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Safety of tacrolimus 0.03% and 0.1% ointments in young children with atopic dermatitis: a 36-month follow-up study

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Summary

Background. Topical tacrolimus is used off-label in young children, but data are limited on its use in children under 2 years of age and for long-term treatment.

Aim. To compare safety differences between topical tacrolimus (0.03% and 0.1% ointments) and topical corticosteroids (mild and moderate potency) in young children with atopic dermatitis (AD).

Methods. We conducted a 36-month follow-up study with 152 young children aged 1–3 years with moderate to severe AD. The children were followed up prospectively, and data were collected on infections, disease severity, growth parameters, vaccination responses and other relevant laboratory tests were gathered.

Results. There were no significant differences between the treatment groups for skin-related infections (SRIs) ($P = 0.20$), non-SRIs ($P = 0.20$), growth parameters height ($P = 0.60$), body weight ($P = 0.81$), Eczema Area and Severity Index (EASI) ($P = 0.19$), vaccination responses ($P = 0.62$), serum cortisone levels ($P = 0.23$) or serum levels of interleukin (IL)-4, IL-10, IL-12, IL-31 and interferon-γ. EASI decreased significantly in both groups ($P < 0.001$). In the tacrolimus group, nine patients (11.68%) had detectable tacrolimus blood concentrations at the 1-week visit. There were no malignancies or severe infections during the study, and blood eosinophil counts were similar in both groups.

Conclusions. Topical tacrolimus (0.03% and 0.1%) and topical corticosteroids (mild and moderate potency) are safe to use in young children with moderate to severe AD, and have comparable efficacy and safety profiles.

Introduction

Atopic dermatitis (AD) is one of the most common skin diseases of early childhood, and causes a notable burden to young children, families and the healthcare system.[1] Intermittent courses of mild topical corticosteroids (TCS) are used as first-line treatment in young children.[2] In unresponsive cases, moderate-potency TCS or topical calcineurin inhibitors are prescribed, but because of concern about safety issues associated with these drugs, there is a risk of undertreatment of AD in children.[3]

Topical tacrolimus (TAC) 0.03% ointment is approved from 2 years of age, but there have been concerns regarding its immunosuppressive potential.[4] TAC 0.1% ointment has been used off-label in young children, but there is a lack of data regarding its use as long-term treatment in children aged < 2 years.[5] TAC 0.03% and 0.1% ointments were approved for use in AD in 2002 and to date, no studies have directly linked the topical use of these ointments to systemic immunosuppression or an increased incidence of malignancies.[6,7] However, there have been reports associating severe and uncontrolled

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AD with increased cutaneous infections and a slightly elevated risk of developing malignancies, especially cutaneous lymphomas.[8] If topical treatments were to induce systemic immunosuppression and increase the infections rate, detectable blood levels or lowered vaccination responses should be observable.[9,10]

In this study, we aimed to compare safety differences between topical TAC (0.03% and 0.1% ointments) and TCS (mild and moderate potency) in a cohort of young children with moderate to severe AD.

Methods

The study was approved by the Medicine Ethics Committee, Hospital District of Helsinki and Uusimaa Finland. The local ethics committee of the Helsinki University Hospital and the Finnish Medicines agency approved the study protocol. Parents/caregivers gave written informed consent for their children to participate in the study, and any mentioned in this manuscript gave written informed consent to publication of their child's case details and images.

Study design

We performed a single-centre investigator-initiated clinical study. Patient and parental advice, dermatological treatments and follow-up visits were carried out in the Skin and Allergy Hospital, Helsinki University Hospital (Helsinki, Finland). We compared two different types of topical therapy for the treatment of children with AD: TCS [mild-potency (hydrocortisone acetate 1%) and moderate-potency (hydrocortisone 17-butyrate 0.1%)] and TAC ointments (0.03% and 0.1%). The study was conducted as a randomized nonblinded follow-up study with a prior 1-week washout period. Selection, inclusion and randomization of the study patients was carried out in the paediatric unit. General patient characteristics are presented in Table 1. In a former publication, we have characterized the baseline patient characteristics in more detail.[5]

Patient characteristics

The investigated patient cohort comprised 152 young children, aged 1–3 years (mean age 1.43 years) with equal sex distribution and AD rated as moderate (score 4.5–7.5) to severe (score 8–9) on the Rajka and Langeland severity score (Table 1).[11]

Study design

The study size was based on statistical power calculations. The same experienced dermatologists carried out the diagnosis of AD and subsequent follow-up visits. Patients were randomized 1 : 1 into two treatment groups: (i) TCS group (hydrocortisone acetate 1% cream and if needed, hydrocortisone-17-butyrate 0.1% cream), and (ii) TAC group (topical TAC 0.03% ointment and if needed, TAC 0.1% ointment).

Table 1 Characteristics of the treatment groups at baseline and at the 3-month follow-up visit.

	Patients			TCS vs. TAC[a]	
Parameter	All	TCS group	TAC group	*P*	95% CI
Patients, *n* (M : F)	152 (79 : 73)	75 (44 : 31)	77 (35 : 42)		
Mean age at baseline (years)	1.43	1.44	1.42		
Baseline AD severity,[b] *n* (%)					
Mild	0	0	0	0.86[c]	0.50–0.87
Moderate	82 (53.9)	41 (54.6)	41 (53.2)		
Severe	70 (46.1)	34 (45.3)	36 (46.7)		
Withdrawals, *n* (%)	27 (17.7)	12 (16.0)	15 (19.4)	0.58[c]	0.36–0.67
Patients with pathological vaccination responses, *n* (%)	28 (18.4)	15 (20.0)	13 (16.8)	0.60[c]	0.39–0.68
Blood eosinophil count, $\times^9$: /L					
Baseline					
Median (IQR)	0.43 (0.25–0.68)	0.44 (0.25–0.68)	0.41 (0.26–0.69)	0.95[d]	0.94–1.00
Mean (range)	0.55 (0.01–3.09)	0.51 (0.05–1.83)	0.59 (0.01–3.09)		
36 months					
Median (IQR)	0.37 (0.23–0.71)	0.37 (0.21–0.67)	0.37 (0.23–0.76)	0.56[d]	0.49–0.65
Mean (range)	0.51 (0.02–3.31)	0.51 (0.02–3.31)	0.51 (0.09–2.10)		

AD, atopic dermatitis; IQR, interquartile range; TAC, tacrolimus; TCS, topical corticosteroids. [a]Statistical significance was set at $P < 0.05$. [b]Based on the Rajka and Langeland severity score. [c]Pearson χ^2 test. [d]Mann–Whitney *U*-test.

Parents/caregivers were thoroughly instructed regarding the topical treatments, and told to apply sufficient amounts of TCS twice daily for courses of 3–7 days (TCS group) or topical TAC twice daily until clearance was achieved and afterwards twice weekly, if needed (TAC group). At their discretion parents/caregivers could switch to the more potent topical treatment in each group (hydrocortisone-17-butyrate 0.1% ointment in the TCS group and TAC 0.1% ointment in the TAC group). Study follow-up visits (including assessment of treatments and responses, infections, AD severity) were performed at baseline, the end of Week 1, at Months 1, 3, 6, 9 and 12, and every 6 months thereafter, with the complete follow-up period being 36 months.

Endpoints

Safety concerns (infection rate, growth parameters) of TAC 0.03% and 0.1% ointment compared with mild- and moderate-potency TCS were determined as the primary endpoints of the study analysis. The secondary endpoints were significant differences between the treatment groups in treatment response [as measured by the Eczema Area and Severity Index (EASI)], vaccination responses (described in detail in Supplementary Tables S1 and S2) and other safety relevant laboratory values. Data on skin-related infections (SRIs) and non-SRIs were acquired retrospectively, based on information from parents/caregivers. Infection type and severity could not be confirmed by health record data or other documented data. Growth parameters (height and weight) and EASI were measured at each follow-up visit.[12]

Exclusion criteria and withdrawals

Patients with recurrent infections (otitis, pneumonia and recurrent skin infections), signs of immune deficiency, chronic diseases (asthma, autoimmune diseases, gastrointestinal diseases, malignancies and kidney diseases), continuous medications or need for continuous inhaled corticosteroids were excluded. During the follow-up period, 27 of the 152 patients withdrew from the study.

Laboratory tests

Serum cytokine levels [interleukin (IL)-4, IL-10, IL-13, IL-31 and interferon (IFN)-γ] were measured with sensitive ELISA tests in both the TCS and TAC groups at baseline and at 36 months (endpoint of the follow-up period). Total serum cortisone levels were measured by immunochemiluminometric assay at baseline, 12, 24 and 36 months, while blood TAC concentrations were measured by fluid chromatography–tandem mass spectrometry at the Week 1 and Month 12, 24 and 36 follow-up visits. In both groups, differential blood counts with total blood eosinophil counts were investigated by flow cytometry) at the baseline, Month 12 and Month 36 follow-up visits. All laboratory tests were performed in the Laboratory of Helsinki University Hospital (HUSLAB®) and were based on accredited methods.

Statistical analyses

Descriptive statistics and group comparisons were calculated with IBM SPSS software (V27.0; IBM SPSS, Armonk, NY, USA). The Mann–Whitney *U*-test was used to compare quantitative data and the Pearson's χ^2 test was used. Results were considered statistically significant at $P < 0.05$.

Results

Skin-related infections

There were 223 SRIs observed (mean 1.50 SRIs per patient) during follow-up; 105 bacterial SRIs (impetigo, folliculitis, boils, erysipelas; mean 0.7 per patient), 88 viral SRIs (warts, molluscum, herpes simplex; mean 0.59 per patient) and 31 other SRIs (tinea, *Candida*; 0.21 per patient) (Table 2, Fig. 1a). In the TCS group there were 100 SRIs (mean 1.35 per patient) detected: 51 bacterial SRIs (mean 0.69 per patient), 38 viral SRIs (mean 0.51 per patient) and 11 other SRIs (mean 0.15 per patient). In the TAC group, 123 SRIs (mean 1.64 per patient) were detected: 54 bacterial SRIs (mean 0.72 per patient), 50 viral SRIs (mean 0.67 per patient) and 20 other SRIs (mean 0.27 per patient).

Group comparisons between TCS and TAC groups did not show any significant differences in total SRIs ($P = 0.20$, 95% CI 0.15–0.28), bacterial SRIs ($P = 0.89$, 95% CI 0.87–0.96), viral SRIs ($P = 0.16$, 95% CI 0.10–0.21) or other SRIs ($P = 0.34$, 95% CI 0.24–0.39) (Table 2, Fig. 1b). There was a trend towards higher numbers of viral SRIs in the TAC group, but the difference was not statistically significant.

Nonskin-related infections

There were 1357 non-SRIs (mean 9.11 per patient) (Table 2, Fig. 1a). Most of these (980 infections) were respiratory (upper respiratory infections, pharyngitis,

Table 2 Infections during the 36-month follow-up in children with moderate to severe atopic dermatitis.

	Patients			TCS vs. TAC[a,b]	
Parameter	All	TCS group	TAC group	*P*	95% CI
All SRIs				0.20	0.15–0.28
Total	223	100	123		
Median (IQR)	1.00 (0.00–2.00)	1.00 (0.00–2.00)	1.00 (0.00–2.00)		
Mean (range)	1.50 (0–14)	1.35 (0–12)	1.64 (0–14)		
Bacterial SRIs				0.89	0.87–0.96
Total	105	51	54		
Median (IQR)	0.00 (0.00–1.00)	0.00 (0.00–1.00)	0.00 (0.00–1.00)		
Mean (range)	0.7 (0–12)	0.69 (0–12)	0.72 (0–12)		
Viral SRIs					
Total	88	38	50	0.16	0.09–0.21
Median (IQR)	0.00 (0.00–1.00)	0.00 (0.00–1.00)	0.00 (0.00–1.00)		
Mean (range)	0.59 (0–3)	0.51 (0–3)	0.67 (0–3)		
Other SRIs				0.34	0.24–0.39
Total	31	11	20		
Median (IQR)	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.00 (0.00–0.00)		
Mean (range)	0.21 (0–5)	0.15 (0–3)	0.27 (0–5)		
Non-SRIs				0.50	0.44–0.60
Total	1357	671	686		
Median (IQR)	9.00 (6.00–11.50)	9.00 (6.00–11.25)	8.00 (5.00–12.00)		
Mean (range)	9.11 (0–30)	9.07 (0–26)	9.15 (0–30)		
Respiratory infections				0.27	0.24–0.38
Total	980	498	482		
Median (IQR)	6.00 (3.00–9.00)	7.00 (3.75–9.00)	6.00 (3.00–8.00)		
Mean (range)	6.58 (0–26)	6.73 (0–23)	6.43 (0–26)		
Viral rash				0.66	0.89–0.74
Total	74	33	41		
Median (IQR)	0.00 (0.00–1.00)	0.00 (0.00–1.00)	0.00 (0.00–1.00)		
Mean (range)	0.5 (0–5)	0.45 (0–2)	0.55 (0–5)		
Otitis media				0.85	0.84–0.94
Total	163	78	85		
Median (IQR)	1.00 (0.00–2.00)	1.00 (0.00–2.00)	0.00 (0.00–2.00)		
Mean (range)	1.09 (0–8)	1.05 (0–8)	1.13 (0–6)		
Other					
Total	139	61	78		0.33–0.49
Median (IQR)	1.00 (0.00–1.00)	1.00 (0.00–1.00)	1.00 (0.00–2.00)	0.50	
Mean (range)	0.93 (0–9)	0.82 (0–4)	1.04 (0–9)		

AD, atopic dermatitis; IQR, interquartile range; SRI, skin-related infection; TAC, tacrolimus; TCS, topical corticosteroids. [a]Statistical significance was set at $P < 0.05$. [b]Mann–Whitney *U*-test.

tonsillitis and laryngitis), with a mean of 6.58 per patient). In addition, there were 74 viral rashes (mean 0.5 per patient), 163 otitis media (mean 1.09 per patient) and 139 other infections (mostly gastrointestinal and urogenital; mean 0.92 per patient). In the TCS group, there were 671 non-SRI infections (mean 9.07 per patient): 498 respiratory infections (mean 6.73 per patient), 33 viral rashes (mean 0.45 per patient), 78 otitis media (mean 1.05 per patient) and 61 other infections (mean 0.82 per patient). In the TAC group, there were 686 non-SRIs (mean 9.15 per patient): 482 respiratory infections (mean 6.43 per patient), 41 viral rashes (mean 0.55 per patient), 85 otitis media (mean 1.13 per patient) and 78 other infections (mean 1.04 per patient).

Group comparisons showed no significant differences in the number of non-SRIs ($P = 0.50$, 95% CI 0.44–0.60) or in the number of individual types: respiratory infections ($P = 0.27$, 95% CI 0.24–0.38), viral rashes ($P = 0.66$, 95% CI 0.59–0.74), otitis media ($P = 0.85$, 95% CI 0.84–0.49) and other infections ($P = 050$, 95% CI 0.33–0.49) (Table 2, Fig. 1b). During follow-up, there were no severe or life-threatening infections observed.

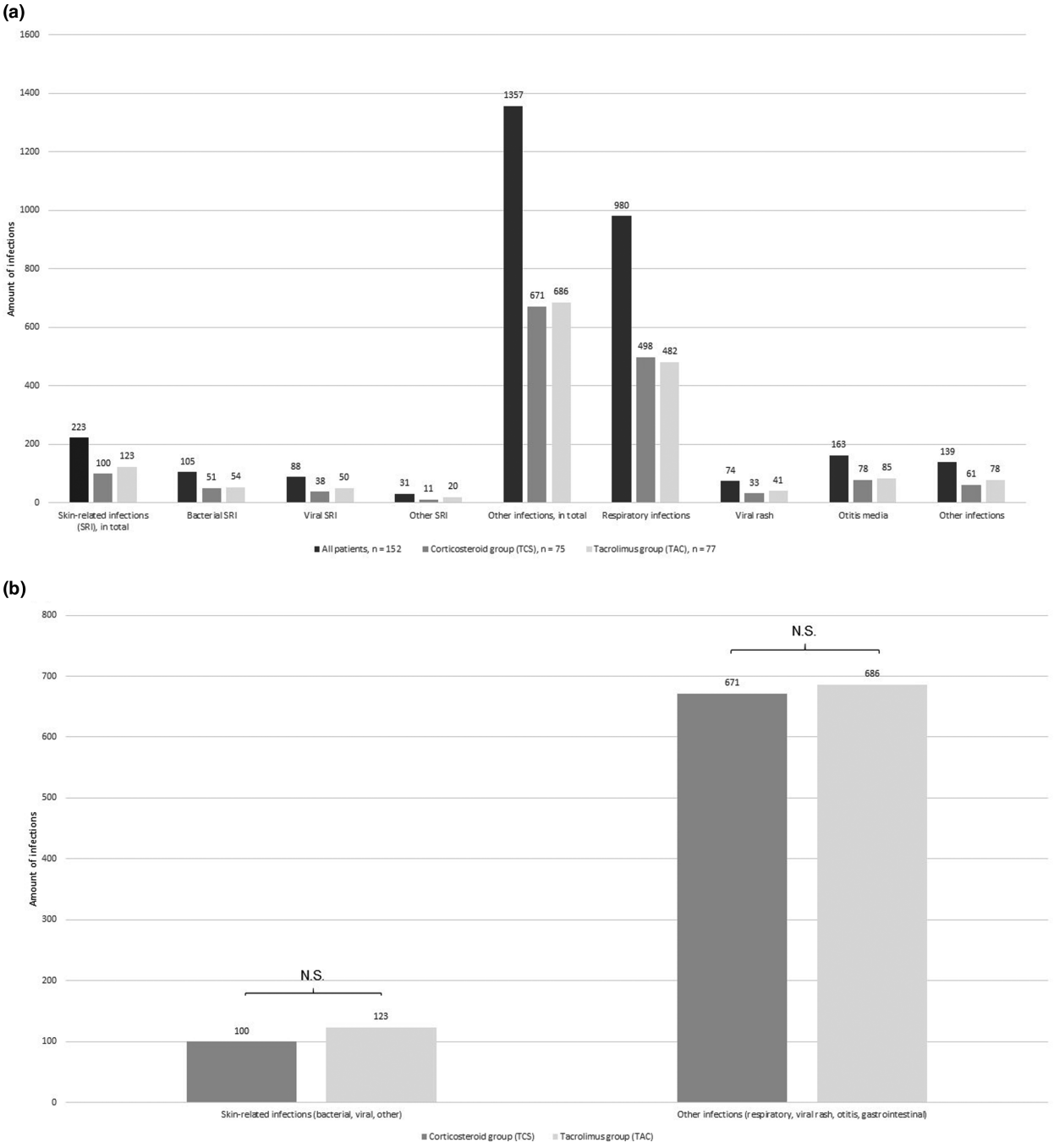

Figure 1 (a) Number of different types of infections during 36 months of follow-up in young children with moderate to severe atopic dermatitis treated with tacrolimus (TAC) or topical corticosteroids (TCS); (b) group comparisons of skin-related infections (SRIs) and non-SRIs at the same timepoints.

Growth parameters

In both treatment groups (TCS and TAC), physical growth parameters at baseline were below the SD for young children in Finland.[13] The median height at baseline was 81.2 cm [interquartile range (IQR) 78.2–89.5] and median SD was –0.20 (IQR −1.20 to 0.1) in the TCS group and 82.0 cm (IQR 78.2–88.1), with SD –0.63 (IQR –1.60 to 0.45) in the TAC group. After 36 months, there was a significant increase in height

in both treatment groups, but both groups were still below the Finnish SD. The median height at 36 months was 108.5 cm (IQR 104.8–113.7) and median SD –0.17 (IQR –0.80 to 0.35) in the TCS group and 108.0 cm (IQR 104.9–113.0) and SD –0.50 (IQR –1.30 to 0.30) in the TAC group. Weight measurements showed similar results (Table 3, Fig. 2a). Comparisons between the TCS and TAC groups showed no significant differences in height ($P = 0.60$, 95% CI 0.54–0.70) or weight ($P = 0.81$, 95% CI 0.75–0.87) at baseline or 36 months (Table 3, Fig. 2b).

Cutaneous or internal malignancies

There were no cutaneous or internal malignancies identified during the 36-month follow-up period in either group.

Eczema Area and Severity Index

In both treatment groups, EASI decreased significantly ($P < 0.001$, 95% CI 0.00–0.02) during follow-up. At baseline the median EASI was 9.00 (IQR 6.50–17.10) in the TCS group and 10.1 (IQR 6.30–17.47) in the TAC group, while at 36 months, the median EASI was 1.20 (IQR 0.00–3.40) and 0.80 (IQR 0.00–2.27), respectively. Comparisons of both treatment groups showed no significant differences at baseline ($P = 0.45$, 95% CI 0.40–0.56) or at 36 months ($P = 0.19$, 95% CI 0.17–0.30) (Table 3).

Tacrolimus blood concentrations

The therapeutic blood concentrations of TAC is 5.0–15.0 μg/L when used systemically after solid organ transplantations. In the TAC group, nine patients (11.68%) had detectable TAC blood concentrations (range 1.5–5.6 μg/L) at the Week 1 visit (i.e. after 1 week of topical therapy), and most of these patients had more severe disease with extensive areas of skin involvement. Of these nine patients, four had the same serum concentration (1.5 μg/L) of TAC (EASI was 17.5, 7.8, 11.8 and 5.1), while in the other five patients, the concentrations were 2.2, 2.3, 3.0, 3.2 and 5.6 μg/L (with EASI of 11.3, 32.0, 6.0, 45.0 and 10.2, respectively). Contrary to our instructions, each of the nine patients had been treated with topical TAC on the same day that blood samples were taken. None of these patients had detectable TAC (levels < 1.5 μg/L) in the control sample taken 4 weeks later. Two of the nine patients had as an additional diagnosis of ichthyosis vulgaris. At the 1-year visit, only one patient had a detectable TAC blood concentration (4.7 μg/L; EASI 1.70); this patient had used TAC ointment on the same day that the blood sample was taken, and was experiencing an acute flare of AD due to undertreatment and noncompliance. TAC was undetectable in this patient's control blood sample taken 4 weeks later. At the Month 24 and Month 36 visits, no patients had detectable TAC blood concentrations (all patients had levels < 1.5 μg/L).

Vaccination responses

In the full study cohort, 28 patients (18.4%) had pathological vaccination responses (described in detail in Supplementary Tables S1 and S2): 15 patients (20.0%) in the TCS group and 13 patients (16.8%) in the TAC group, with no significant differences between the two treatment groups ($P = 0.62$, 95% CI 0.39–0.68). The AD features of these patients were similar in both groups and there were no significant differences in baseline EASI ($P = 0.57$, 95% CI 0.28–0.65). Patients with pathological vaccination responses showed similar serum concentrations of IL-4, IL-10, IL-13, IL-31 and IFN-γ (Table 4). In both groups, there were more infections observed in patients with pathological vaccination responses than in patients with normal vaccination responses. In the TCS group, there was a mean of 2.33 SRIs per patient and 10.2 non-SRIs per patient in the patients with pathological responses, compared with 1.35 SRIs and 9.07 non-SRIs for those with normal responses, while in the TAC group there were 1.69 SRIs per patient and 12.31 non-SRIs per patient for those with pathological responses, compared with 1.64 SRIs and 9.15 non-SRIs for those with normal responses. Concerning patients with pathological vaccination responses, there were no differences between the treatment groups regarding SRIs ($P = 0.24$, 95% CI 0.06–0.07) or non-SRIs ($P = 0.12$, 95% CI 0.02–0.03). Characteristics of the patients with pathological vaccination responses are presented in Supplementary Tables S1 and S2.

Serum cortisone concentrations

Serum cortisone concentrations were similar in both treatment groups throughout the follow-up with no clinical signs of adrenal insufficiency. In the TCS group, the median serum cortisone concentration was 168.0 nmol/L (IQR 138.0–218.0) at baseline and 206.0 nmol/L (IQR 153.5–280.0) at 36 months, while

Table 3 Growth parameters, Eczema Area and Severity Index and serum cortisone levels of children with moderate to severe atopic dermatitis, at baseline and at the 36-month follow-up.

	TCS		TAC		TCS vs. TAC[a,b]			
					Baseline		36 months	
Parameter	Baseline	36 months	Baseline	36 months	*P*	95% CI	*P*	95% CI
Height, cm								
Median (IQR)	81.2 (78.2–89.5)	108.5 (104.8–113.7)	82.0 (78.2–88.1)	108.0 (104.9–113.0)	0.97	0.95–1.00	0.60	0.54–0.70
Mean (range)	83.3 (71.0–104.1)	109.5 (98.4–122.0)	83.0 (66.5–100.9)	108.8 (96.3–129.9)				
Height SD[c]								
Median (IQR)	−0.20 (−1.20 to 0.1)	−0.20 (−0.80 to 0.35)	−0.75 (−1.60 to 0.45)	−0.50 (−1.30 to 0.30)	0.26	0.21–0.35	0.29	0.25–0.40
Mean (range)	−0.40 (−3.40 to 3.00)	−0.17 (−2.30 to 2.20)	−0.63 (−4.10 to 2.00)	−0.37 (−2.70 to 2.80)				
Weight, kg								
Median (IQR)	11.00 (10.0–12.55)	18.50 (17.00–20.45)	11.50 (10.27–12.72)	19.30 (17.00–20.40)	0.36	0.35–0.51	0.81	0.75–0.87
Mean (range)	11.61 (7.9–19.5)	19.93 (15.0–29.4)	11.73 (6.80–17.40)	18.79 (13.8–24.7)				
EASI								
Median (IQR)	9.00 (6.50–17.10)	1.20 (0.00–3.40)	10.1 (6.30–17.47)	0.80 (0.00–2.27)	0.45	0.40–0.56	0.19	0.17–0.30
Mean (range)	11.35 (0.00–31.50)	2.53 (0.00–22.80)	3.32 (1.50–46.00)	2.40 (2.28 (0.00–30.50))				
Serum cortisone, nmol/L[d]								
Median (IQR)	168.0 (138.0–218.0)	206.0 (153.5–280.0)	152.0 (123.5–187.7)	170.5 (137.5–170.5)	0.36[c]	0.25–0.40	0.23	0.16–0.29
Mean (range)	176.4 (55.0–319.0)	224.6 (76.0–542.0)	165.1 (82.0–289.0)	204.9 (65.0–579.0)				

EASI, Eczema Area and Severity Index; IQR, interquartile range; TAC, tacrolimus; TCS, topical corticosteroids. [a]Statistical significance was set at $P < 0.05$. [b]Mann–Whitney *U*-test. [c]Saari *et al.*[13] [d]Baseline serum cortisone concentration was measured at the 3-month visit.

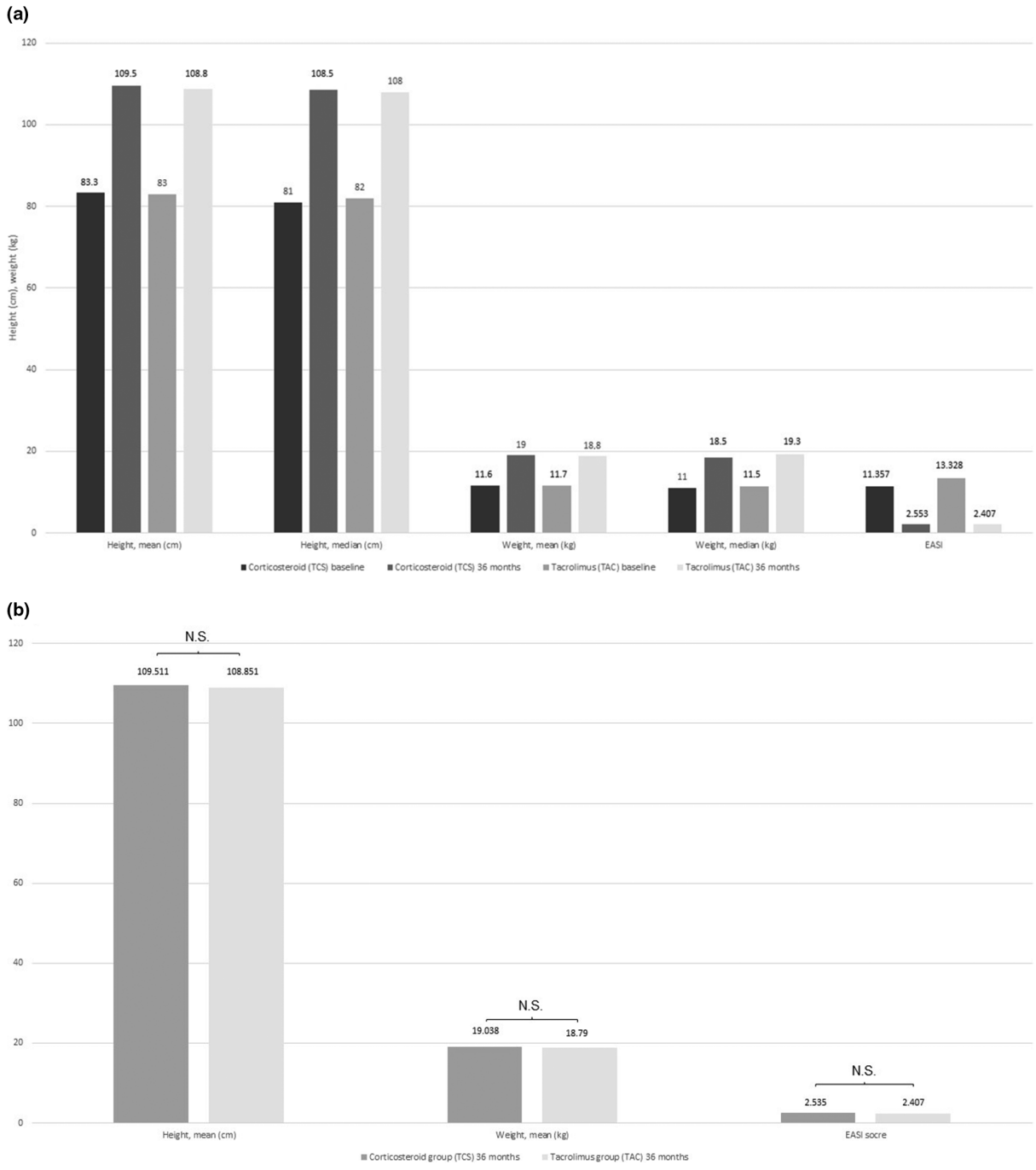

Figure 2 (a) Growth parameters (mean and median height and weight) and disease severity [measured by Eczema Area and Severity Index (EASI)] at baseline and at 36 months in young children with moderate to severe atopic dermatitis treated with tacrolimus (TAC) or topical corticosteroids (TCS); (b) group comparisons of height, weight and disease severity (EASI) at the same timepoints.

in the TAC group, the numbers were 152.0 nmol/L (IQR 123.5–187.7) at baseline and 170.5 nmol/L (IQR 137.5–170.5) at 36 months (Table 3, Fig. 3a). In the TCS group, there was one patient with a concentration below the reference range for children (55 nmol/L reference range 69–632 nmol/L) at 3 months but the level

Table 4 Serum concentrations of the cytokines.

	All patients		TCS		TCS baseline vs. 36 months[a,b]		TAC		TAC baseline vs. 36 months[a,b]		TCS vs. TAC[a,b]			
											Baseline		36 months	
	Baseline	36 months	Baseline	36 months	*P*	95% CI	Baseline	36 months	*P*	95% CI	*P*	95% CI	*P*	95% CI
IL-4, pg/mL					0.91	0.84–0.97			0.89	0.83–0.96	0.28	0.19–0.33	0.55	0.51–0.66
Median (IQR)	98.72 (0.00–388.05)	71.21 (0.00–459.75)	57.59 (0.00–333.77)	67.67 (0.00–326.67)			148.40 (0.00–464.70)	72.48 (0.00–593.20)						
Mean (range)	1088.00 (0.00–16 850.00)	2553.28 (0.00–84 480.00)	1052.44 (0.00–16 850.00)	1993.10 (0.00–84 480.00)			1122.92 (0.00–14 970.00)	3103.28 (0.00–77 280.00)						
IL-10, pg/mL					0.70	0.55–0.76			0.90	0.80–0.95	0.66	0.61–0.76	0.67	0.67–0.81
Median (IQR)	227.85 (4.92–1539.00)	160.70 (11.84–1036.55)	208.70 (0.00–1485.00)	169.55 (0.00–831.75)			239.00 (27.79–1543.00)	143.30 (35.27–1150.00)						
Mean (range)	2863.04 (0.00–47 410.00)	4362.22 (0.00–120 800.00)	3421.24 (0.00–47 410.00)	3035.24 (0.00–98 240.00)			2325.14 (0.00–35 640.00)	5665.08 (0.00–120 800.00)						
IL-13, pg/mL					0.76								0.28	0.24–0.39
Median (IQR)	2075.00 (568.55–12 755.00)	1657.00 (610.15–10 234.00)	1715.50 (378.80–5643.75)	1480.00 (578.07–6341.50)		0.68–0.87	3534.00 (765.90–1 6530.00)	1983.00 (633.90–16 600.00)	0.86	0.81–0.96	0.17	0.11–0.22		
Mean (range)	40 900.04 (0.00–1 582 000.00)	61 175.18 (0.00–1 792 000.00)	46 961.67 (0.00–1 582 000.00)	51 158.84 (0.00–1 792 000.00)			34 948.62 (0.00–562 000.00)	71 009.43 (0.00–1 532 000.00)						
IL-31, ng/mL					0.77				0.65	0.60–0.80	0.76	0.67–0.81	0.72	0.68–0.83
Median (IQR)	52.75 (7.52–471.20)	65.50 (11.45–404.55)	46.62 (7.41–519.80)	69.74 (3.86–309.77)		0.59–0.80	77.97 (8.93–389.10)	65.20 (12.79–653.50)						
Mean (range)	723.57 (0.00–9380.00)	1044.29 (0.00–30 680.00)	888.24 (0.00–9380.00)	1352.25 (0.26–30 680.00)			561.89 (0.00–8925.00)	741.92 (0.00–13 865.00)						
IFN-γ, pg/mL					0.12	0.98–0.23			0.35	0.24–0.46	0.75	0.74–0.87	0.90	0.85–0.94
Median (IQR)	0.00 (0.00–39.95)	0.00 (0.00–15.99)	0.00 (0.00–56.54)	0.00 (0.00–17.19)			0.00 (0.00–36.41)	0.00 (0.00–16.98)						
Mean (range)	205.05 (0.00–9968.00)	179.42 (0.00–8735.00)	341.45 (0.00–9968.00)	159.60 (0.00–7173.00)			71.12 (0.00–763.30)	198.88 (0.00–8735.00)						

IFN, interferon; IL, interleukin; IQR, interquartile range; TAC, tacrolimus; TCS, topical corticosteroids. [a]Statistical significance was set at $P < 0.05$. [b]Mann-Whitney *U*-test.

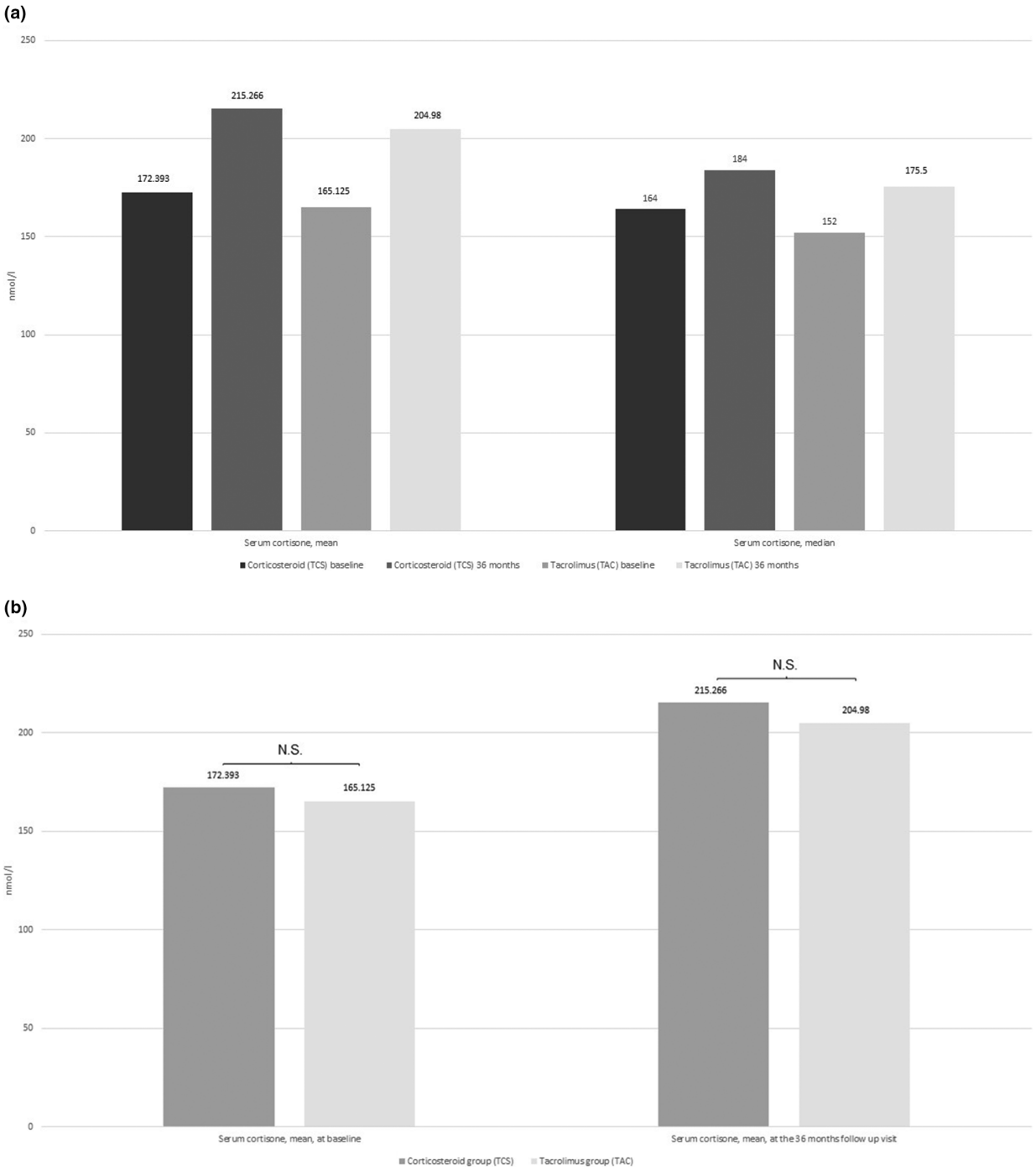

Figure 3 (a) Serum cortisone levels (nmol/L) at baseline and 36 months in young children with moderate to severe atopic dermatitis treated with tacrolimus (TAC) or topical corticosteroids (TCS); (b) group comparisons of serum cortisone levels at the same timepoints.

was normal at subsequent visits. There were no significant differences between the groups at baseline ($P = 0.36$ 95% CI 0.25–0.40) or at 36 months ($P = 0.23$, 95% CI 0.18–0.29) (Table 3, Fig. 3b).

Blood eosinophil counts

In both groups, blood eosinophil counts were similar at baseline and at 36 months. The median blood

eosinophil count was 0.44×10^9/L (IQR 0.25–0.68) at baseline and 0.37×10^9/L (IQR 0.23–0.71) at 36 months In the TCS group, while in the TAC group, it was 0.41×10^9/L (IQR 0.26–0.69) and 0.37×10^9/L (IQR 0.23–0.76) at 36 months. There were no significant differences between the treatment groups ($P = 0.56$, 95% CI 0.49–0.65) (Table 1).

Discussion

TAC ointment has been used for nearly 20 years for the treatment of AD in adults and children.[14] TAC 0.03% has licensed approval for children aged 2–15 years, although off-label use of the more potent 0.1% ointment is common because of its higher efficacy.[15,16] However, there are still only limited clinical data on the use of topical TAC (any dose) for children aged < 2 years of age and for TAC 0.1% ointment in children aged < 16 years.[17]

In our cohort of young children with moderate to severe AD, both TAC 0.03% and 0.1% ointments and hydrocortisone acetate 1% and hydrocortisone-17-butyrate 0.1% creams were effective and safe topical treatments. Similar observations have been reported previously, mostly in toddlers and older children (aged 2–15 years). Doss *et al.*[18] conducted a noninferiority study on 479 children aged 2–15 years with moderate to severe AD, comparing TAC 0.03% and fluticasone 0.005% (moderate-potency TCS) ointments, and found that the efficacy of TAC 0.03% ointment as a second-line treatment was not inferior to that of fluticasone 0.005% ointment, with similar clinical improvement. Reitamo *et al.*[19] performed a 2-week pharmacokinetic study in 53 infants aged 3–24 months with TAC 0.03% ointment, and reported that 97% of the blood samples assayed contained TAC concentrations of < 1 ng/mL, which was comparable to the levels seen in older children and adults. The same children were then allowed to participate in a 2-year safety study, which showed significant clinical improvements, with treatment tolerability and TAC blood levels comparable to those of older children or adults.[20] There are a few studies in which TAC 0.1% ointment has been used in children. Remitz *et al.*[21] treated children aged 2–15 years with TAC 0.03% ointment and if needed, TAC 0.1% ointment, with follow-up durations of up to 4 years. They found that about 70% of the patients needed the more potent TAC 0.1% ointment, and no safety concerns were observed.[21]

To our knowledge, the current study is the first comparative long-term study comparing TAC 0.03% and 0.1% ointments with TCS in children aged 1–3 years. In addition, the follow-up period of 36 months was relatively long compared with former studies. We wanted to focus particularly on safety issues such as infection rate, growth parameters and vaccination responses, as these are clinically relevant because there are concerns about the use of TAC ointment in young children, which may have limited its usage in paediatric AD up to now.

In both treatment groups, only minor AEs (mainly skin burning sensation after TAC application) were noted; any withdrawals were mostly due to noncompliance or to the family moving away. We observed some SRIs and other non-SRIs (mainly respiratory infections), but there were no significant differences in these between the TAC and TCS groups. Although the growth parameters were below the Finnish SD both at baseline and at the end of follow-up, all patients in both treatment groups showed a consistent increase in height and weight, taking them closer to the SD of Finnish children. Our observations support the results of former studies, which have shown that topical TAC used in young children with AD does not impair physical growth and generally does not lead to a higher incidence of infections.[22,23]

Pathological vaccination responses were observed in 28 patients (18.4%), but there were no significant differences between the two treatment groups. There have been previous reports on vaccination responses in children with AD, which have not found any signs that topical AD treatments decrease vaccination responses. Schneider *et al.*[24] investigated immune responses to the varicella vaccine in children with AD compared with healthy controls, and found similar responses in both groups. In another open-label study with 23 children with AD, Stiehm *et al.*[25] observed that TAC 0.03% ointment had no effect on the serological responses to pneumococcal vaccine, or on T- and B-cell-mediated immune responses. In addition, Hofman *et al.*[26] showed in a controlled clinical trial that immune responses to meningococcal vaccine were comparable in children that were treated with either TAC 0.03% ointment or hydrocortisone 1% cream. Thus, topical AD treatments do not seem to influence immediate responses to vaccination, immune memory, or humoral and cell-mediated immunity.

Systemic absorption of TAC after topical treatment has been shown to be very low in AD, and occurs mainly in patients with active and severe disease.[27] After response to therapy, systemic TAC absorption stops.[28] In our study cohort, nine patients of the TAC group (11.6%) showed detectable TAC blood concentrations, but these were all low (1.5–5.6 μg/L), and most of the patients had used TAC ointment on the

sampling day, contrary to instructions. TAC levels were undetectable in control samples.

Mild- and moderate-potency TCS have been shown to be safe to use in young children if they are used in the short term; however, data on long-term safety are limited. In their recent meta-analysis, Axon *et al.*[29] found no evidence of safety issues in children when TCS were used intermittently. The risk for systemic absorption, immunosuppression and adrenal insufficiency seems to be very low.[30] Davallow Ghajar *et al.*[31] conducted a meta-analysis of serum cortisone concentrations in small children with AD during therapy with mild- and moderate-potency TCS; the percentage of laboratory-confirmed adrenal insufficiency with TCS use was 2.7% but none of the cases had corresponding clinical symptoms. Similarly, in our cohort, no clinical signs of adrenal insufficiency were observed, and serum cortisone concentrations were similar in both the TCS and TAC groups. Our observations support the current understanding that mild- and moderate-potency TCS are safe to use intermittently in young children.[32]

The cytokines, IL-4, IL-10, IL-13 and IL-31, are considered important markers of enhanced T helper (Th)2 inflammation seen in AD.[33] Recent studies have highlighted the importance of an immunological Th2 shift and its relation with the skin immune system, epidermal barrier and the cutaneous microbiome in the pathogenesis of AD in infants and children.[34] IFN-γ has recently been linked to the natural killer cell–innate lymphoid cell 2 inhibitory axis, which may be a regulatory mechanism of innate immunity and constitute a part of the cutaneous immunological barrier.[35] Many novel cytokine discoveries have now been translated clinically into more targeted therapies.[36] We did not observe significant changes in the serum concentrations of IL-4, IL-10, Il-13, IL-31 or IFN-γ in our study cohort (Table 4). In both the TCS and TAC groups, the concentrations of IL-4, IL-13 and IL-31 increased from baseline to 36 months, but the changes were not statistically significant, while IL-10 and IFN-γ levels did not show any consistent patterns or significant changes. To our knowledge, serum concentrations of the investigated cytokines have not been formerly characterized to this extent in young children with AD.

The main limitation of the present study is the relatively small patient cohort (n = 152), due to this being a single-centre investigator-initiated clinical study with young children and relatively frequent follow-up visits. In addition, there were 27 withdrawals (12 in the TCS group and 15 in the TAC group) registered during the follow-up period. The study cohort represented selected patients of a tertiary-care centre, and we could not analyse long-term data on child development, growth parameters and AD disease course because the follow-up time was limited to 36 months. Possible delayed effects after the end of the follow-up period, such as developmental problems or malignancy incidence could not be investigated. Another limitation was that the infection data were retrieved retrospectively at each follow-up visit, and that these data were based mainly on information from parents/caregivers, thus the type, severity and treatments of infections could not be confirmed completely from health record data or other documented sources.

Conclusions

Topical TAC (0.03% and 0.1% ointments) and TCS (mild and moderate potency) were safe to use in young children with moderate to severe AD and showed similar efficacy and generally a good safety profile. No safety issues were observed in the use of the more potent TAC 0.1% ointment in small children with AD.[37] In many cases of moderate to severe AD in young children, the use of moderate-potency TCS or TAC 0.1% ointment is necessary to achieve appropriate therapeutic responses.[38,39] As shown in our patient cohort, courses of TAC 0.1% ointment seem to be a good and safe alternative in small children who need recurrent courses of moderate-potency TCS.[40] We consider it reasonable to use TAC 0.03% ointment in younger children when their AD is not sufficiently controlled with mild TCS. If needed, TAC 0.1% ointment can be used as a second- or third-line treatment in children, because it clearly shows higher efficacy than the TAC 0.03% ointment. This is often required especially for lichenified lesions on the limbs. There is a need for more studies on optimal course durations, effects of long-term and intermediate use of TAC 0.03% and 0.1% ointments and of moderate-potency TCS in young children with moderate to severe AD.[41,42]

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What's already known about this topic?

- There is a risk of undertreatment in paediatric AD because of safety concerns about the use of topical calcineurin inhibitors or moderate-potency TCS.
- Topical TAC is used off-label in young children, but data are limited for children < 2 years of age and for long-term treatment.

What does this study add?

- In our prospective clinical study with 152 young children aged 1–3 years, TAC 0.03% and 0.1% ointments and mild- and moderate-potency TCS were all effective and showed similar safety profiles in the treatment of AD.
- TAC 0.03% could be a useful steroid-sparing alternative.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Characteristics of patients with pathological vaccination responses in the topical corticosteroid group (TCS), and their serum cytokine levels and infections.
Table S2. Characteristics of patients with pathological vaccination responses in the topical tacrolimus group (TAC), and their serum cytokine levels and infections.

