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New treatments for atopic dermatitis

Good news, but when and how to use tacrolimus and pimecrolimus is a muddle

Atopic dermatitis now affects 15% to 20% of children in developed countries, and prevalence in cities in developing countries undergoing rapid demographic changes is quickly following suit.[1] Most cases of atopic dermatitis in a given community are mild, but children with moderate to severe disease can have continuous itching and associated loss of sleep. The social stigma of a visible skin disease can also be soul destroying for both patient and family. A few studies have suggested that some degree of prevention of the disease is possible,[2] although these measures have not been taken up widely. In the absence of any treatment that is known to alter the clinical course of the disease, most treatment is aimed at reducing symptoms and signs. After a relative lull of almost 40 years, new drugs—tacrolimus and pimecrolimus—have appeared that offer different approaches to managing this miserable disease. Do they work? Are they safe? And how do they compare with existing treatments?

A suitable place to start putting the 47 existing treatments into context is the NHS health technology assessment systematic review of randomised controlled trials for atopic dermatitis.[3] This report concluded that the evidence base for the treatment of atopic dermatitis is characterised by poor standards of reporting of clinical trials and a lack of common outcome measures that are important to patients. The direction of trials over the past 40 years has been driven largely by the agenda of the pharmaceutical industry with a profusion of short term trials of "me too" products and a lack of comparative data that help clinicians answer the question "which is the best?" Good randomised controlled trials support some treatments, such as ultraviolet light, but provide no evidence for some commonly used rituals such as combinations of topical antibiotic and corticosteroid or antiseptic bath additives. Enough evidence to make clear recommendations on interventions like Chinese herbal treatment is lacking, and there is no evidence from randomised controlled trials on issues such as organisation of care or use of water softeners. So, do the new treatments help us to move forward?

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Tacrolimus and pimecrolimus are two new topical preparations that have been or are in the process of being licensed throughout the world for use in atopic dermatitis. They are similar macrolactam molecules that probably work by suppressing T lymphocyte responses through inhibiting calcineurin.[4] Unlike topical steroids, they do not cause skin thinning, which could be a major advantage for long term use.[5]

Do they work? In comparison with placebo, the answer is an unreserved yes. However, clinicians are often more interested in how new treatments compare with existing treatments such as topical corticosteroids, and this is where the evidence is unclear. Tacrolimus seems to be equivalent to potent topical steroids,[6–8] and it is clearly superior to weak preparations such as 1% hydrocortisone.[9] Pimecrolimus, on the other hand, has not been compared with 1% hydrocortisone, and when compared with betamethasone, a commonly used potent topical steroid, it seems to be nowhere near as effective.[10] Interestingly, topical tacrolimus and pimecrolimus seem not to have been compared, but it takes little imagination to predict which would emerge as the most effective.

If topical tacrolimus is indeed equivalent to a potent topical steroid, how should it be used – as monotherapy, instead of topical steroids, or only when topical steroids fail? The current wording of product licences suggests that it should be used for people with moderate to severe disease "who have failed to respond adequately to conventional therapy"—that is, as a second line agent. None of the randomised controlled trials, however, have included such people. True tropical steroid failures—that is, those patients who "get stuck" needing continuous use or those who develop local side effects such as thinning of the skin—are rare nowadays. Nevertheless, it seems reasonable to use topical tacrolimus in such people, especially in more sensitive sites such as the face or eyelids where local side effects of topical steroids might be more of a problem.

The place of pimecrolimus is even more unclear, although given its probably lower potency, it is clearly positioning itself to take on the weaker topical steroids in people with mild to moderate atopic dermatitis. To secure such a market, a recent study (published in abstract form) found that early use of pimecrolimus prevented more flares—which then needed treatment with a potent topical steroid—when compared with the vehicle (10th congress of European Academy of Dermato-Venereology, Munich, 2001). This study documented a steroid sparing effect and examined long term control, which is appropriate in a chronic condition like atopic dermatitis. But it was a placebo controlled study, and early use of another active compound such as weak 1% hydrocortisone may have also prevented such flares.

Both products have not been tested against current optimal use of topical steroids in a pragmatic way—that is, short bursts of once daily products for flare ups of disease followed by periods of rest when only emollients were used. Data on cost effectiveness are also missing—an important consideration given that topical tacrolimus is at least 10 times as expensive as standard topical steroids.

Are these drugs safe? Studies done so far suggest that they are—at least in the short term. It is, however, worth remembering that these products are immunosuppressive drugs. Oral tacrolimus is one of the most powerful immunosuppressive drugs known—hence its use to prevent rejection of transplants.

Although systemic absorption seems to be low in most people using these preparations, there is a need for careful and long term surveillance for visceral and skin cancers. This concern was recently reinforced when the US Food and Drug Administration granted the product licence for pimecrolimus on the basis of preclinical studies showing increased photocarcinogenicity and an increase in lymphomas and thyroid adenomas in mice.[11]

It is tempting to discuss only pharmacological developments and ignore other developments in the management of atopic dermatitis, such as biological approaches. Probiotics (harmless cultures of bacteria) prevented atopic dermatitis in half the individuals who participated in one study.[12] Another study showed that vaccination with *Mycobacterium vaccae* can have substantial effects in ameliorating existing disease.[13] Further trials are going on using these approaches, and both approaches may make big contributions in the prevention and management of atopic dermatitis.

Both topical tacrolimus and pimecrolimus are welcome additions to the treatment of atopic dermatitis. Little doubt exists that they work and that they are probably safe, at least in the short term. Yet, because of the lack of essential comparisons, clinicians are left confused as to how and when to use these drugs and whether they are cost effective. Given the widespread and often irrational fear of topical corticosteroids, manufacturers of both drugs are likely to make a handsome profit in return for their investment—an inevitable consequence of the current licensing processes and the complete lack of independent studies using appropriate comparators.

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Yukihiro Ohya, National Children's Hospital, Tokyo, identified and translated the Japanese studies.

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Long term care for older people

Increasing pressure for change

Long term care is a reality for thousands of frail older people, a source of great anxiety for many more and, across the developed world, a political hot potato that shows no sign of cooling. The heat is fuelled by two factors. Firstly, current government policy in many countries is widely perceived to be unjust, with older people themselves paying an ever greater proportion of the costs of health care. Secondly, the rising percentage of older people in the population, while fuelling doom laden economic projections, is inexorably increasing the power of the older vote, producing democratic pressure for change

See also *News* p 1542

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