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REVIEW ARTICLE

Topical tacrolimus and pimecrolimus in the treatment of cutaneous lupus erythematosus: an evidence-based evaluation

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Abstract
Background Lesions of cutaneous lupus erythematosus (CLE) are refractory to a wide range of topical or systemic therapies. The pathogenesis of CLE is multifactorial and polygenic, and many of its details remain unclear. However, immunologic evidence suggests the possible therapeutic use of tacrolimus and pimecrolimus. CLE is one of the most common dermatological autoimmune disorders worldwide, which includes systemic lupus erythematosus (SLE) with malar rash, subacute cutaneous lupus erythematosus (SCLE) and discoid lupus erythematosus (DLE).
Objective Our aim was to determine the efficacy of topical pimecrolimus and tacrolimus in the treatment of cutaneous lupus erythematosus.
Methods The literature was systematically reviewed. Medline, Embase, and the Cochrane Database were searched for systemic reviews, randomised controlled trials and nonrandomised clinical trials using the search terms "pimecrolimus", "Elidel", "SDZ ASM 981", "tacrolimus", "Protopic", "FK506" and "cutaneous lupus erythematosus". Studies were assessed independently by two authors.
Results Five studies were eligible for inclusion in this review. Only one of them was a randomised controlled trial (RCT). There was no significant difference between tacrolimus and clobetasol; however, evidence indicates the highest tolerability of tacrolimus compared with corticosteroids. This review indicates the efficacy of tacrolimus and pimecrolimus in, at least initial, cutaneous lesions of SLE. However, in SCLE and DLE lesions, the efficacy appears to be lower, perhaps due to the chronicity of those lesions.
Conclusion The lack of RCTs is characteristic. Future studies should focus on efficacy, short- and long-term effects and cost-effectiveness. However, tacrolimus and pimecrolimus show efficacy, and such effort is worthwhile.

Keywords Cutaneous lupus erythematosus · FK506 · Pimecrolimus · SDZ ASM 981 · Tacrolimus

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Introduction

Lupus erythematosus (LE) is a complex autoimmune disease with a broad spectrum of clinical manifestations ranging from localised skin lesions to systemic disease. Pure cutaneous subtypes (CLE) are distinguished from systemic subtypes (SLE). However, overlaps and transitions from CLE into SLE are observed in 10–40% of patients [1]. Acute CLE (ACLE) typically presents in the context of a systemic illness, and 100% of patients develop SLE. Localised ACLE commonly manifests as a classic malar, or "butterfly" rash [1]. Chronic discoid LE (CDLE) is the most common subtype of CLE, which presents with scarring erythematous macules and plaques localised to the face or to the capillitium (localised CDLE), whereas subacute CLE (SCLE) represents 10–15% of CLE cases and appears with annular or psoriasiform lesions in sun-exposed areas [2]. Rare subtypes of CLE include lupus profundus (LEP), characterised by panniculitis, chilblain LE, which presents with pernio-like skin lesions [3], and lupus tumidus (LET) [4], with urticarial lesions appearing in sun-exposed areas. The majority (75%) of LE patients develop cutaneous lesions at some point during the course of their disease. About 20% of patients initially present

with cutaneous findings [5]. Although pure CLE is not life threatening, cutaneous lesions are clinically significant and in many cases disfiguring and debilitating. Mechanisms of pathogenesis are not well understood, but the autoimmune response in skin can be described in three phases: initiation, amplification of the immune response and target damage [5]. Skin is considered to be the site of autoimmune initiation in LE.

There is a characteristic lack of randomised controlled trials and evidence-based approaches for the treatment of CLE. Current treatments for CLE rely largely on general immunosuppressive agents, such as corticosteroids [5]; topical, systemic or intralesional, antimalarials (hydroxychloroquine) [6], thalidomide [7] and low-dose methotrexate [8]. However, there is no consensus algorithm for treatment, and the overall efficacy of current treatment regimens is poor. The side effects of corticosteroids, such as thinning of the skin and adrenal gland suppression in the case of prolonged application, limit their long-term use.

The topical calcineurin inhibitors pimecrolimus and tacrolimus provide an effective and safe alternative, especially for long-term control of chronic inflammatory skin diseases. Topical tacrolimus is recognised as an effective treatment not only for atopic dermatitis [9] but also for other chronic inflammatory skin diseases such as pyoderma gangrenosum, psoriasis, actinic dermatitis and erosive lichen planus [10–13]. Nowadays, tacrolimus and pimecrolimus are used as treatments in many case series for "off-label" skin conditions. Herein, the literature is systematically reviewed to determine the efficacy of topical pimecrolimus and tacrolimus in the treatment of CLE.

Action mechanism of tacrolimus and pimecrolimus

Pimecrolimus (SDZ ASM 981) and tacrolimus (FK506) are immunomodulators belonging together with cyclosporine to the family of calcineurin inhibitors. They bind to the cytoplasmic protein macrophilin-12, and the resulting complex binds calcineurin, thus inhibiting its ability to dephosphorylate the nuclear transcription factor of activated T cells (NF-AT) [14]. Dephosphorylated NF-AT can translocate into the nucleus and facilitate the transcription of several growth factor and inflammatory genes [15].

Pimecrolimus and tacrolimus inhibit T-cell proliferation and production and the release of several growth factors and proinflammatory cytokines, such as interleukin-2 (IL-2), IL-4, interferon-γ (IFN-γ) and tumour necrosis factor-α (TNF-α) [14]. It also targets masts cells, inhibits mast-cell degranulation and prevents release of mediators such as histamine, cytokines, tryptase and eicosanoids [16, 17]. In contrast to tacrolimus, pimecrolimus has no effects on dendritic cells [14]. Tacrolimus has been shown to reduce the incidence of skin lesions in the autoimmune-prone MRL/Mp-lpr/lpr mouse, an animal model for the cutaneous lesions seen in human lupus erythematosus [18].

In contrast to corticosteroids and other systemic treatments such as gold therapy (auranofin), antimalarials (hydroxychloroquine), methotrexate and thalidomide, pimecrolimus and tacrolimus do not affect endothelial cells and fibroblasts so do not induce telangiectasia and skin atrophy and do not have the side effects of systemic treatments, such as anorexia, diarrhoea, leucopenia, glucose intolerance and osteoporosis [7, 19]. Furthermore, the propensity of pimecrolimus and tacrolimus to pass through the skin is about 90 and 10 times, respectively, lower than corticosteroids [20], thus making uptake into the systemic circulation less likely. Therefore, topical therapy might be preferable to treat CLE lesions.

Methods

We systematically searched Medline, Embase and the Cochrane Database for systematic reviews, randomised controlled trials and nonrandomised clinical trials to August 2007 using the search terms "pimecrolimus", "Elidel", "SDZ ASM 981", "tacrolimus", "Protopic", "FK506" and "cutaneous lupus erythematosus". Studies were assessed independently by two authors (TGT, DK) and conclusions reached by consensus. Due to the insufficient number of randomised controlled trials, it was decided to include prospective open-label uncontrolled trials. Design characteristics that could affect interpretation of the results and applicability of findings were taken into consideration. Selection of publications was done using the following criteria: Studies should be prospective and have as high an evidence level as possible. Only studies of evidence level 4 or above were included [21]. Retrospective studies, case series patients and unclear publications were not considered. Trials fulfilling the eligibility criteria were suitable for inclusion, regardless of language or publication status.

Results

Out of 32 studies retrieved, five were eligible for inclusion (Table 1) [22–26]. Most of the excluded studies were just case series of CLE treated with topical tacrolimus or pimecrolimus. Characteristically, only one of the included studies was a randomised controlled trial [25].

Tacrolimus vs. clobetasol propionate

As indicated from the only randomised controlled trial in the literature so far, there is no significant difference

Table 1 The five studies that were eligible for inclusion in this review

Citation	Design	Type of CLE	Intervention	Results	Limitations
22	Open, uncontrolled clinical trial with 11 patients	4 patients with DLE 3 with SLE 2 with SCLE 2 with lupus tumidus	Pimecrolimus 1% cream twice daily for 3 weeks under semiocclusive conditions	Significant regression of skin lesions 57% improvement on clinical severity score ($p<0.001$)	Open uncontrolled study, limited number of cases, poor outcome measure (clinical score)
23	Open-label phase II uncontrolled trial with 10 patients	DLE	Pimecrolimus 1% cream twice daily for 8 weeks	52% decrease in clinical severity score ($p=0.005$) 46% improvement in quality-of-life score ($p=0.008$)	Open uncontrolled study, small number of cases
24	Open, uncontrolled clinical trial with 12 patients	6 with DLE 4 with SCLE 2 with SLE	Tacrolimus 0.1% ointment twice daily for 6 weeks	6 patients clearly improved 4 remained the same, 1 minor remission, 2 SCLE significant regression, 2 SCLE no improvement, 3 DLE improvement, 2 without response, 2 SLE significant amelioration	Open uncontrolled study, very poor and biased outcome measure, small number of cases
25	Randomised, double-blind, bilateral comparison study with 20 patients	Facial CLE 13 malar rash of SLE 4 DLE 1 SCLE	Twice-daily 0.1% tacrolimus ointment on one side of the face, 0.05% clobetasol propionate ointment to the other side for 4 weeks	No significant difference between tacrolimus and clobetasol, lesions worsened at week 8, still better than at baseline; 11 patients (61%) developed telangiectasia on the clobetasol side as early as week 3 ($p<0.05$) compared with tacrolimus	Outcome measure based only to clinical features
26	Open, uncontrolled clinical trial with 7 patients	Facial CLE 3 SLE 4 DLE	Tacrolimus ointment 0.1% once a day (average daily dose within 0.3 g) for 4 weeks	3 SLE showed marked regression, 1 DLE showed marked regression, 3 DLE resistant to therapy, 2 out of 6 good responders showed recurrence	Open uncontrolled study, small number of cases, very poor outcome measure

CLE cutaneous lupus erythematosus, *SLE* systemic lupus erythematosus, *SCLE* subacute cutaneous lupus erythematosus, *DLE* discoid lupus erythematosus

between tacrolimus and clobetasol [25], However, 11 patients (61%) developed telangiectasia on the clobetasol side as early as week 3 ($p<0.05$) compared with tacrolimus. This result clearly indicates the highest tolerability of tacrolimus compared with corticosteroids and its—at least short-term—safety. There is no available data for pimecrolimus compared with corticosteroids in the literature so far. However, taking into consideration its specificity for inflammatory skin diseases, pimecrolimus should be tested also.

Tacrolimus and pimecrolimus for SLE cutaneous lesions

The data analysed in this review indicate the efficacy of tacrolimus and pimecrolimus in cutaneous lesions of SLE. Tacrolimus treatment showed good response for the initial skin lesions of SLE erythematous lesions with edematous or telangiectatic changes [26] within 2 weeks after treatment initiation. It also showed a marked improvement in the extensive photosensitive rash in SLE [24]. Pimecrolimus showed the same efficacy, with marked improvement of cutaneous lesions [22]. Based on the evidence provided so far, topical tacrolimus and pimecrolimus may be considered for the treatment of cutaneous SLE lesions, either as a monotherapy or combined with systemic maintenance treatment.

Tacrolimus and pimecrolimus for SCLE

Even though the evidence for tacrolimus and pimecrolimus in SCLE treatment are less than for SLE, it appears to be efficacious [22, 24, 25]. However, the results appear to be

less promising, perhaps due to unresponsiveness of skin-infiltrating cells themselves to the drug in the chronic lesion, which implies that in DLE and SCLE, infiltrating cells have different characteristics compared with early lesions of SLE, as indicated by Yoshimasu et al. [26]. Furthermore, the efficacy of topical corticosteroids or other systemic treatments in SCLE is low [5].

Tacrolimus and pimecrolimus for DLE

The amount of evidence for pimecrolimus and tacrolimus for DLE treatment point out their efficacy [22–26]. Pimecrolimus shows a good efficacy, not only on clinical variables but on quality-of-life (QOL) scores [22, 23]. Tacrolimus seems to be less effective, but a comparison with pimecrolimus cannot be performed [24–26]. One study by Yoshimasu and colleagues [26] shows the least efficacy for tacrolimus; however, this can be attributed to low dosage, as they applied tacrolimus only once daily [26]. They also suggest a low efficacy imputed to low drug absorption due to hyperkeratotic and acanthotic changes. However, when Tzung et al. used microdermabrasion once weekly to accelerate the delivery of tacrolimus, total clearance of the lesions was rarely achieved [25]. Patients with hyperkeratotic DLE did not respond well to tacrolimus treatment [24]. Therefore, it can be considered that, as with SCLE, low efficacy of tacrolimus can be attributed to unresponsiveness of skin-infiltrating cells themselves to the drug in the chronic lesion [26]. The efficacy of topical corticosteroids or other systemic treatments in DLE is low also [5].

Discussion

The above evidence-based evaluation indicates the efficacy of tacrolimus and pimecrolimus in the treatment of SLE cutaneous lesions SCLE and DLE. However, the place of pimecrolimus and tacrolimus in the treatment of cutaneous lupus will depend on its efficacy when compared with established topical treatments, such as corticosteroids.

The studies so far had an open-label design and involved only a small number of patients and no control group. Therefore, double-blind, placebo controlled studies are needed to confirm the existing data for efficacy and for safety on short- and long-term usage as well. The main long-term safety concern is the carcinogenic potential of at least tacrolimus. In a recent review, Rustin points out that systemic absorption of tacrolimus when applied topically is very low. Moreover, in the same review, it is stated that there is no evidence of an increased risk of malignancy and that epidemiological studies have failed to demonstrate an increased incidence of cancer in patients using topical calcineurin inhibitors [27]. On the other hand, as other authors point out [28], the recent recommendations from the United States Food and Drug Administration prompted the addition of a black-box warning for topical use of tacrolimus and pimecrolimus based on a theoretical risk of malignancy. However, they also state that there is no data suggesting that application of topical calcineurin inhibitors increases the risk of malignancy and that the black-box warning also stated no established causal link [28]. In conclusion, there is a great need of epidemiological studies with sufficient follow-up, systematic reviews and meta-analyses on this issue.

As tacrolimus and pimecrolimus are still expensive, cost-effectiveness studies should be performed. Future studies will determine the schema employed, the duration of treatment or the method of assessing improvement. The Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) has been recently proposed as a novel clinical scale focused on measurement of cutaneous disease [29, 30]. QOL should also be considered to measure objectively how the patient's life is affected by the disease. Skindex-29 is a generic and widely validated instrument to measure QOL in patients with skin diseases. This evidence-based evaluation, however, clearly indicates that such efforts are worthwhile.

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