The use of topical calcineurin inhibitors in chronic wound management

Sussman G

ABSTRACT

The management of wounds has evolved over many years and with a greater understanding of the mechanisms of skin repair, a recent approach to treatment is to address the changes in tissue. Complex chronic wounds place a significant challenge on health professionals working with these patients, in accurately identifying the underlying cause of the wound and the tissue factors impacting on wound healing. Many different types of dressings are used with limited success; however, dressings do not address the imbalances in tissue. Once a clear diagnosis has been established, the approach is to try to address this underlying imbalance in the tissues. Calcineurin inhibitors were approved for topical use in 2000–2001 for the treatment of atopic dermatitis. Since that time, their use has expanded to treat a number of chronic wounds, including pyoderma gangrenosum, cutaneous lupus erythematosus and other uncommon chronic wounds, with some success. This approach, in contrast to dressings that only impact on the wound environment, addresses the need to restore tissue balance and thus encourage wound healing.

Keywords: Calcineurin inhibitors, tacrolimus, pimecrolimus, pyoderma gangrenosum.

BACKGROUND

The use of topical calcineurin inhibitors in chronic wounds has developed since early 2000, with their extensive use in dermatology, in atopic dermatitis and for mild to moderate eczema. Over the past 10 years, their use has expanded to include use in complex chronic wounds[1]. There were concerns expressed by the FDA[2] over risks, including skin cancer and lymphoma; however, these concerns have not been demonstrated in the evidence[3,4] The report of the American Academy of Dermatology Association Task Force conference found no causal proof that topical calcineurin inhibitors cause lymphoma or non-melanoma skin cancer[5].

Geoff Sussman
OAM, FPS, FACP, FAIPM, FAWMA, FRVAHJ
Associate Professor of Wound Care
Monash Institute for Health and Clinical Education
Faculty of Medicine, Nursing and Health Science
Monash University, VIC, Australia
Email geoff.sussman@monash.edu

Calcineurin inhibitors were originally prescribed to prevent allograft rejection post transplant. They have been demonstrated to have anti-inflammatory activity and immunosuppression[6-8]. They have also been shown to have little risk of skin atrophy when compared with topical corticosteroids[7]. They also have been shown to induce initial release of substance P that helps to explain their efficacy in pruritis and sensory side effects[9].

Calcineurin inhibitors form complexes with cytoplasmic immunophilins, which block the action of calcineurin in activated T-cells. This prevents production of interleukin-2 and other cytokines that normally stimulate T-cell proliferation and differentiation[10]. Calcineurin inhibitors are used for the prevention of solid organ transplant rejection[11] and for the prevention and treatment of graft-versus-host disease in stem cell transplants. These drugs are normally administered by IV injection or orally[12].

CLINICAL USE

Over the past 10 years calcineurin inhibitors such as tacrolimus have been employed in the treatment of a wide range of dermatological diseases and chronic wounds. They promote melanocyte and melanoblast growth and create a favourable milieu for cell migration via keratinocytes: possible mechanisms of how tacrolimus ointment induces re-pigmentation in patients with vitiligo[13-16].

Topical tacrolimus and pimecrolimus are now used more extensively in the treatment of pyoderma gangrenosum with good results; a case study of this use is included[17-22 ,24-35].

Some of the more recent uses of calcineurin inhibitors are in the treatment of necrobiotic xanthogranuloma, where tacrolimus is applied topically in a 0.1–0.02% ointment. Topical tacrolimus does not negatively impact acute skin wound healing. Altieri *et al.* reported on the success of topical tacrolimus for parastomal pyoderma gangrenosum in two patients[21]. Rice *et al.*[23] used topical tacrolimus 0.1% ointment for the treatment of cutaneous Crohn's disease in an open-label, observational study of 20 patients with heterogeneous forms of cutaneous Crohn's disease, using topical tacrolimus 0.1% ointment once-daily to the affected areas for 12 weeks. Of the 17 patients completing the 12-week study, 15 improved using a specifically designed physicians' global severity scale. One patient cleared, four showed a pronounced improvement (51–75%) and 10 demonstrated a mild (1–25%) or moderate improvement (25–50%) in 12

Table 1

Calcineurin inhibitors	Strength	Product
Pimecrolimus	1%	Elidel®
Tacrolimus	0.03–0.1%	Compounded

weeks. They concluded that "0.1% tacrolimus ointment was safe and effective in treating cutaneous manifestations of Crohn's disease, particularly perineal disease and pyoderma gangrenosum, yet it seldom cleared the condition".

Topical calcineurin inhibitors have been used in the management of a number of other conditions, including lichen planus and lichen sclerosus[26-29], cutaneous lupus erythematosus and dermatomyositis[30,31], necrobiosis lipoidica, pemphigus vulgaris, pityriasis versicolor, nail psoriasis and the treatment of secondary lymphoedema[32-37].

Elidel® is the only commercial form of Pimecrolimus cream available in Australia. In the case of topical tacrolimus, the ointment form is required to be compounded by a pharmacy (see Table 1).

PUBLISHED CLINICAL STUDIES

There are an increasing number of published studies of the clinical use of calcineurin inhibitors (Table 2). The more recent conduct of RCTs helps to strengthen the level of evidence for their use.

PRECAUTIONS

On 15 February 2005, the Pediatric Advisory Committee of the Food and Drug Administration (FDA) recommended 'black box' warnings for pimecrolimus cream (Elidel®) and tacrolimus ointment (Protopic®) because of concerns of potential safety risks (including skin cancer and lymphoma). On 10 March 2005, the FDA issued a Public Health Advisory[2] informing health-care providers of the Agency's safety concerns associated with use of these drugs. However, there is no evidence that topical use of pimecrolimus and tacrolimus causes malignancies[3]. A consensus statement published in *Dermatology*[4] stated that the recommendations of the Pediatric Advisory Committee and the FDA Health Alert are not justified based on the scientific evidence and should be reconsidered. The report of the American Academy of Dermatology Association Task Force[5] conference found no causal proof that topical calcineurin inhibitors cause lymphoma or non-melanoma skin cancer.

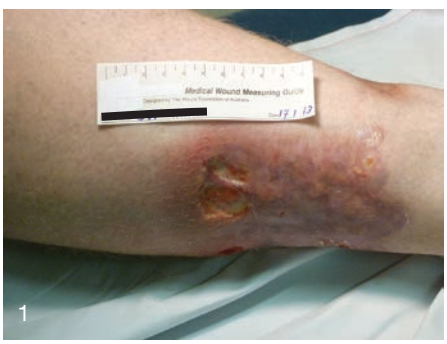
CLINICAL CASE STUDIES OF THE USE OF CALCINEURIN INHIBITORS

Case 1: Use in necrobiotic xanthogranuloma (NXG)

NXG is a rare, chronic granulomatous disorder characterised by indurated plaques and nodules of the skin[10]. NXG initially presents with yellowish papules and nodules that coalesce into indurated plaques, usually 0.5–2.0 cm. Lesions often show superficial telangiectasias and can scar and ulcerate in 40–50% of patients. Skin lesions can recur rapidly and lesion size typically increases with recurrence. Despite these potential complications, incisional biopsy is recommended to confirm the diagnosis when NXG is suspected clinically. Most NXG skin lesions (60–70%) first appear on the trunk or extremities. Patient JH was a 55-year-old male with a history of diagnosed NXG, who had a number of different treatments with limited success. Treatment with topical tacrolimus was commenced on 17 January 2013 (Figure 1), reviewed in four weeks (Figure 2) and continued treatment until healing was achieved by 14 March 2013 (Figure 3).

Case 2: Use in pyoderma gangrenosum (PG)

PG is a rare, inflammatory, non-infective skin disease resulting in destructive, painful, rapidly enlarging ulcers that are irregular and raised, with reddish borders, a necrotic base and undermined bluish or purplish-red edges. It is associated with inflammatory bowel diseases and immune system abnormalities. PG is difficult to diagnose and is mostly diagnosed by exclusion of the typical causes of leg ulcers. A wound biopsy will often help to exclude other causes. It is often the case if a biopsy is taken that the wound will enlarge; this is described as pathergy. PG is difficult to treat as this involves pain management, maintaining a moist environment, and the systemic use of medication including steroids, cyclosporin or dapsone.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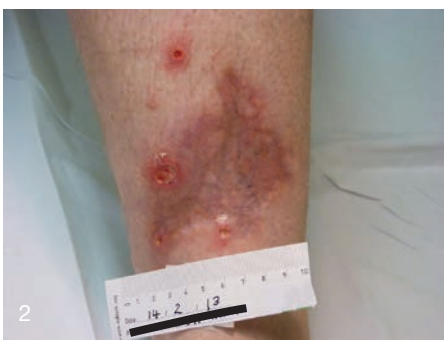
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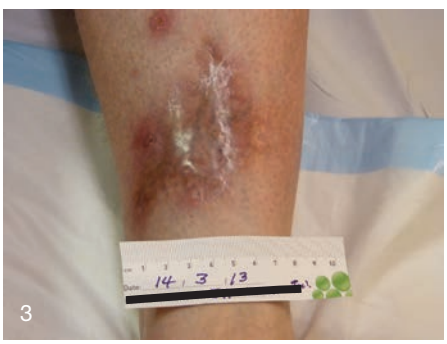
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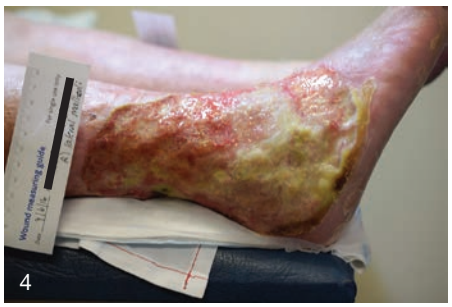
Table 2: Calcineurin inhibitors clinical studies

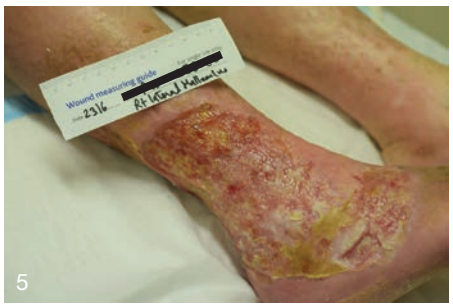
Author	Title	No.	Study type	Outcome
Tzellos TG, Kouvelas D. Eur J Clin Pharmacol 2008 Apr 1;64(4):337–41.	Topical tacrolimus and pimecrolimus in the treatment of cutaneous lupus erythematosus (SLE): an evidence-based evaluation	47	Review	This review evaluated the efficacy of tacrolimus and pimecrolimus in, at least initial, cutaneous lesions of SLE. 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.
Altieri M, Vaziri K, Orkin BA. Ostomy Wound Manage 2010 Sep 1;56(9):32–36.	Topical tacrolimus for parastomal pyoderma gangrenosum (PPG)	2	Case series	Two case reports concur with the available literature regarding successful treatment of PPG with topical tacrolimus. Although PPG is rare and large randomised trials are unavailable, topical tacrolimus used in conjunction with good stoma care can be a useful and successful treatment strategy for refractory PPG.
Rice SA, Woo PN, El-Omar E, Keenan RA, Ormerod AD BMC Res Notes 2013 Dec;6(1):19. doi: 10.1186/1756-0500-6-19.	Topical tacrolimus 0.1% ointment for treatment of cutaneous Crohn's disease	20	Open study	Tacrolimus ointment was safe and effective in treating cutaneous manifestations of Crohn's disease, particularly perineal disease and pyoderma gangrenosum, yet it seldom cleared the condition.
Grimes PE, Soriano T, Dytoc MT., J Am Acad Dermatol 2002 Nov 1;47(5):789–91.	Topical tacrolimus for repigmentation of vitiligo	6	Case series	Tacrolimus ointment may be a rapidly efficacious and safe option for the treatment of vitiligo. The ease of topical self-administration with minimal side effects makes this novel immunomodulatory agent a promising addition to the therapeutic armamentarium for vitiligo. However, to further evaluate the efficacy of tacrolimus ointment, controlled, randomised double-blind studies are essential.
Ho N, Pope E, Weinstein M, Greenberg S, Webster C, Krafchik BR. Br J Dermatol 2011 Sep 1;165(3):626–32.	A double-blind, randomised, placebo-controlled trial of topical tacrolimus (T) 0.1% vs clobetasol propionate (CP) 0.5% in childhood vitiligo	90	RCT	In the facial group, 58% of the CP 0Æ05% group responded successfully, compared with 58% of the T 0Æ1% group, and in the nonfacial group, 39% of the CP 0Æ05% group responded, compared with 23% of the T 0Æ1% group (P > 0Æ05). There was a significant difference in response between the CP 0Æ05% group vs placebo (P < 0Æ0001) and the T 0Æ1% group vs placebo (P = 0Æ0004).
Hettiarachchi PV, Hettiarachchi RM, Jayasinghe RD, Sitheeque M. J Invest Clin Dent 2017 Nov 1;8(4) doi: 10.1111/jicd.12237.	Comparison of topical tacrolimus and clobetasol in the management of symptomatic oral lichen planus (OLP): A double-blinded, randomised clinical trial in Sri Lanka	68	RCT	The results suggest that tacrolimus 0.1% cream is an effective alternative to topical steroid and can be considered a first-line therapy in OLP. However, further studies are needed to confirm the effectiveness of this treatment before it is recommended for use in clinical practice.

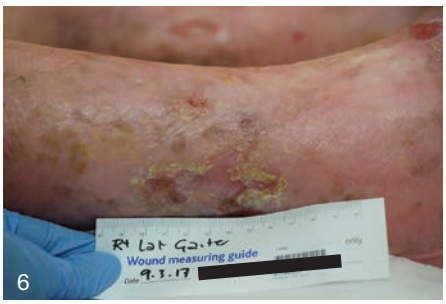
Table 2 (continued): Calcineurin inhibitors clinical studies

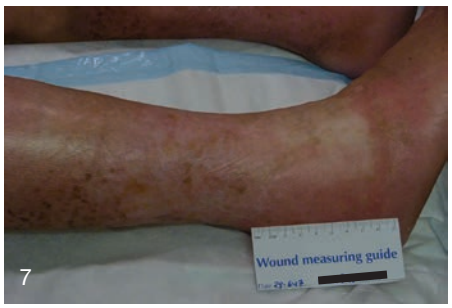
Author	Title	No.	Study type	Outcome
Sepaskhah M, Sadat MS, Pakshir K, Bagheri Z. Mycoses 2017 May 1;60(5):338–42.	Comparative efficacy of topical application of tacrolimus and clotrimazole in the treatment of pityriasis versicolor (PV): A single-blind, randomised clinical trial	50	RCT	In spite of the lack of efficacy of tacrolimus on PV-induced hypopigmentation, the therapeutic effect on PV introduces tacrolimus as a therapeutic option for PV, especially when early vitiligo is among the differential diagnoses without concerning the aggravating effect of topical corticosteroids on PV.
Udompataikul M, Boonsupthip P, Siriwattanagate R. Dermatol 2011 Jun 1;38(6):536–40.	Effectiveness of 0.1% topical tacrolimus in adult and children patients with vitiligo	42	Open study	It was recommended that, other than in the vulgaris type, topical tacrolimus may be considered as a treatment for two difficult to treat types of vitiligo: acrofacialis and segmentalis, before considering other modalities.
Arduino PG, Carbone M, Della Ferrera F *et al.* J Eur Acad Dermatol Venereol 2014 Apr 1;28(4):475–82.	Pimecrolimus vs tacrolimus for the topical treatment of unresponsive oral erosive lichen planus (OLP): an 8-week, randomised, double-blind controlled study	30	RCT	Both medications would currently appear to be a treatment of choice for patients with unresponsive atrophic-erosive OLP. Pimecrolimus seemed to be more effective in providing long-term resolution of signs and symptoms. Future efforts are, however, needed to obtain more objective evidence of the benefit of these medications in the treatment of immunologically mediated oral mucosal lesion.
De Simone CL, Maiorino A, Tassone F, D'Agostino MA, Caldarola G. Tacrolimus J Eur Acad Dermatol Venereol 2013 Aug 1;27(8):1003–6.	Tacrolimus 0.1% ointment in nail psoriasis: a randomised, controlled, open-label study	21	Open-label RCT study	This study showed that tacrolimus 0.1% ointment may be an efficacious and safe therapeutic opportunity in the treatment of nail psoriasis. The data should be confirmed by a double-blind study with a larger sample of patients.
Kim GW, Park HJ, Kim HS *et al.* J Dermatol 2012 Feb 1;39(2):145–50.	Topical tacrolimus ointment for the treatment of lichen sclerosus, comparing genital and extragenital involvement	16	Open study	Topical tacrolimus ointment was a safe and effective treatment for genital lichen sclerosus and should be used for long-term duration to prevent relapse. However, it was not useful for patients with extragenital lichen sclerosus.
Lo YH, Cheng GS, Huang CC, Chang WY, Wu CS. J Dermatol 2010 Feb 1;37(2):125–9.	Efficacy and safety of topical tacrolimus for the treatment of face and neck vitiligo	61	Open-label, non-comparative study	Tacrolimus ointment is effective and well tolerated for the treatment of patients with vitiligo in Taiwan. It will be another drug of choice for persons with vitiligo who are unable to receive regular phototherapy and fear the side effects of topical steroid in long-term use.

Patient PW was an 84-year-old female with a long history of non-healing leg ulcers. They had been treated as venous leg ulcers with dressings and compression. One ulcer on the right medial malleolus deteriorated and a new diagnosis of PG was made. Topical tacrolimus was commenced on 9 June 2016 (Figure 4) and within five weeks of use there was a significant improvement in wound size and condition (Figures 5 and 6). The treatment was continued over the next few months and the wounds rapidly improved and, on review in March 2017, were healed (Figure 7).









DISCUSSION

Immunosuppression administered systemically is often part of the management of wounds related to PG, vasculitis and other complex autoimmune diseases. The difficulty faced with this method of administration is that given that the dosage needs to be at a level for a therapeutic outcome, the risk of side effects is much greater. The use of topical immunosuppression is one option that may overcome the potential side effect profile of many of the medications used. Topical calcineurin inhibitors, such as tacrolimus, have been shown to suppress T-cell activation and act as an immune suppressor without the risks of significant side effects. They do not cause skin atrophy, they work locally and, because of the very low strength, there is little risk of systemic absorption of the drug, which does not have a negative impact on wound healing.

CONCLUSION

Topical calcineurin inhibitors have been used dermatologically for many years in the management of eczema and atopic dermatitis. The extension of their use in the management of complex, chronic, non-healing wounds is increasing with the publication of their successful use in a wider range of wounds, including some RCTs. At present, there is no commercial form of topical tacrolimus; it needs to be manufactured by a compounding pharmacy or hospital pharmacy department.

There is a need for more clinical studies of the use of topical calcineurin inhibitors and publication of results to build a sound level of evidence for the role of these compounds in wound practice to become more widespread.

CONFLICT OF INTEREST

The author declares no conflicts of interest.

FUNDING

The author received no funding for this study.

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