topical calcineurin inhibitors as part of active disease prevention and treatment.

Learning Points

1. Topical calcineurin inhibitors are generally well tolerated, the most common side effect of is dysaesthesia ('burning' or 'stinging'). (Evidence level A)
2. Topical calcineurin inhibitors have been effective in treating ACLE, SCL and DLE. (Evidence level C)
3. Topical calcineurin inhibitors can be used in conjunction with topical steroids or systemic therapy. (Evidence level C)
4. Efficacy of topical calcineurin inhibitors can be enhanced through mechanisms to increase penetration of the skin such as microbrasion, increased concentration or concomitant use of salicylic acid. (Evidence level C)

Guide to levels of evidence[68]

- Level A: Consistent Randomised Controlled Clinical Trial, cohort study, clinical decision rule validated in different populations.
- Level B: Consistent Retrospective Cohort, Exploratory Cohort, Ecological Study, Outcomes Research, case-control study; or extrapolations from level A studies.
- Level C: Case-series study or extrapolations from level B studies.
- Level D: Expert opinion without explicit critical appraisal, or based on physiology, bench research or first principles.

Disclosure

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

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