

# Study and Therapy News

## Therapeutic Update: Tacrolimus in Dermatology

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### Tacrolimus: background and chemistry

Tacrolimus was discovered in 1984 by the Fujisawa Pharmaceutical Company, based in Japan. It is structurally a macrolide, produced by *Streptomyces tsukubaensis*, a soil fungus originally found on Mount Tsukuba, Japan. The original research compound designation for tacrolimus was FK506, a name which is still frequently used in transplantation

literature. Based on its immunomodulating properties, tacrolimus for systemic use by peroral or intravenous administration was initially developed to prevent organ rejection following allogeneic liver or kidney transplantation. For these indications, tacrolimus was approved by the FDA, under the trade name Prograf® for clinical use in the USA in 1994. In the Nordic countries Prograf was approved by the Swedish and Danish health authorities in 1995, and it has been available in all Nordic countries since 1997. The mechanism of action for tacrolimus when used systemically in transplantation is a direct inhibition of interleukin 2 (IL-2) transcription in T lymphocytes. This results in a decreased responsiveness of T lymphocytes to foreign antigens, and clinically tacrolimus is used as a baseline therapy in the immunosuppressive regimen following allogeneic solid organ transplantation, mainly liver and kidney. A large number of studies have demonstrated tacrolimus to be a highly effective agent for the prevention of organ rejection and for the rescue of patients experiencing acute and chronic rejection while on other immunosuppressive regimens. Additional clinical trials are ongoing to address the efficacy and safety of tacrolimus after allogeneic transplantation of heart, lung, intestines, pancreas and bone marrow. A comprehensive summary of the clinical efficacy and safety of systemic tacrolimus therapy in transplantation indications has recently been published (1).

As with other drugs used to prevent allograft rejection, tacrolimus is associated with side effects when used systemically. Adverse events associated with systemic tacrolimus mainly concern the nervous system (e.g. tremor), gastrointestinal system (e.g. diarrhea) and urogenital system (increased creatinine). Generally, the side effects appear to be related to dose and blood concentrations. Immunosuppressive regimens are also known to increase the risk of infections and malignancies. In observational studies on the development of various tumours, skin tumours are the most commonly encountered type after liver transplantation (2, 3). There are observations indicating a lower incidence of skin tumour development on tacrolimus than on cyclosporine (2), but the majority of previous studies report the overall therapeutic immunosuppressive dose to be the most important risk factor rather than individual agents (4, 5).

To ensure adequate efficacy and safety, monitoring of whole-blood concentrations of tacrolimus is recommended when using the drug systemically, and target levels of 5–20 ng/ml are to be aimed for during the first year after transplantation. However, the patient status regarding rejection and toxicity always takes precedence over whole-blood levels when assessing the appropriate dose. For the prevention of rejection following solid organ transplantation, the currently recommended initial dose of oral tacrolimus ranges from 0.10 to 0.30 mg/kg/day for adults.

## **Tacrolimus in dermatology – mechanism of action**

The use of immunomodulating drugs in dermatology to treat severe atopic dermatitis and psoriasis has been studied extensively for more than 15 years. Despite extensive experience in the clinical use of topical corticosteroids, these compounds still have limitations, like the risk of skin atrophy. New therapeutic modalities (PUVA, UVA, calcipotriol) have also shown limitations in their efficacy, and for these reasons immunomodulating drugs for topical use have been sought out. Peroral cyclosporine has been used systemically in severe atopic dermatitis with shown efficacy, but its use is limited by toxicity, in particular with regard to kidney function. For this reason, there has been significant interest in the development of topical formulations of either cyclosporine or tacrolimus, with the hope that topically applied formulations would eliminate all or most of the systemic toxicity of these agents. Cyclosporine, however, has proven to be unsuccessful as a topical agent in clinical studies on atopic dermatitis, alopecia areata and psoriasis, most likely due to poor penetration (6–8).

In contrast, topical tacrolimus has successfully been used to treat atopic dermatitis, first shown by Nakagawa et al. (9). The clinical development of tacrolimus for moderate to severe atopic dermatitis has been performed with an ointment formulation. The size of the tacrolimus molecule, with a molecular weight of 822 Daltons, along with its lipophilic character,

allows for a predictable and sufficient penetration into the skin (6).

The mechanism of action for topically applied tacrolimus is based on its immunomodulatory properties, focused on the activation of T-lymphocytes and the release of various cytokines. The complex immune mechanisms that play central roles in the pathogenesis of atopic dermatitis, psoriasis and other inflammatory dermatoses, are mainly altered through the direct effect of tacrolimus on the T-lymphocytes, especially CD4+ cells, by binding to immunophilins (FK-binding protein 12; FKBP-12). The drug-immunophilin complex binds competitively to and inhibits calcineurin, a phosphatase that is only active when bound simultaneously to calcium and calmodulin. This binding inhibits in turn the ability of calcineurin to activate the promoter region, via a transcription factor (nuclear factor of activated T-cells; NF-AT) for the gene encoding for IL-2. As increased secretion of IL-2 is a crucial event for the growth and proliferation of cytotoxic T-cells, the presence of tacrolimus inhibits the ability of T-cells to respond to activation signals. The transcription of other cytokine and stimulation factor genes is also inhibited by tacrolimus (e.g. IL-3, IL-4, IL-5, IL-12, granulocyte/macrophage colony stimulation factor, tumour necrosis factor  $\alpha$ , and interferon  $\gamma$ ). All these factors are involved at the early stages of the activation of T-cells and are considered to play important roles in the pathogenesis of atopic dermatitis and psoriasis. As atopic dermatitis is a complex disease that involves not

only T-cells, but also inflammatory mediators and Langerhans' cells, other targets have been investigated as well. Of particular interest has been the ability of tacrolimus to down-regulate the high-affinity IgE receptor on Langerhans' cells (10) and to inhibit the release of histamine and inflammatory mediators from mast cells and basophils.

## **Clinical efficacy and safety in atopic dermatitis**

Clinical phase-II trials in adults and children have been carried out with three different concentrations of the ointment (0.03, 0.1 and 0.3% (w/w)) used twice daily (11, 12). In these short-term trials significant reductions in the severity of pruritus, of the involved body surface area and severity of the disease were demonstrated. Recently, results from long-term studies have been published, providing data from up to 2 years of therapy with topical tacrolimus in Japanese patients, and up to 12 months in US and European patients (13). In the European long-term study, adult patients with moderate to severe atopic dermatitis affecting up to 100% of their total body surface area were treated with 0.1% tacrolimus ointment twice daily. Clinical efficacy was assessed by a combined symptom score, by a physician-rated global response, and by the affected body surface area (Table I). Improvement was apparent after 1 week of treatment, and the ointment was well tolerated. As all efficacy endpoints showed improvement over time, signified by rapid and maintained improvement of the disease mani-

**Table I.** Clinical efficacy of tacrolimus ointment in atopic dermatitis assessed by a combined symptom score, body surface affected and investigators global assessment, in an open, 12-month study comprising 316 patients (adapted with permission from Reitamo et al. (13))

	Baseline	Week 1	Month 6	Month 12
Combined symptom score <sup>a</sup>	23.7	13.5	6.1	6.1
Body surface area affected <sup>b</sup>	34%	28%	12%	11%
Clearance of disease or marked or excellent improvement <sup>c</sup>	-	54%	81%	86%

<sup>a</sup>Reported as modified Eczema Area and Severity Index (mEASI), which includes severity scores for individual symptoms of atopic dermatitis weighted according to the extent of affected body surface area. The mEASI is a variant of EASI; an assessment of itch is included in the former.

<sup>b</sup>The size of the treated area was almost identical to the size of the affected area.

<sup>c</sup>Investigators assessment of overall clinical improvement used the following terms: cleared, 100%; excellent, 90–99%, marked, 75–89%.

festations despite a decrease in the frequency and amount of ointment use, tacrolimus ointment seems to offer the possibility of long-term disease control.

From a safety point of view, one specific concern has been the extent to which tacrolimus is absorbed through intact and inflamed skin. In short-term as well as long-term studies, the systemic exposure determined by whole blood concentration has been found to be minimal. In healthy subjects, the highest tacrolimus concentration observed with 0.3% ointment administered on 1000 cm<sup>2</sup> once daily for 14 days was 0.127 ng/ml, confirming *in vitro* findings that the penetration of tacrolimus through intact skin and systemic exposure to tacrolimus is minimal (14). In the European 12-month observational study, whole blood

tacrolimus concentrations below 1 ng/ml were found in 77% of the adult patients, and no systemic toxicity or effects on the cellular immunity were observed (13). Similar results have been obtained in two 3-month studies in which a total of 383 patients were treated with tacrolimus ointment for atopic dermatitis in the USA (15, 16), and only rarely were concentrations >5 ng/ml found. In phase-II trials in adults and children the tacrolimus whole blood concentrations were found to decrease over time during therapy, indicating diminished absorption following clinical improvement and recurrence of a normal skin barrier function (11, 12).

To date, no safety concerns related to systemic exposure of topical tacrolimus have been identified. Local side effects include a commonly reported (approx. 40% of patients during the

first days of therapy) feeling of warmth, in some patients accompanied by pruritus and erythema. These reactions at the application site tend to subside rapidly, and have been generally well tolerated by patients. It should be noted that skin atrophy has not been reported with tacrolimus ointment, and one study compared specifically the potential for skin atrophy by betamethasone-valerate and tacrolimus (17). In this 7-day trial the compounds were administered under occlusion, and topical betamethasone-valerate was found to reduce skin thickness as measured by ultrasound and also to reduce the local production of procollagen peptides in suction blister fluid, while no such changes were seen for tacrolimus. As with other treatment modalities aiming at immunomodulatory effects in the skin, there is a need to closely monitor the risk for skin tumour development. There has been no evidence so far for photocarcinogenic potential in humans (18), but as a general precaution patients using tacrolimus ointment in ongoing studies are instructed to minimise UV radiation when under treatment.

## Conclusion

Topical tacrolimus administered as ointment has shown great promise in the therapy of atopic dermatitis. Ongoing phase-III trials will address the optimal therapeutic regimen for its use in atopic dermatitis. In the future, other dermatoses may be considered for therapy with topical tacrolimus, but this needs to be investigated further in clinical trials.

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