



Medicines Evidence Commentary

commentary on important new evidence from Medicines Awareness Weekly

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Vitiligo: systematic review and meta-analysis investigates topical calcineurin inhibitors

A systematic review and meta-analysis found that topical calcineurin inhibitors (tacrolimus and pimecrolimus) increased repigmentation in people with vitiligo, particularly for lesions on the face and neck. Further analyses suggested that topical calcineurin inhibitors may be more effective in children, although this was based on a small number of studies. The review found that combination treatment with phototherapy was also effective, however the summary of product characteristics for the topical calcineurin inhibitors advise that people using these medicines should avoid excessive ultraviolet light exposure (including solariums and phototherapy).

Overview and current advice

Vitiligo is a chronic skin condition characterised by patchy loss of skin pigmentation. Vitiligo affects around 0.5% to 2% of the population worldwide, affecting people of any age or ethnic background. Vitiligo can have a negative psychosocial impact on people, especially those with dark or tanned skin, or when it affects the face or hands. The cause of vitiligo is poorly understood, but it may be an autoimmune condition which destroys melanocytes (pigment cells; [Whitton et al. 2015](#)).

NICE does not have guidance for managing vitiligo, however the British Association of Dermatologists has published a guideline on the [diagnosis and management of vitiligo](#) (Gawkrodger et al. 2008; NICE accredited process). The guideline recommends a short trial of a potent or very potent corticosteroid as first-line topical therapy, noting the risk of skin atrophy with these treatments. A topical calcineurin inhibitor may be used as an alternative to topical corticosteroids due to their better short-term safety profile.

New evidence

[Lee et al. \(2019\)](#) report on a systematic review and meta-analysis of 56 prospective and experimental studies worldwide that investigated the efficacy, safety and mechanism of action of the topical calcineurin inhibitors tacrolimus and pimecrolimus (either alone or in combination with phototherapy). Response to treatment was classified as mild (at least 25% repigmentation), moderate (at least 50% repigmentation) or marked (at least 75% repigmentation).

For **topical calcineurin inhibitor monotherapy** the review included 36 studies (total n=941). Responses to treatment were:

- mild in 55.0% of people (95% [confidence interval](#) [CI] 42.2 to 67.8%; 21 studies; n=560)
- moderate in 38.5% of people (95% CI 28.2 to 48.8%; 23 studies; n=619)

- marked in 18.1% of people (95% CI 13.2 to 23.1%; 19 studies; n=520).

Further analysis in all people found topical calcineurin inhibitor monotherapy was more effective on lesions on the face and neck (73.1% mild response; 35.4% marked response; 14 studies; n=312) compared with the trunk and extremities (34.2% mild response; 2.3% marked response; 7 studies; n=153) and hands and feet (15.1% mild response; 0% marked response; 8 studies; n=185).

Another subgroup analysis of 5 studies (n=162) suggests this treatment is most effective in children, with a mild response seen in 66.4% of children (95% CI 43.2 to 89.7%) and a marked response seen in 31.7% of children (95% CI 6.7 to 56.8%).

The most common adverse events reported with topical calcineurin inhibitor monotherapy (n=296) were a burning sensation (9.8%), pruritus (7.4%) and erythema (2.4%), all were transient and did not require additional treatment. No studies reported treatment discontinuation as a result.

For **topical calcineurin inhibitor plus phototherapy** the review included 12 studies (total n=558). The phototherapy was narrowband UVB in 10 studies and excimer laser in 2 studies. Responses to treatment were:

- mild in 89.5% of people (95% CI 81.1 to 97.9%; 8 studies; n=433)
- moderate in 72.9% of people (95% CI 57.6 to 88.2%; 10 studies; n=486)
- marked in 47.5% of people (95% CI 30.6 to 64.4%; 9 studies; n=490).

The review did not report on adverse events with topical calcineurin inhibitor plus phototherapy.

For **topical calcineurin inhibitor maintenance therapy** only 1 double-blind [randomised controlled trial](#) (RCT) (n=35) was investigated. After a 24-week follow-up period, depigmentation was observed in 9.7% of people treated with tacrolimus ointment, compared with 40.0% in people using placebo.

This systematic review has some limitations; it included all study types and while a small number of studies were multi-arm, double-blind RCTs, many were lower quality, including single-arm, open-label studies. The review authors noted there was considerable [heterogeneity](#) in patient characteristics between studies. The authors also state that the quartile scale used to report treatment response may be somewhat arbitrary, however this is the most commonly used measure, and the authors suggest this would have been one of the best estimates of response at this time. Most studies investigated short-term use of topical calcineurin inhibitors (median duration of monotherapy studies was 3 months, range 2 to 7 months), with only 1 study on longer-term maintenance therapy.

Commentary

Commentary provided by Dr Tang Shim, Consultant Dermatologist, University Hospital Coventry and Warwickshire

This meta-analysis looked at the role of topical calcineurin inhibitors and combination treatment in vitiligo. At the time of writing there are no licensed treatments for vitiligo. In current practice, topical corticosteroids and topical calcineurin inhibitors are widely used as first line treatment for limited vitiligo. Topical calcineurin inhibitors have been used on areas of the body where prolonged use of potent topical corticosteroids is a concern, such as the face, neck and genitals where the skin is generally thin.

The location of the depigmentation is the most important prognostic factor in predicting response to treatment for vitiligo. The head-and-neck region generally demonstrates superior repigmentation compared with the extremities and trunk ([Taieb et al. 2013](#)). As the melanocyte reservoir is predominantly located in the hair follicle, areas with low follicular density (for example, the hands and feet) are harder to repigment.

The summary of product characteristics (SPCs) for [tacrolimus](#) and [pimecrolimus](#) report that cases of malignancies, including cutaneous and other types of lymphoma, and skin cancers have been reported in people using these medicines. This risk is also flagged in a [2012 Drug Safety Update](#) on tacrolimus ointment. The SPCs also warn that excessive exposure of the skin to ultraviolet light including light from a solarium, or therapy with PUVA, UVA or UVB should be avoided during treatment with tacrolimus or pimecrolimus, which suggest concerns with topical calcineurin inhibitor plus phototherapy (the studies did not report adverse effects in this group).

Although long-term safety studies of the topical calcineurin inhibitors for atopic dermatitis are reassuring, data are still lacking for vitiligo. Clinicians and patients will need to weigh up the benefits and risks of topical calcineurin inhibitors in comparison to those of other therapies.

The optimal duration and regimen of topical calcineurin inhibitors treatment are not known, although they are usually prescribed twice daily for 6 months at first instance. An important consideration when using topical calcineurin inhibitors to treat vitiligo is the price; these medicines cost around £19 to £23 per 30-gram tube.

This new evidence suggests that topical calcineurin inhibitors may be a promising treatment for vitiligo affecting the face and neck, especially in children.

Declaration of interests:

Dr Tang Shim has spoken at or attended events sponsored by L'Oréal, Leo Pharma and Galderma.

Study sponsorship

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