

Tacrolimus Ointment for Long-term Treatment of Atopic Dermatitis

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Johanna Mandelin, MD, defended her PhD thesis in Helsinki, Finland, on March 26, 2010. The thesis was supervised by Docent Sakari Reitamo from the Department of Dermatology, Allergology and Venereology, University of Helsinki and the opponent was Professor Thomas Bieber from the Department of Dermatology and Allergy, University of Bonn, Germany.

Atopic dermatitis (AD) or atopic eczema is characterized by a superficial skin inflammation with an overall Th2 cell dominance and impaired function of the epidermal barrier. Patients are also at increased risk for asthma and allergic rhinitis. Treatment with tacrolimus ointment inhibits T-cell activation and blocks the production of several inflammatory cytokines in the skin, without suppressing collagen synthesis.

The aims of this thesis were to determine: (i) the long-term efficacy, safety, and effects on cell-mediated immunity and serum IgE levels in patients with moderate-to-severe AD treated for one year with tacrolimus ointment or a corticosteroid regimen; (ii) the 10-year outcome of eczema, respiratory symptoms, and serum IgE levels in patients with AD initially treated long-term with tacrolimus ointment; and (iii) the pharmacokinetics and long-term safety and efficacy of 0.03% tacrolimus ointment in infants under the age of 2 years with AD.

Cell-mediated immunity, reflecting Th1-cell reactivity, was measured by recall antigens and was lower at baseline in patients with AD compared with healthy controls. Treatment with either 0.1% tacrolimus ointment or a corticosteroid regimen for one year enhanced recall antigen reactivity. Transepidermal water loss (TEWL), an indicator of skin barrier function, decreased at months 6 and 12 in both tacrolimus- and corticosteroid-treated patients; TEWL for the head and neck was significantly lower in tacrolimus-treated patients. Patients in the 10-year, open, follow-up study showed a decrease in affected body surface area from a baseline 19.0% to a 10-year 1.6% and those with bronchial hyper-responsiveness at baseline showed an increase in the provocative dose of inhaled histamine, producing a 15% decrease in FEV1, indicating less hyper-responsiveness. Respiratory symptoms (asthma and rhinitis) reported by the patient decreased in those with active symptoms at baseline. A good treatment response after one year of tacrolimus treatment predicted a good treatment response throughout the 10-year follow-up



Fig. 1. Johanna Mandelin defended her PhD thesis in Helsinki. Sakari Reitamo (right) was the supervisor and custos, and Thomas Bieber (left) from Bonn was the opponent.

and a decrease in total serum IgE levels at the 10-year follow-up visit. The 2-week pharmacokinetic and the long-term study with 0.03% tacrolimus ointment showed good and continuous improvement of AD in the infants. Tacrolimus blood levels were low throughout the study and treatment was well tolerated.

This thesis underlines the importance of effective long-term topical treatment of AD. When the active skin inflammation decreases, cell-mediated immunity of the skin improves and a secondary marker for Th2 cell reactivity, total serum IgE, decreases. Respiratory symptoms seem to improve when the eczema area decreases. All these effects can be attributed to improvement of skin barrier function. One potential method to prevent a progression from AD to asthma and allergic rhinitis may be avoidance of early sensitization through the skin, therefore early treatment of AD in infants is crucial. Long-term treatment with 0.03% tacrolimus ointment was effective and safe in infants over the age of 3 months.