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TITLE PAGE

**Young children with moderate-to-severe atopic dermatitis can be treated safely and effectively with either topical tacrolimus or mild corticosteroids**

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**Short title:**

**Therapy in paediatric atopic dermatitis**

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## ABSTRACT

**Aim:** We collected evidence and safety data for topical tacrolimus in small children with atopic dermatitis (AD) and compared the usage with topical corticosteroid.

**Methods:** This was an interim analysis of 75 patients (55% female) at one year of an ongoing three-year randomized open-label comparative follow-up study of topical tacrolimus vs. corticosteroid treatment. One- to three-year-old children with moderate-to-severe eczema referred to the Skin and Allergy Hospital in Helsinki, Finland, were enrolled.

**Results:** Efficacy parameters, the Eczema Area and Severity Index (EASI), Investigator's Global Assessment (IGA), transepidermal water loss (TEWL), eczema area, serum total immunoglobulin E (IgE) and the blood eosinophil count, showed improvement in both groups during the study. However, patients with signs of early sensitisation at baseline (elevated serum total IgE, elevated eosinophil count, positive prick tests or specific IgEs to aero or food allergens) had statistically significantly lower TEWL at the eczema site and a smaller eczema area at 12 months in the tacrolimus group. No severe adverse effects were seen during the treatment.

**Conclusion:** Children with AD and signs of early sensitisation appeared to benefit more from early tacrolimus than corticosteroid treatment. Small children may need stronger but nevertheless safe ointment options when treating moderate-to-severe AD.

**Keywords:** Atopic dermatitis, Child, Corticosteroid, Sensitisation, Tacrolimus

## Key Notes:

- Small children may need stronger but nevertheless safe ointment options when treating moderate-to-severe atopic dermatitis.
- Efficacy parameters such as transepidermal water loss (TEWL) and eczema area improved in both tacrolimus and corticosteroid groups during follow-up, but more so in early-sensitized patients in the tacrolimus group.
- Nearly 70% of the patients required a stronger ointment regimen.

## INTRODUCTION

Atopic dermatitis affects up to 25% of the paediatric population (1). A disrupted skin barrier plays a major role in the pathogenesis predisposing to eczema and further to allergic rhinitis and asthma (2). Up to 16% of children with moderate-to-severe atopic dermatitis show sensitisation to food allergens in the first two years of life (3). They are at later risk of sensitisation to inhaled allergens (4), which, again, is a risk factor for respiratory diseases such as asthma and airway hyperresponsiveness (2).

Infants with moderate-to-severe dermatitis are often undertreated due to concern about adverse effects from topical medications. In atopic dermatitis, the epidermal barrier function is deficient, resulting in increased allergen and microbe penetration and leading to increased water loss (5). The aim of topical treatment is to normalize the skin barrier.

Topical corticosteroids, the first-line treatment, are anti-inflammatory and symptom relieving but also affect other cells contributing to the structure of the skin barrier and lipid layer formation (6). Long-term use can lead to skin atrophy and even systemic effects, such as

growth restriction or impaired adrenal function (6,7). Findings suggesting that non-lesional atopic skin with a normal appearance also exhibits signs of subclinical inflammation have further raised a need for safe long-term treatment management (8).

The topical calcineurin inhibitors tacrolimus and pimecrolimus are anti-inflammatory drugs. They act by inhibiting the function of T lymphocytes and Langerhans cells and by suppressing cytokine-mediated responses (9,10). They repair the disturbed epidermal barrier, reduce the incidence of flares and cause no skin atrophy, making them suitable for long-term treatment (6,11-14). The most common side effects are pruritus and a burning sensation on the skin. The efficacy and safety of topical calcineurin inhibitors has been documented in both adults and children (10-13,15-19), but there is still little documentation for tacrolimus, especially the 0.1% formulation, in children under two years of age. However, in a pharmacokinetic study in children from three months of age, no safety problems occurred during a two-year follow-up with the 0.03% formulation (15).

The objective of this study was to collect evidence and safety data for topical tacrolimus in small children and compare its usage with topical corticosteroid in moderate-to-severe atopic dermatitis. This, to our knowledge, is the first long-term comparative follow-up study in toddlers from the age of one year onwards.

## **PATIENTS AND METHODS**

This study formed part of an ongoing three-year randomized open-label comparative follow-up study of topical tacrolimus vs. corticosteroid ointment in toddlers with moderate-to-severe atopic dermatitis. In this one-year follow-up analysis, the primary aim was to evaluate possible differences between the groups receiving tacrolimus and corticosteroid therapy. Safety data for both corticosteroid and tacrolimus usage were collected as a secondary endpoint. The study began in March 2013 and was conducted as a single-centre investigator-driven study in Helsinki, Finland. The local ethics committee and the Finnish Medicines Agency approved the study protocol.

In total, 152 children aged from one to three years and referred to the Skin and Allergy Hospital in Helsinki were enrolled. They were experiencing moderate (score 4.5–7.5) or severe (score 8–9) atopic dermatitis based on the Rajka & Langeland Eczema Severity Score (20). Atopic dermatitis was diagnosed and evaluated by a dermatologist. The patients were randomized 1:1 to treatment with 0.03%, and if needed, 0.1% tacrolimus ointment, or 1% hydrocortisone acetate ointment, and if needed, hydrocortisone butyrate 0.1% ointment. Patients with a constant need for inhaled corticosteroids were excluded. This one-year follow-up comprised 75 patients who had reached the 12-month follow-up point. For baseline characteristics see Table 1.

All parents or legal guardians provided written informed consent. Moisturising emollients were permitted, but treatments such as other corticosteroid regimens, systemic corticosteroids, ultraviolet therapies and systemic immunosuppressive agents were prohibited. During the study, antihistamines and topical/systemic antimicrobials were permitted, if needed.

This study consisted of hospital visits at baseline and after one week, one, three, six and nine months, and one year. Patient medical histories were collected. A general physical examination was performed. Blood samples for analysis of the tacrolimus concentration and cortisol levels allowed the gathering of safety data, in addition to total and specific serum immunoglobulin Es (IgEs) at baseline, the blood count and kidney values. For age-adjusted reference values for the serum total IgE concentration, the blood eosinophil count and serum cortisol level, see Table 2. Sensitisation to food allergens was defined as a specific serum IgE concentration of  $\geq 0.35$  kU/l against one of the following: peanuts, milk, egg white, soy, cod or wheat. Sensitisation to aeroallergens was defined as a specific serum IgE concentration of  $\geq 0.35$  kU/l in serum against one of the following: timothy, birch, mugwort, horse, cat, dog, *Cladosporium herbarum* or house dust mite. In addition, skin prick tests (SPTs) were performed with prick positivity defined as a positive reaction to birch, timothy, mugwort, cat, dog, horse, house dust mite, *Cladosporium herbarum*, egg white, milk, soy, cod, wheat, peanuts or shrimp. Early sensitisation was defined as a patient with one or more

of the following: a positive SPT, specific IgE to food or aeroallergens, elevated serum total IgE or an elevated eosinophil count at baseline.

Atopic dermatitis was treated according to the treatment protocol of the Skin and Allergy Hospital. In the corticosteroid therapy group, eczema lesions were treated twice daily for three to seven days, followed by a treatment pause lasting a minimum of three to seven days. In the tacrolimus therapy group, treatment was administered twice daily until clearance was achieved, after which it continued as twice-weekly maintenance therapy. To ensure adherence, the study nurse weighed the treatment tubes at each study visit. The treatment response was evaluated with efficacy measures including the Rajka & Langeland Severity Score (20), Investigator's Global Assessment, the Eczema Area and Severity Index (21) and the percentage of the body surface area affected. At each follow-up visit, information was collected on flares, other atopic symptoms, skin infections, other diseases, concomitant medications and commitment to treatment. Transepidermal water loss (22) was measured from the most severe eczema lesion at baseline, and after that at 12 months from the currently most severe lesion. In addition, control measurement was performed in an eczema-free area of the left arm. Measurements were taken with a VapoMeter (Delfin Technologies, Kuopio, Finland).

### **Statistical analysis**

All statistical analyses were performed with the statistical software package SPSS 21 and 22 for Mac software (IBM Corp, New York, USA). Statistical significance was set at p-value of  $<0.05$ . Variables were compared between therapy groups with the chi-square test, and if a variable had small expected cell numbers, which only occurred for a family history of atopic symptoms, Fisher's exact test was used. We compared quantitative parameters between therapy groups at each follow-up visit with the Mann-Whitney U-test and changes in parameters during the 12-month follow-up with the Wilcoxon signed-rank test. Correlations between the area of eczema and transepidermal water loss were analysed with the

Spearman test. The results are presented as medians with the interquartile range (IQR, with the 25<sup>th</sup> [Q1] to 75<sup>th</sup> [Q3] percentile).

## **RESULTS**

### **Patients and characteristics**

This analysis included 75 patients (55% female) who attended the 12-month follow-up visit (Tables 1 and 2). At baseline, before active treatment, there were no significant differences between the groups.

### **Clinical responses**

We analysed parameters that could reflect the treatment response (serum total IgE, eosinophil count, area of eczema, transepidermal water loss and eczema severity indices). Most of these improved in both therapy groups during the 12-month follow-up with active treatment (Table 2). The area of eczema at 12 months correlated with transepidermal water loss in both clinically clear and eczematous skin (both  $p \leq 0.001$ ). Baseline values for the eczema area and severity index correlated with serum total IgE at baseline ( $p = 0.361$  and  $p = 0.01$ , respectively). Severe and moderate disease groups did not differ in their response to treatment.

### **Signs of sensitisation**

**IgE.** The median serum total IgE level in both therapy groups increased during follow-up with no statistically significant differences between the groups. Patients with elevated serum total IgE at baseline had significantly lower median transepidermal water loss at the eczema site at 12 months in the tacrolimus ( $n = 12$ ) than in the corticosteroid group ( $n = 12$ ): 14.5 (11.6 to 22.9) vs. 25.4 (17.6 to 39.2),  $p = 0.012$  (Fig. 1).

**Blood eosinophils.** In both therapy groups, the blood eosinophil count decreased (Table 2), but changes between the groups were statistically non-significant. Patients who had an elevated eosinophil count at baseline had a significantly smaller median area affected by eczema at the 12-month visit in the tacrolimus ( $n = 9$ ) than in the corticosteroid group ( $n = 7$ ): 0.2 (0.0 to 1.3) vs. 4.6 (1.7 to 7.9),  $p = 0.016$  (Fig. 2).

Skin prick tests. Patients with a positive SPT at baseline had significantly lower median transepidermal water loss at the eczema site in the tacrolimus (n = 14) than in the corticosteroid group (n = 17) at the 12-month visit: 13.0 (8.7 to 18.0) vs. 22.6 (18.0 to 27.7), p = 0.001 (Fig. 1). They also had a smaller median area affected by eczema in the tacrolimus (n = 14) than in the corticosteroid group (n = 18): 0.4 (0.2 to 3.0) vs. 3.5 (1.1 to 8.9), p = 0.014 (Fig. 2).

Aero and food allergens. Patients with sensitisation to aeroallergens at baseline had statistically significantly lower median transepidermal water loss at the eczema site at 12 months in the tacrolimus (n = 7) than in the corticosteroid group (n = 10): 12.8 (8.5 to 16.9) vs. 19.4 (16.8 to 28.8), p = 0.043 (Fig. 1). At baseline, 42 patients were sensitised to food allergens (Table 1). At 12 months, these patients had significantly lower median transepidermal water loss at the eczema site in the tacrolimus (n = 18) than in the corticosteroid group (n = 16) : 13.1 (9.9 to 19.2) vs. 23.1 (18.7 to 30.1), p = 0.001 (Fig. 1). They also had a smaller median area affected by eczema in the tacrolimus (n = 20) than in the corticosteroid group (n = 19): 0.5 (0.2 to 2.3) vs 4.0 (0.6 to 7.9), p = 0.024 (Fig. 2).

### **Safety and ointment usage**

To define the systemic absorption of the treatment drugs, the serum cortisol level and tacrolimus concentration were measured. For reference values for serum cortisol levels, see Table 2. Only one patient in the corticosteroid group had a cortisol value below normal (56 nmol/l) at the one-year follow-up. During this period, the patient had consumed 773 g of 1% hydrocortisone acetate ointment and 1264 g of 0.1% hydrocortisone butyrate. Due to the abnormal cortisol level and after paediatric consultation, an adrenocorticotrophic hormone (ACTH) stimulation test was performed in this case, with a normal result (0 value 225 nmol/l, 30-minute value 394 nmol/l).

In the tacrolimus group, the blood concentration of tacrolimus was measured at the one-week and one-year follow-up visits. Three patients at week one had a tacrolimus concentration above normal (2.4 µg/l, 3.0 µg/l and 3.2 µg/l, respectively), but all values had normalized (<1.5 µg/l) in the following week's samples. The tacrolimus ointment

consumption at week one for the first, second and third patient was 73 g (0.03%), 2 g (0.03%) + 4 g (0.1%) and 42 g (0.03%), respectively. The patients with peak values of 2.4 and 3.0 µg/l tacrolimus were also diagnosed immediately afterwards with mild ichthyosis vulgaris in addition to atopic dermatitis, which could have affected ointment absorption. Both were excluded from the study after the ichthyosis diagnosis to verify safe long-term skin treatment.

During the first year of the study, 69% (52/75) of the patients required a stronger treatment option. In the corticosteroid treatment regimen, 64% (24/36) of the patients used 0.1% hydrocortisone butyrate besides the milder 1% hydrocortisone acetate, while 72% (28/39) of the patients required stronger 0.1% ointment in the tacrolimus group. There was no significant difference between the treatment groups in the requirement for stronger treatment (chi-square test,  $p = 0.63$ ).

## DISCUSSION

To our knowledge, this was only the second study to analyse the efficacy and safety of tacrolimus ointment in children below two years of age. No previous studies on this age group have examined the relative long-term efficacy of tacrolimus and hydrocortisone. In our interim analysis after 12 months of a three-year follow-up study of toddlers with moderate-to-severe atopic dermatitis, those patients with signs of early sensitisation at baseline had a tendency to benefit from tacrolimus therapy. Although the study population was small, this appeared as lower transepidermal water loss and a smaller affected area of eczema, indicating skin barrier repair.

An impaired skin barrier in childhood appears to be a key factor in the development of atopic dermatitis and the further initiation of possible atopic march (5). Epidermal permeability correlates with disease severity (5), as has been shown by increased transepidermal water loss values after skin barrier impairment (5,22). Therefore, in already established atopic dermatitis, active treatment may be beneficial. This secondary prevention implies effective treatment of the skin barrier and eczema exacerbation, possibly preventing the development

of other atopic disorders (5). In our study, lower transepidermal water loss and a smaller eczema area were more evident in the tacrolimus treatment group in early sensitised patients, despite the fact that the differences in this interim analysis were small.

A high proportion of children with early atopic dermatitis go into remission before adolescence (2). Risk factors for persistent eczema and other atopic comorbidities include severe, early-onset atopic dermatitis and allergic sensitisation (23). In small children with early-onset atopic dermatitis, increased transepidermal water loss values correlate with some biomarkers of T helper cell types 2 and 17/22, showing the interplay between barrier alterations and cytokine activation (24). These alterations and cytokine cascades may lead to allergic sensitisation and atopic manifestations.

Elevated total IgE and eosinophil levels, positive SPT and specific IgEs are all considered as signs of early sensitisation referred to as extrinsic atopic dermatitis (25). However, a natural moderate increase in total IgE during the first years of life is expected and considered as normal. This was also demonstrated in our population. Blood eosinophilia in atopic dermatitis, especially with respiratory atopy, is a common feature (25). In our study, signs of early sensitisation at baseline appeared in 54 of 75 patients. IgE-mediated sensitisation to food allergens was most common. Elevated IgE levels are not typical in newborns, but later, chronic skin inflammation precedes IgE-associated sensitisation, usually towards food allergens and other environmental allergens, as well as other atopic comorbidities (25,26).

Early suppression of inflammation with adequate therapy in atopic dermatitis may be beneficial, although more controlled studies are needed (26). Effective long-term treatment normalises the skin barrier function and reduces the effect of environmental antigens on the skin (27). This results in reduced T helper cell type 2 inflammation and improved T helper cell type 1 reactivity (26). Previous studies have shown that early application of moisturizing emollients may prevent the development of eczema, demonstrating the possibility of modulating the disease course (5,28).

Topical calcineurin inhibitors have served as a second-line treatment, and especially tacrolimus for more severe eczema. While corticosteroid treatment disrupts the structure and function of the skin barrier and reduces the skin's natural moisturizing factor (6), a four-week comparative study of adults with clinically non-active atopic dermatitis showed tacrolimus to improve the skin barrier (29). Other studies have yielded similar findings of epidermal barrier restoration and better disease control after topical calcineurin inhibitor treatment (6,11-12). Investigations of the systemic absorption of tacrolimus in children, even under one year of age, have demonstrated very low systemic exposure in a pharmacokinetic and a two-year open-label follow-up study: blood levels of tacrolimus were comparable to those of older children and adults with atopic dermatitis (15,30). Systemic exposure tends to increase when the area of the body surface treated increases (30). Inflamed skin is also more absorbent (31). In ichthyosis vulgaris, the protecting and moisturizing skin barrier is lost, leading to scaly skin with unpredictable ointment absorption.

To achieve better disease control, nearly 70% of the patients in the present study required a stronger ointment regimen during the first year of follow-up. This applied to both treatment groups. This is notable, since small children are generally treated with only very mild ointment options. However, the results of our study on moderate-to-severe atopic dermatitis patients indicate that mild treatment might not be sufficient, especially when treating limbs. Stronger ointment options, namely 0.1% hydrocortisone butyrate and 0.1% tacrolimus, were well tolerated in the respective treatment groups, both having a desirable safety profile.

This study had some limitations. It was an early interim analysis of a long-term study with a small number of patients. The difference we observed between effect of the two treatments in early sensitised patients was relatively small. Further, transepidermal water loss was measured from the most severe eczema lesion at baseline, and after that at 12 months from the currently most severe lesion. We estimated this to be the most representative one.

During the study, however, we took notice that it might not have been optimal due to possible site variation. This is why we planned the final measurement at three-year follow-

up appointment to be taken at the same site as at baseline. However, due to the tendency for providing relief, even using only ointments, the difference between the two treatments can be significant. Another limitation was the lack of a placebo group. Due to the long-term nature of the trial, we considered a placebo group unethical, since severe eczema (moderate to severe in this study) causes a high disease burden in families.

Although the findings are of interest, they are preliminary, and further evidence is needed from future larger prospective trials.

In conclusion, this one-year interim analysis of an ongoing three-year study demonstrated clinical improvement of moderate-to-severe eczema among most patients in both therapy groups. Our preliminary results imply that small children may require stronger but nevertheless safe ointment options when treating moderate-to-severe atopic dermatitis. In addition, patients at high risk of allergic diseases (early sensitised patients) may benefit from early effective tacrolimus treatment, which remains to be seen in larger prospective trials.

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## CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

## ABBREVIATIONS

IgE, immunoglobulin E

SPT, skin prick test

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## FIGURE LEGENDS:

### Fig. 1.

Transepidermal water loss (TEWL) at the eczema site after 12 months in tacrolimus and corticosteroid groups. Results for subgroups with elevated IgE (IgE+), an elevated eosinophil count (Eos+), positive skin prick tests (SPT+) and elevated specific IgEs for aero (IgE aero+) and food allergens (IgE food+). The horizontal lines of the box represent the lower quartile, median and upper quartile.

### Fig. 2.

Affected eczema area after 12 months in tacrolimus and corticosteroid groups. Results for subgroups with elevated IgE (IgE+), an elevated eosinophil count (Eos+), positive skin prick tests (SPT+) and elevated specific IgEs for aero (IgE aero+) and food allergens (IgE food+). The horizontal lines of the box represent the lower quartile, median and upper quartile.

**TABLE 1.** Baseline characteristics

| <b>Variable</b>                                         | <b>Corticosteroid group,<br/>N = 36</b> | <b>Tacrolimus group,<br/>N = 39</b> |
|---------------------------------------------------------|-----------------------------------------|-------------------------------------|
| <b>Sex, n (%)</b>                                       |                                         |                                     |
| Male                                                    | 19 (52.8)                               | 15 (38.5)                           |
| Female                                                  | 17 (47.2)                               | 24 (61.5)                           |
| <b>Age (years), median (Q1–Q3)</b>                      | 1.4 (1.2–2.2)                           | 1.6 (1.3–2.2)                       |
| <b>Severity of AD<sup>a</sup>: moderate / severe, n</b> | 18 / 18                                 | 20 / 19                             |
| <b>Positive prick tests, n (%)</b>                      | 19 (52.8)                               | 16 (42.1)                           |
| <b>Family history of AD, n (%)</b>                      | 26 (78.8)                               | 37 (97.4)                           |
| <b>Elevated specific IgEs: food allergens, n (%)</b>    | 20 (55.6)                               | 22 (56.4)                           |
| <b>Elevated specific IgEs: aeroallergens, n (%)</b>     | 13 (36.1)                               | 8 (20.5)                            |

<sup>a</sup> = According to the Rajka-Langeland criteria

There were no statistically significant differences between the groups at baseline.

AD = Atopic dermatitis, IgE = Immunoglobulin E

**TABLE 2.** Comparison of treatment groups at baseline and after 12 months

| <b>Variable</b>                                      | <b>Corticosteroid group,<br/>N = 36</b> |                 | <b>Tacrolimus group,<br/>N = 39</b> |                 |
|------------------------------------------------------|-----------------------------------------|-----------------|-------------------------------------|-----------------|
|                                                      | <b>Median (Q1–Q3)</b>                   | <b>p-value*</b> | <b>Median (Q1–Q3)</b>               | <b>p-value*</b> |
| <b>Area of eczema, %</b>                             |                                         |                 |                                     |                 |
| <i>Baseline</i>                                      | 21.3 (10.1–39.5)                        |                 | 19.0 (8.1–41.0)                     |                 |
| <i>Month 12</i>                                      | 1.9 (0.5–5.1)                           | <0.001          | 0.5 (0.2–5.15)                      | <0.001          |
| <b>EASI score</b>                                    |                                         |                 |                                     |                 |
| <i>Baseline</i>                                      | 9.1 (5.5–18.4)                          |                 | 9.1 (5.6–14.3)                      |                 |
| <i>Month 12</i>                                      | 1.3 (0.3–3.7)                           | <0.001          | 1.1 (0.4–2.5)                       | <0.001          |
| <b>IGA score</b>                                     |                                         |                 |                                     |                 |
| <i>Baseline</i>                                      | 3.0 (3.0–4.0)                           |                 | 4.0 (3.0–4.0)                       |                 |
| <i>Month 12</i>                                      | 1.0 (1.0–2.0)                           | <0.001          | 1.0 (1.0–2.0)                       | <0.001          |
| <b>TEWL atopy</b>                                    |                                         |                 |                                     |                 |
| <i>Baseline</i>                                      | 41.3 (29.6–53.9)                        |                 | 41.4 (30.8–58.8)                    |                 |
| <i>Month 12</i>                                      | 20.8 (13.9–27.4)                        | <0.001          | 16.9 (12.0–24.9)                    | <0.001          |
| <b>TEWL control, left forearm</b>                    |                                         |                 |                                     |                 |
| <i>Baseline</i>                                      | 12.9 (10.3–15.6)                        |                 | 14.9 (10.1–20.7)                    |                 |
| <i>Month 12</i>                                      | 8.2 (5.7–10.2)                          | <0.001          | 8.8 (6.7–12.3)                      | <0.001          |
| <b>Serum total IgE level kU/ml <sup>a</sup></b>      |                                         |                 |                                     |                 |
| <i>Baseline</i>                                      | 70.0 (28.5–258.0)                       |                 | 41.0 (14.0–172.0)                   |                 |
| <i>Month 12</i>                                      | 105.0 (23.0–246.8)                      | 0.003           | 93.0 (20.5–242.0)                   | 0.148           |
| <b>Elevated serum total IgE, n (%) <sup>a</sup></b>  |                                         |                 |                                     |                 |
| <i>Baseline</i>                                      | 15 (40.7)                               |                 | 15 (38.5)                           |                 |
| <i>Month 12</i>                                      | 17 (47.2)                               |                 | 18 (48.6)                           |                 |
| <b>Eosinophil count, E9/l <sup>b</sup></b>           |                                         |                 |                                     |                 |
| <i>Baseline</i>                                      | 0.52 (0.26–0.72)                        |                 | 0.47 (0.30–0.75)                    |                 |
| <i>Month 12</i>                                      | 0.32 (0.17–0.71)                        | 0.53            | 0.44 (0.23–0.67)                    | 0.217           |
| <b>Elevated eosinophil count, n (%) <sup>b</sup></b> |                                         |                 |                                     |                 |
| <i>Baseline</i>                                      | 7 (19.4)                                |                 | 10 (25.6)                           |                 |
| <i>Month 12</i>                                      | 19 (52.8)                               |                 | 23 (63.9)                           |                 |
| <b>Serum cortisol level, nmol/l <sup>c</sup></b>     |                                         |                 |                                     |                 |
| <i>Month 3</i>                                       | 167.5 (142.5–222.0)                     |                 | 188.5 (125.0–249.3)                 |                 |

Month 12 162.0 (131.5–209.8) 0.375 157.0 (119.5–222.0) 0.594

<sup>a</sup> = Reference values for total serum IgE: <sup>b</sup> = Reference values for blood eosinophil count:

6 months to 1 year, 0–70 kU/l

1 month to 1 year, 0.2–1.7 E9/l

2–3 years, 0–110 kU/l

2–4 years, 0–0.3 E9/l

4–7 years 0–130 kU/l

<sup>c</sup> = Reference values for serum cortisol levels:

2 months to 1 year, 66–632 nmol/l

2–13 years, 69–632 nmol/l

\*Changes within the groups after 12 months of treatment (Wilcoxon signed-rank test).

There were no statistically significant differences between the groups at baseline or at 12 months.

EASI = Eczema area and severity index, IgE = Immunoglobulin E, IGA = Investigator's global assessment, TEWL = Transepidermal water loss

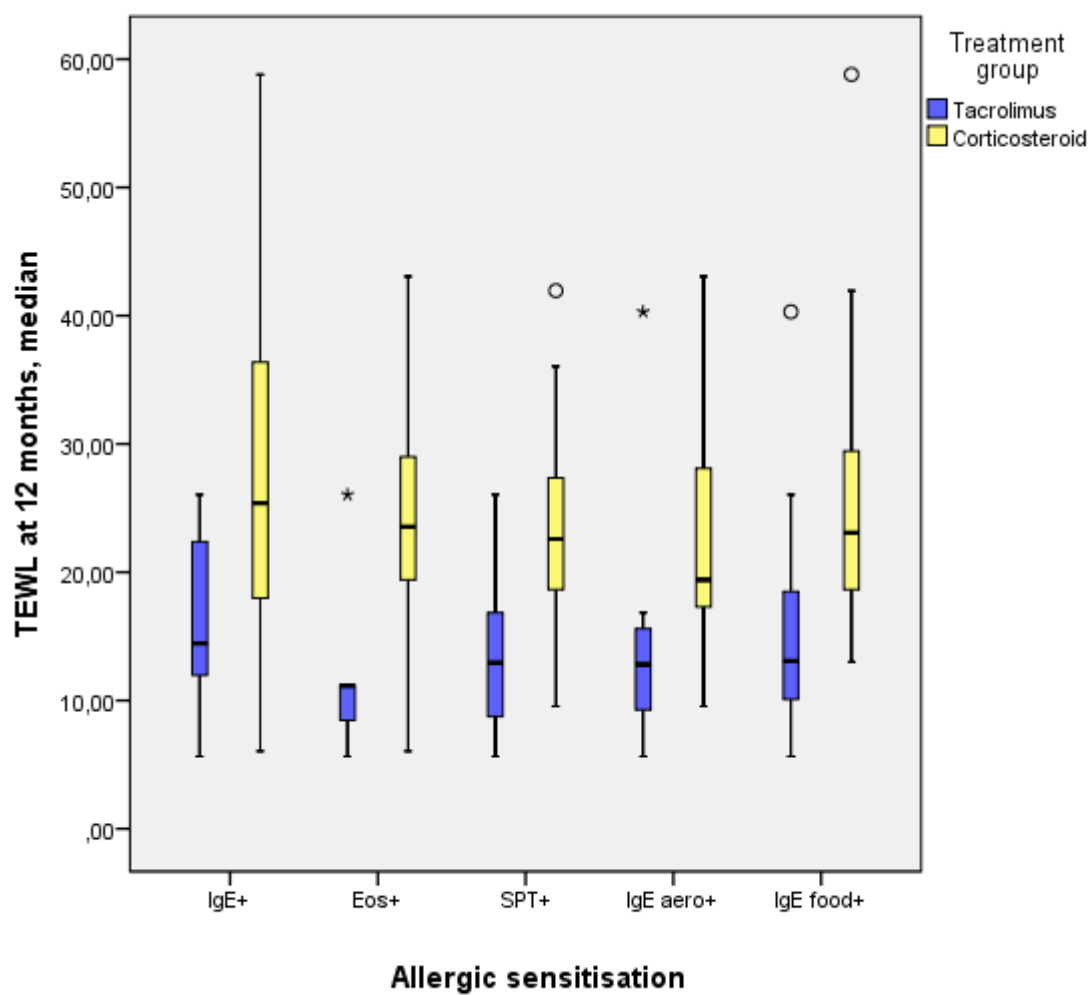


Figure 1

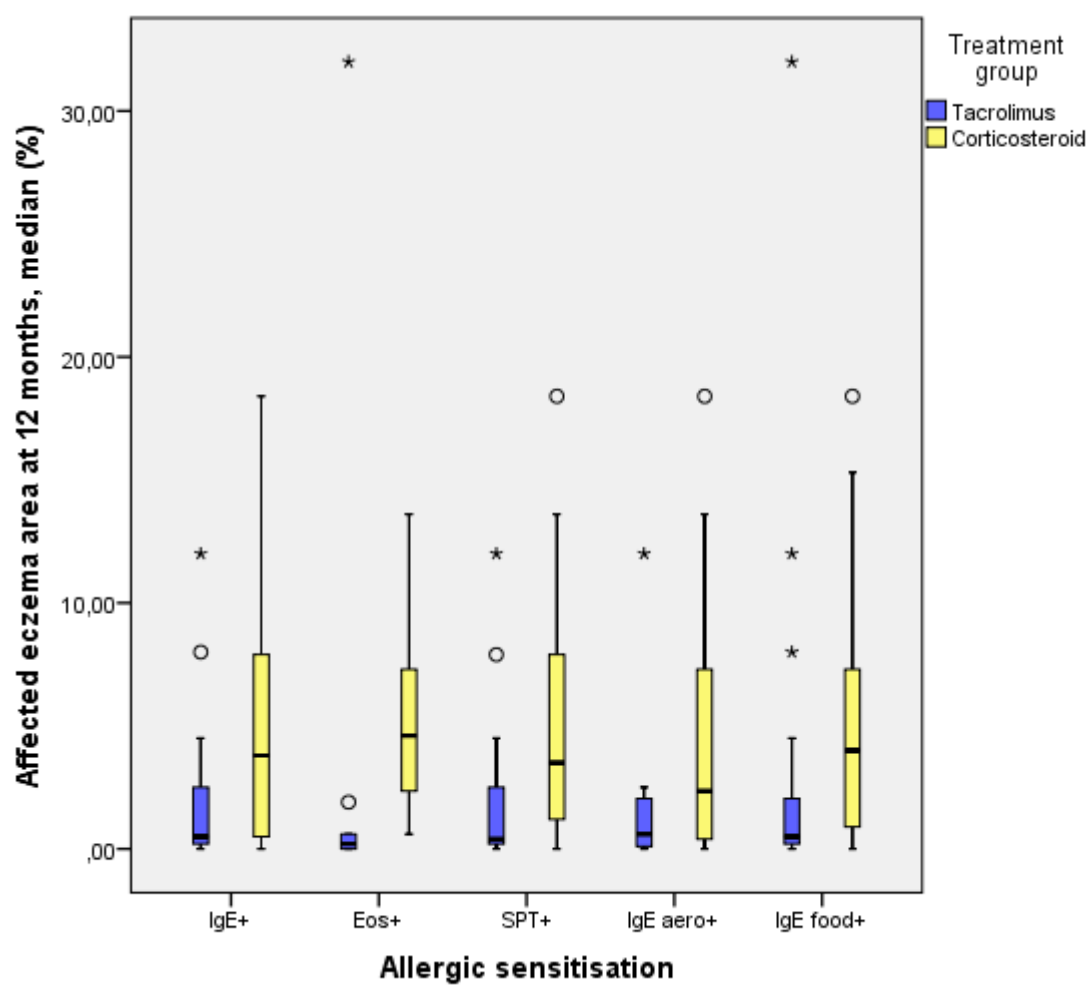


Figure 2