



Topical treatment with calcineurin inhibitors in dermatology practice

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Topical calcineurin inhibitors (TCIs) are a new generation of topical immunomodulating agents. They were initially developed for the treatment of atopic dermatitis (AD), a chronic or chronically relapsing skin condition most prevalent in infants and children. These immunomodulatory agents (e.g. tacrolimus, or pimecrolimus) are an alternative to topical steroids. Tacrolimus is the first one of these immunosuppressants. It is an immunomodulator macrolide, which was isolated from *Streptomyces tsukubaensis*, a funguslike bacterium identified in Japan in mid1980s and confirmed to have immunomodulatory properties in 1987. The name 'tacrolimus' is derived from a combination of the words 'Tsukuba' (the name of the mountain from which the soil sample was extracted), 'macrolide' (the chemical class), and 'immunosuppressant'. In the early 1990s, Fujisawa developed an ointment formulation of tacrolimus, the first topical calcineurin inhibitor, specifically developed for the treatment of AD (first reported in the Lancet, 1994). Since then, tacrolimus ointment has been studied in the most extensive and comprehensive clinical development programme in dermatology, with clinical trials conducted in Europe, Japan and North America. As of September 2004, more than 30 clinical studies, both short and long-term, have investigated the efficacy and safety of tacrolimus ointment in 16 000 AD patients including 3000 children. To date, more than 35 million prescriptions have been written for tacrolimus ointment in Europe alone. Tacrolimus acts as an immunosuppressant by inhibiting the proliferation and activation of CD4⁺ T helper cells by binding to the cellular receptor known as FK506-binding protein (FKBP). The tacrolimus-FKBP complex further binds to calcineurin, preventing the dephosphorylation of the nuclear factor of activated T cells and blocking the cascade of cytokine gene transcription. This mechanism was likely evolved by *Streptomyces tsukubaensis*, which does not have calcineurin, to inhibit the calcineurin function in their fungal eukaryotic competitors. Other immunomodulatory effects of tacrolimus include the inhibition of mast cell adhesion, the inhibition of the release of mediators from mast cells and basophils, and the down-regulation of the expression of interleukin-8 receptor and FcεRI on Langerhans' cells.

Pimecrolimus is a new, non-steroid, cell-selective, cytokine inhibitor, which belongs to the class of ascomycin macrolactams. It was specifically developed for the treatment of inflammatory skin diseases, such as atopic eczema. It is finally selected among more than 400 derivatives as a macrocyclic natural product derived from *Streptomyces hygroscopicus*. Pimecrolimus is a cell-selective inhibitor of inflammatory cytokines. It primarily targets T cells, which have a key role in the pathology of atopic eczema. In the T cell, pimecrolimus binds to the cytosolic receptor, macrophilin-12, and inhibits calcineurin, a phosphatase required for the translocation of the nuclear factor of activated T cells (NF-AT) to the nucleus. This, in turn, prevents the formation and release of inflammatory cytokines (e.g. IL-2, IL-3, IL-4, IL-8, IL-10, INFγ, TNFα) and the proliferation of T cells in response to T-cell receptor stimulation. Pimecrolimus also prevents the release of inflammatory mediators from activated mast cells (e.g. histamine, tryptase, TNFα). In contrast to pimecrolimus and tacrolimus, corticosteroids have a non-selective mode of action leading to side-effects. They inhibit collagen synthesis by fibroblasts, resulting in skin atrophy. Furthermore, corticosteroids affect Langerhans' cells, which play a key role in the skin immune system. Topical treatment of mouse skin with the corticosteroids clobetasol, betamethasone and hydrocortisone results in elimination of Langerhans' cells from the treated skin, whereas pimecrolimus does not. Therefore, pimecrolimus and tacrolimus is unlikely to interfere with local immunosurveillance. Tacrolimus and pimecrolimus are structurally similar with molecular weight of 822.05 DA and 810.48 DA respectively. TCIs are macrolide lactones. They are more lipophilic than topical corticosteroids. Topical corticosteroids increase their side effects according to their efficacy – the more potent more side effects they will have. That is why they are used for short-term treatment and have less effective long-term management. Long-term treatment with TCIs shows sustained superiority to corticosteroids.