

ORIGINAL ARTICLE

Clinical Allergy

Temperature-controlled laminar airflow (TLA) device in the treatment of children with severe atopic eczema: Open-label, proof-of-concept study

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Summary

Background: Children with severe, persistent atopic eczema (AE) have limited treatment options, often requiring systemic immunosuppression.

Objective: To evaluate the effect of the temperature-controlled laminar airflow (TLA) treatment in children/adolescents with severe AE.

Methods: We recruited 15 children aged 2-16 years with long-standing, severe AE and sensitization to ≥ 1 perennial inhalant allergen. Run-in period of 6-10 weeks (3 visits) was followed by 12-month treatment with overnight TLA (Airsonett[®], Sweden). The primary outcome was eczema severity (SCORAD-Index and Investigator Global Assessment-IGA). Secondary outcomes included child/family dermatology quality of life and family impact questionnaires (CDQLI, FDQLI, DFI), patient-oriented eczema measure (POEM), medication requirements and healthcare contacts. The study is registered as ISRCTN65865773.

Results: There was a significant reduction in AE severity ascertained by SCORAD and IGA during the 12-month intervention period ($P < .001$). SCORAD was reduced from a median of 34.9 [interquartile range 28.75-45.15] at Baseline to 17.2 [12.95-32.3] at the final visit, and IGA improved significantly from 4 [3-4] to 2 [1-3]. We observed a significant improvement in FDQLI (16.0 [12.25-19.0] to 12 [8-18], $P = .023$) and DFI ($P = .011$), but not CDQLI or POEM. Compared to 6-month period prior to enrolment, there was a significant reduction at six months after the start of the intervention in potent topical corticosteroids ($P = .033$). The exploratory cluster analysis revealed two strongly divergent patterns of response, with 9 patients classified as responders, and 6 as non-responders.

Conclusion and Clinical Relevance: Addition of TLA device to standard pharmacological treatment may be an effective add-on to the management of difficult-to-control AE.

KEYWORDS

aeroallergen exposure, allergen avoidance, atopic eczema, environmental control, particle reduction, temperature-controlled laminar airflow

1 | INTRODUCTION

The prevalence of atopic eczema (AE) in children and adolescents has been reported to be as high as 24%, with up to a quarter of patients having moderately severe disease, and 2%-7% being severely affected.¹ Persistence of early-life AE beyond the age of 8 years occurs in 20% of patients, and in 5% for ≥ 20 years; however in children with severe disease, persistence rates are above 50%.¹ Comorbidities, such as allergic rhinoconjunctivitis and asthma, are common,² particularly amongst the more severely affected children, and have additional adverse impact on already impaired quality of life of patients and their families.^{3,4} Healthcare costs associated with AE are high, with an estimated 3 billion dollars being spent per annum in the United States.^{1,4} Topical anti-inflammatory medications and emollients remain the mainstay of treatment, which is increasingly intensive and complex as the severity increases, in particular among patients with comorbidities.⁵ Children with persistent severe AE often require systemic immunosuppression and/or systemic corticosteroids, with associated significant long-term side-effects. New emerging monoclonal antibody treatments are promising,⁶ but are expensive, and potential long-term risks in children are unclear. There remains a great need for novel effective treatments, particularly amongst patients at the severe end of the AE spectrum.

Sensitization rates to inhalant allergens among patients with AE are high,⁷ and there is evidence that aeroallergen exposure can trigger AE exacerbations.⁸⁻¹¹ However, studies investigating the use of allergen avoidance and allergen-specific immunotherapy in the treatment of AE have yielded mixed results, and these interventions are currently not recommended in the disease management.^{12,13} A recent meta-analysis of seven studies of house dust mite (HDM) allergen avoidance highlighted the very low-quality evidence currently available,¹² with no studies to date investigating the effect of environmental control among patients with severe AE. We hypothesized that effective reduction in exposure to inhaled allergens and other environmental triggers remains a potentially effective intervention which may reduce disease severity amongst sensitized patients with severe AE. One intervention that has been shown to markedly reduce personal exposure to inhaled allergen, and other inhaled particles are the temperature-controlled laminar airflow (TLA) device.^{14,15} TLA reduces the allergen and particle load in the patients' breathing zone by vertically displacing the contaminations originating from the bed and the room environment¹⁶ and has been shown to be effective in the treatment of atopic asthma.^{16,17} Therefore, to address our hypothesis, we undertook an open-label, proof-of-concept study of the efficacy of a TLA device as an add-on to pharmacological management of children and adolescents with very severe AE.

2 | METHODS

2.1 | Study design and oversight

This open-label, proof-of-concept study was conducted in a single centre, a tertiary referral Pediatric Allergy Unit at St Mary's Hospital, London, UK. The protocol development, data collection and analyses

What is already known about this topic?

Aeroallergen exposure control measures, such as mite-proof bedding, acaricides, air-filtration devices, are of limited benefit in atopic eczema. Overnight temperature-controlled laminar airflow treatment reduces personal allergen exposure and can improve severe atopic asthma.

What does this article add to our knowledge?

Reduction of allergen and particle exposure in the breathing zone using overnight temperature-controlled laminar airflow treatment may substantially improve severe atopic eczema.

How does this study impact current management guidelines?

Overnight TLA device treatment could be considered as an effective add-on to standard pharmacological management of difficult-to-control atopic eczema. A randomized controlled trial is urgently required.

were completed by investigators. The manufacturer of TLA device (Airsonett AB, Ängelholm, Sweden) provided the devices free of charge, but was not involved in the study design or the interpretation of the results. The protocol was approved by the local research ethics committee. All parents provided written informed consent and children assent. The study is registered as ISRCTN65865773.

2.2 | Patients

We enrolled 15 children and adolescents aged 2-16 years with severe AE. AE severity was defined as persistent uncontrolled AE, despite documented high medication requirement. Participants were skin prick tested to HDM, cat, dog, pollen and other allergens if applicable (Stallergenes, Paris, France) and classed as sensitized if the weal diameter was at least 3 mm greater than the negative control. Only children sensitized to at least one perennial inhalant allergen were recruited. Prior to enrolment, all patients underwent a full multidisciplinary assessment and intensive education programme about the treatment plan (including allergen reduction) for their eczema, and relevant comorbidities (food allergy, asthma/whoeze, allergic rhinoconjunctivitis). During the study, the care of all study participants was provided by one clinician (CG), to minimize variability. Medication management plan was based upon current best-practice clinical guidelines.^{18,19}

2.3 | Study intervention

Each study participant received an active TLA device, which was installed in their bedroom. The mode of action of the device is

described in the supplementary appendix. Participants were asked to turn their device on when they went to bed each night, and off in the morning. We assessed adherence by an electronic counter which recorded the total hours of use.

2.4 | Study assessments and procedures

Overview of the trial design is shown in Figure 1. Baseline evaluation included questionnaires on demographics, past medical and family history, sleeping arrangements and pet exposure.

Following the baseline assessment, participants completed a run-in period of 6-10 weeks to ensure that their treatment was medically optimized prior to intervention. During the run-in, patients attended three study visits (Baseline Visit, Visits 1 and 2).

Run-in period was followed by a 12-month active treatment period, during which patients attended eight follow-up visits (day 3, 1, 2, 3, 4, 6, 9 and 12 months). AE severity at each visit was documented using the Scoring Atopic Dermatitis (SCORAD) Index^{20,21} and Investigator Global Assessment (IGA, 5-point scale).²² Patient-reported outcomes and quality of life measures included the Children's Dermatitis Quality of Life Index (CDQLI), Infant Dermatitis Quality of Life Index (IDQoL; age < 4 years), Family Dermatitis Life Quality Index (FDQLI), Dermatitis Family Impact Questionnaire (DFI) and Patient-oriented Eczema Measure (POEM).²³⁻²⁷ For all participants, outcome assessments were performed by the same physician (CG) at all study visits.

We ascertained cumulative quantities of prescribed medications and numbers of healthcare contacts for AE by obtaining prescription records from the hospital pharmacy, child's primary care physician (general practitioner-GP), and from other specialists, for the period of 12 months before TLA treatment was commenced, and for the 12-month intervention period. One healthcare contact was recorded for each GP prescription for eczema, any other AE-related doctor or specialist nurse contact and for each day spent as a hospital inpatient.

In 12 participants, we determined the effect of TLA device on overnight particulate exposure in patients' breathing zone (Visits 3 and 5). Children slept under the TLA device for two nights, one with the device turned off and one with the device turned on. We continuously sampled the air from the patients' breathing zone (10-12 cm above forehead) for a period of 7 hours, and quantified total

airborne particles with aerodynamic equivalent diameter (AED) ≥ 0.5 to $\geq 10 \mu\text{m}$ using a laser AEROTRAK 9306 Particle Counter (TSI Inc, Shoreview, MN).

2.5 | Efficacy outcomes

The primary efficacy end-point was the change in eczema severity (ascertained by SCORAD Total, and Investigator Global Assessment) during the 12-month intervention period compared to baseline.

Secondary end-points included changes in objective and subjective SCORAD, eczema-related quality of life (patient and family), medication requirements and healthcare utilization (unscheduled healthcare visits).

2.6 | Statistical analysis

Detailed description of the statistical analysis is presented in the Supplementary Appendix. Missing data were imputed using the median trajectory. We used nonparametric tests throughout our analyses. We used Friedman test to detect the effect of the treatment and post hoc Wilcoxon signed-rank test to ascertain where the significant differences lie between each pair of observations. All results are presented as medians and interquartile range (IQR). We ascertained change compared to the mid-point run-in visit (Visit 1), unless otherwise indicated. As pilot studies are likely to be underpowered for hypothesis testing at the commonly used significance level of $\alpha = .05$, and given that we aimed to assess preliminary evidence of the efficacy of TLA treatment, we considered a significance level of $\alpha = .1$,²⁸ and corrections for multiple comparisons were not implemented. To provide complete information, *P*-values adjusted by the Benjamini-Hochberg false discovery rate (FDR) are included in the Supplementary Appendix.

As per recent recommendations for reporting of the pilot trials,²⁹ in addition to statistical hypothesis testing of changes in end-points described above, we also assessed confidence intervals (CIs) for the treatment effect with respect to the minimum clinically important difference (MCID), which for SCORAD has been shown to be equal to 8.7 [25]. We calculated the mean difference in SCORAD between visit 1 and visit 12, along with a range of CIs (70%-95%). To ascertain whether there was a significant effect of intervention, we

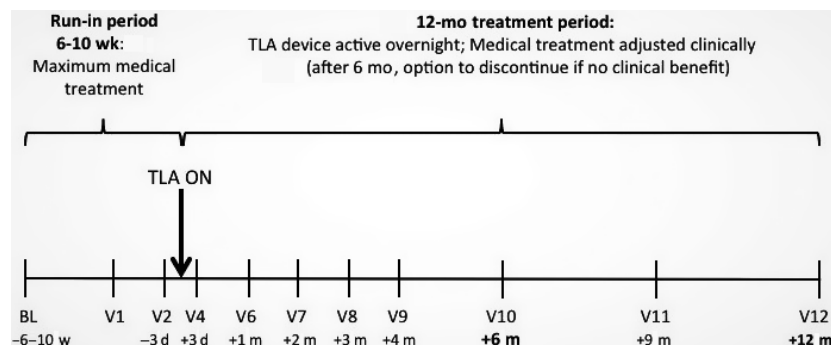


FIGURE 1 Study timeline.

BL = Baseline visit, V = Visit, w = weeks, d = days, m = months; Visit 3 and 5 were home visits to ascertain overnight particle exposure in the participants' bedrooms

compared the CIs with a “zone of clinical indifference,” which we defined as $0 + \text{MCID}$.²⁹

2.6.1 | Exploratory analysis to identify responders to treatment

We used cluster analysis for longitudinal data to identify whether there are subgroups of patients with similar response to TLA treatment. We applied a longitudinal extension of the k-means algorithm (Kml) to SCORAD data, and used the Calinski-Harabasz criterion to determine the optimal number of clusters.³⁰ Results for post hoc longitudinal cluster analysis were obtained through the Kml package developed in the software environment R.³¹

Statistical analyses were carried out using R (<http://www.r-project.org>), SPSS 23.0 (IBM, Armonk, USA) and STATA 14 (StataCorp, College Station, USA).

3 | RESULTS

3.1 | Patients

We recruited 15 children aged 2-16 years (median 10 years [IQR 7.5-12]). All participants had severe long-standing AE, with a median onset at the age of 3 months [1.5-6] and duration of 116.5 months [82-145.5]. Table 1 summarizes the comorbidities and AE severity for each child at enrolment, as well as the information on pet sensitization, pet ownership and HDM control measures taken by the family. All participants had allergic rhinoconjunctivitis, 11 of 15 had asthma or intermittent wheezing, and 14 of 15 had confirmed food allergy. All 15 were sensitized to HDM, 14 of 15 to pollen (tree and/or grasses), 13 of 15 dogs, 14 of 15 to cats, 11 of 15 to moulds. Medication requirements and healthcare utilization were very high: in the 12-month period prior to recruitment, prescriptions per patient were issued for a median of 6550 g [2600 g-13 750 g] of emollients, 580 g [180-945] of topical corticosteroids (including ultrahigh and/or high potency), 510 g [180-630] of topical calcineurin inhibitors and 28 [14-49] days of antibiotic treatment; 11 of 15 subjects required inpatient hospital admission for eczema management. To manage the medical care for their child, 5 of 15 parents had to give up work.

During the run-in period (median 7.1 weeks, range 6-10 weeks), patients were using maximum topical and additional treatments. The severity of their AE remained high (SCORAD 34.9, IGA 4), and we observed no significant changes in severity and other outcomes between the three run-in visits (except for FDLQI).

3.2 | The effect of TLA on overnight particulate exposures in the breathing zone

We observed a highly significant reduction in airborne particle numbers with TLA treatment across all particle sizes ($P < .001$, Table E1), with a 2600-fold (>99%) reduction in exposure to particles of $\text{AED} > 5 \mu\text{m}$ (Figure S1).

3.3 | Primary end-points

Figure 2 shows trajectories of primary outcome measures (SCORAD and IGA) from Baseline to Visit 12. There was a highly significant reduction in eczema severity ascertained by both measures during the 12-month intervention period (Friedman test $P < .001$, Table S2).

Results of Wilcoxon signed-rank test are presented in Table S3 and show no significant changes in SCORAD and IGA during the run-in period, with a significantly lower AE severity for almost all time-points during the treatment phase compared to the pretreatment values. We observed significant improvements as early as 3 days after commencing intervention (Figure 2, Table S3). Despite some fluctuation, these improvements were sustained over the entire 12 months. SCORAD was reduced from 34.9 [28.75-45.15] at Visit 1 to 17.2 [12.95-32.3] at the final visit, $P = .015$, and IGA improved significantly from a median of 4 [3-4] to 2 [1-3], $P = .001$.

Figure S2 shows a range of CIs for the mean difference in SCORAD between Visit 1 and Visit 12 (12 months). None of the CIs crossed both zero and the MCID; 95% CI excluded 0 and crossed the MCID, while all other CIs (70%-90%) excluded both 0 and MCID. This suggests that at all CI levels, there is evidence of a potentially clinically important treatment difference.²⁹

3.4 | Secondary end-points

Trajectories of secondary outcomes from Baseline to Visit 12 are shown in Figure 3. Through the 12-month intervention period, there was a significant improvement in all secondary severity outcomes, FDQLI and DFI, but not CDQLI ($P = .13$) and POEM ($P = .60$) (Table S2).

Compared to Visit 1, FDQLI at Visit 12 was significantly lower (16.0 [12.25-19.0] to 12 [8-18], $P = .02$), suggesting improvement, as did DFI ($P = .01$).

Figure S3 shows data on medication use and healthcare utilization. We examined the differences at comparable time-points (± 12 , ± 6 , ± 3 and ± 1 month from the start of intervention). Although graphical inspection of Figure S3 suggests a reduction in these outcomes, the analysis has shown that this was statistically significant only for potent topical corticosteroids ($P = .033$) and hospital contact for eczema (marginal, $P = .081$) 6 months after the start of the treatment (Table S4).

Results of all analyses adjusted for Benjamini-Hochberg False Discovery Rate are presented in Tables S5-S6 and confirm statistically significant improvements in SCORAD and IGA at 12 months compared to Visit 1 ($P = .05$ and $P = .005$, respectively).

3.5 | Adherence and acceptability

The TLA device was generally acceptable; 14 of 15 children were content to have the device in situ for the duration of the study, and one participant returned the device after 6 months due to the perceived lack of benefit. Participants used the device for a median of 7.69 hours per night [6.91-8.51; data from 14/15 participants]. One

TABLE 1 Characteristics of the study population at enrolment: medical conditions and systemic therapy requirements

No.	Age, years	Ethnicity	CoMorbidity	HDM control measures	Pet sensitization and ownership	Systemic Immunosuppression ever	Oral Prednisolone ever	SCORAD during Run-In (BL, V1, V2)	SCORAD at V12	Cluster
1	M 10	Asian	ARC, mild A, FA	Mattress cover	Cat+, Dog+ Never owned	Azathioprine (failed), 6 mo Methotrexate—current	Yes, previously	52.5, 46.8, 24.2	10.2	A
2	F 9	Asian	Severe ARC, FA	Carpets removed	Not sensitized, never owned	No	No	45.6, 47.5, 43.2	28.3	B
3	F 13	Black	Severe A, ARC, FA	Carpets removed	Cat+, Dog+ Owned cat- removed	No	Only for asthma	52.4 (19.5 ^a , 58.5); ^a oral steroid for asthma)	12.9	A
4	F 15	Asian	Severe ARC, FA, A	Mattress, Pillow cover Carpets removed	Cat+, Dog+ Never owned	No	Yes, previously	34.3, 26.8, 40.4	17.3	A
5	M 14	Caucasian	Severe VKC, A, FA	Mattress, Pillow, Duvet cover Carpets removed	Cat+, Dog+ Never owned	No	For asthma and VKC	28, 34.9, 46.4	14.1	A
6	M 5	Caucasian	A, ARC, FA	Mattress cover	Cat+, Dog+ Dog present since birth ^b	4-month Ciclosporin—current (failing)	16 wk—current weaning	75.5, 51.1, 51.5	43	B
7	F 4	Mixed race	A, ARC, FA	Mattress cover	Cat+, Dog+ Owned dog- removed	No	11 wk—current weaning	21.6 ^b , 32.6, 50.9 (^b oral steroid for eczema)	51	B
8	M 13	Caucasian	ARC, FA	Mattress, Pillow, Duvet cover Carpets removed	Cat+, Dog+ Never owned	No	No	36.7, 39.5, 23.9	8.9	A
9	M 10	Caucasian	ARC, FA, intermittent wheeze	Mattress, Pillow, cover Carpets removed	Cat+, Dog+ Cat removed Dog acquired after severe AD onset ^c	Failed Azathioprine, Ciclosporin, Methotrexate	Yes, previously	7.9 ^c , 23.6, 49.7 (^c recent hospital admission for eczema)	41.9	B
10	M 8	Caucasian	ARC, FA, A	Mattress, Pillow, cover	Cat+, Dog+ Owned dog- removed	Failed Azathioprine	Yes, previously	39.8, 30.7, 46.5	13	A
11	M 12	Caucasian	ARC	Mattress, Pillow, cover	Cat+, Dog+ Owned dog- removed	Failed Azathioprine, failed UV therapy	Yes, previously	42.4, 31.3, 40.8	16.2	A
12	M 8	Asian	A, ARC, FA	Mattress cover	Cat+ Never owned	No	Only for asthma	50.9, 54.5, 46.3	17.2	B
13	F 2.5	Mixed race	ARC, FA, intermittent wheeze	None	Cat+, Dog+ Never owned	No	No	39.9, 26.7, 20.7 (steroid occlusion under wraps)	11.2	A

(Continues)

TABLE 1 (Continued)

No.	G	Age, years	Ethnicity	CoMorbidities	HDM control measures	Pet sensitization and ownership	Systemic Immunosuppression ever	Oral Prednisolone ever	SCORAD during Run-In (BL, V1, V2)	SCORAD at V12	Cluster
14	M	10	Caucasian	A, ARC, FA	Mattress cover	Cat ⁺ , Dog ⁺ Dog removed	Failed Azathioprine, Cyclosporin, Methotrexate, failed UV therapy	Yes, previously	40.5, 37, 43.9	22.1	B
15	F	15	Black	A, ARC, FA	Previous covers, not now Carpet removed	Cat ⁺ , Dog ⁺ Never owned	No	Only for asthma	59, 43.5, 46.4	36.3	A

G, gender; ARC, allergic rhino-conjunctivitis; A, asthma; FA, Food Allergy; VKC, vernal keratoconjunctivitis; Age, age at enrolment; 4 m, 4 mo; HDM, house dust mite.

^bNo change in symptoms when holiday away from dog.

^cNo change in symptoms when dog acquired; Cat or Dog sensitization: either specific IgE > 0.35 and/or skin prick test ≥ 3 mm), Cluster A = responders, Cluster B = non-responders.

A=Asthma, and Cluster A= responders.

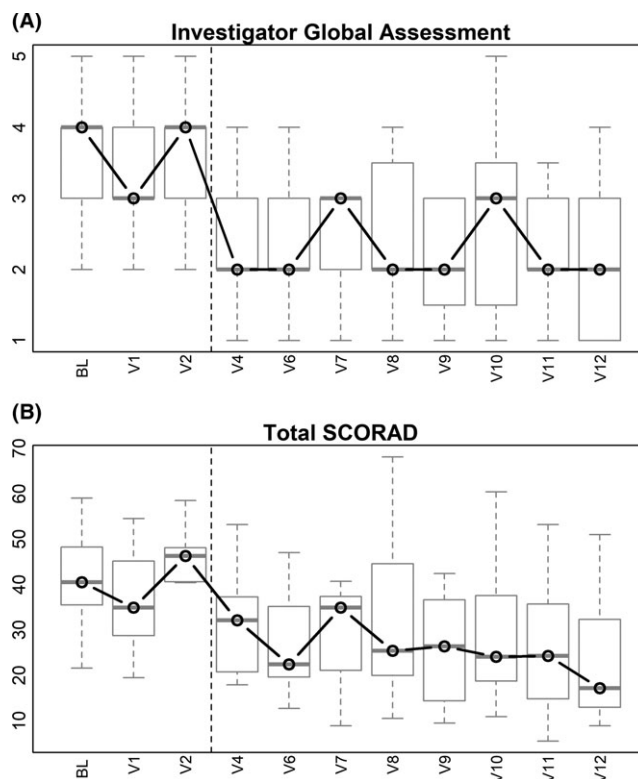


FIGURE 2 Trajectories of the primary outcome measures from Baseline (–10 to –6 wks) to Visit 12 (+12 months). A, Investigator Global Assessment (IGA). B, SCORAD.

patient was initially troubled by the sound (TLA use 4.17 h/night), and one disclosed intermittent cosleeping with a parent (TLA use 4.32 h/night).

3.6 | Exploratory cluster analysis to identify the patterns of response to treatment

A two-cluster model provided optimal solution for the data set in the longitudinal analysis of the changes in SCORAD over the 12-month treatment period. Based on the pattern of response to intervention (Figure 4), we assigned the clusters as: Cluster A ($n = 9$), Responders and Cluster B ($n = 6$), Non-responders. Amongst patients in Cluster A, the mean trajectory had a steady decreasing trend over time, whilst in subjects in Cluster B, the mean trajectory showed no change over time. The two trajectories started at similar scores, but diverged over the treatment period. There were significant differences between the two clusters in IGA, and all secondary outcomes (Figure S4).

To capture factors which may differentiate the cluster membership, we compared the characteristics between the two groups (Table S8). Patients in Cluster A (Responders) were older (11.75 [9.7–13.4] vs 9 [6.58–9.9] years) and had a longer duration of eczema and allergic comorbidities. Patients in Cluster B had a higher prevalence of other medical problems (4 of 6 psychological/behavioural). Two strongly divergent patterns were detected for oral antibiotics, with much higher number of days of use among non-responders (Figure S5).

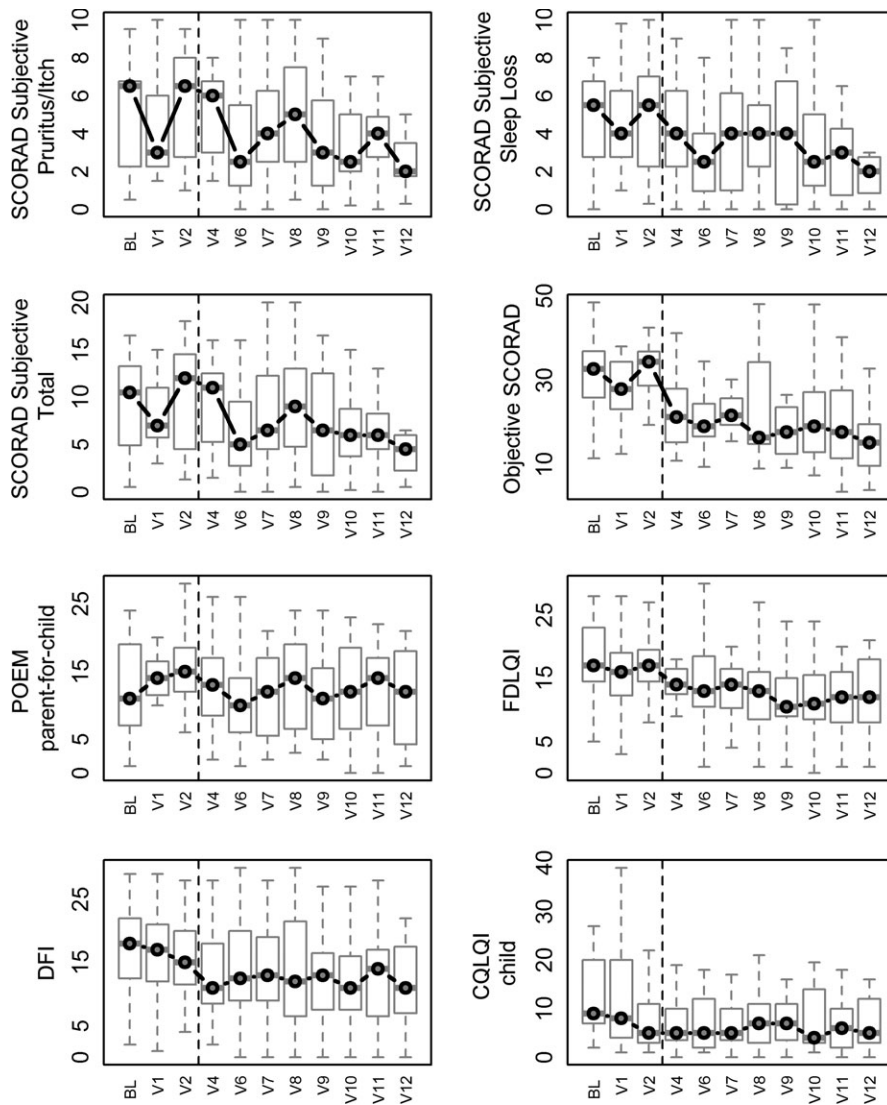


FIGURE 3 Trajectories of secondary outcome measures from Baseline (–10 to –6 wks) to Visit 12 (+12 mo)

4 | DISCUSSION

In this proof-of-concept study, the treatment with TLA device in children with very severe AE led to a rapid and significant improvement in eczema severity, which was accompanied by a reduction in medication use, and was sustained over the period of 12 months. We also observed a significant improvement in some patient-reported outcomes and quality of life measures (FDQLI and DFI), but not in CDQLI and POEM. There were no treatment-related adverse effects, and the device was easy to use.

The main limitation of our study is that it is open-label proof-of-concept, rather than randomized, placebo-controlled trial. As such, our study was not formally powered to assess the effect, but provides evidence to enable a larger definitive trial to be undertaken. However, the range of effects we describe is of interest. We recruited children with very severe AE from the tertiary referral service, which is a patient group for which there is very little evidence to inform management strategies. During the run-in period, patients attended three visits to ensure optimum treatment and adherence,

and achieve as good a control of disease as possible. We cannot exclude the possibility that improved adherence to medications during the treatment period has contributed to some of the improvement which we observed. However, we observed no significant changes in AE severity over the 6–10 weeks of run-in, which makes it unlikely that the later improvements during the intervention phase were due to intensified care, supervision or adherence.

Without a control group, we may have missed spontaneous improvements in AE morbidity. However, this appears unlikely, given the lifelong nature of patients' severe disease, with a median onset of AE at the age of 3 months among subjects in our study. Prior to the inclusion into this study, we observed little changes in AE severity among study participants during a long period of intensive ambulatory multidisciplinary care, which for most patients covered almost entire duration of their disease (median ~10 years).

For some outcomes and time-points, the improvement during the intervention period did not reach formal statistical significance. However, the trends in all outcomes pointed in the same direction that the TLA treatment improved AE control in these severely ill

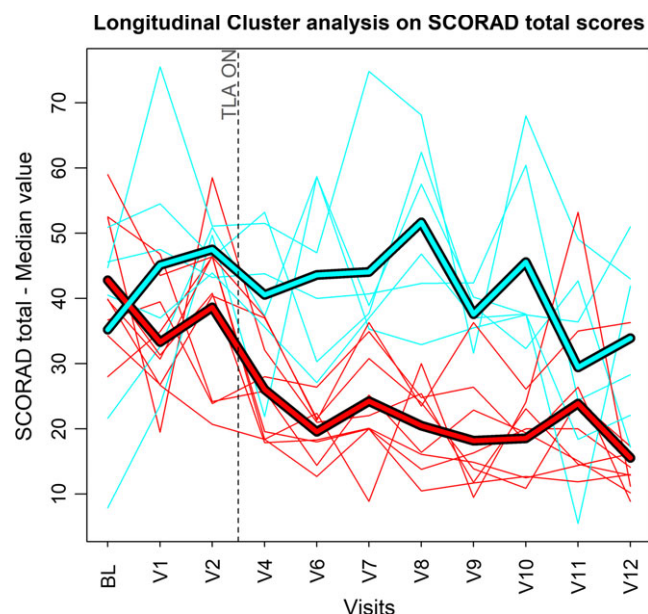


FIGURE 4 Longitudinal cluster analysis on SCORAD total score: Mean trajectories of the 2-clusters solution. Cluster A (red line) = Responders (R); Cluster B (blue) = Non-responders (NR); green line: TLA start-point

patients. The lack of statistical significance can be explained by the heterogeneity of patients' responses to treatment, which was suggested by our cluster analysis, and a relatively small sample size. We wish to emphasize that given the sample size, and the inclusion of only subjects with a very severe disease, any inference about the potential effectiveness of TLA device is limited to this group of patients.

We do not have data to confirm the mechanisms to explain the observed effects. The purported mode of action of TLA is to reduce the overnight exposure to inhalant allergens during sleep.^{14,16,17} We have shown in this study that TLA device in patients' homes significantly reduces personal exposure to particles in the size range encompassing all common aeroallergens.³²⁻³⁴ The magnitude of the reduction was similar to that seen in the experimental chamber studies,¹⁴ confirming that major reduction in exposure in real life is possible. Allergen challenges in AE patients have shown that exposure to sensitizing allergens via inhaled route induces flares of eczema,⁸⁻¹¹ and reduction in allergen exposure may be the mechanism behind the effects observed in our study. However, it remains unclear which other factors in the home "exposome" may be relevant for AE severity. For example, there is ample evidence supporting the adverse health effects of air pollution and environmental tobacco smoke (ETS) exposure, and both of these exposures may have a negative impact on AE severity.^{35,36} It should be noted that TLA reduces exposure to all particles in the inhaled air which can be deposited in the respiratory tract.^{14,15} This may reduce personal exposure to a number of pollutants, irritants and other allergens (such as food proteins which are present in house dust^{37,38}). Thus, potentially important exposures which may be biologically relevant and related to AE severity, and which could be reduced by TLA treatment, include

indoor air pollutants, ETS exposure, other allergens such as staphylococcal enterotoxin,³⁹⁻⁴¹ other micro-organisms⁴² and fungi.^{42,43}

It is unclear why a reduction in allergen and/or other inhaled exposures for only a part of the day (6-8 hours during the night) might have a clinical effect. The bed is a place of close contact with a rich allergen reservoir.^{43,44} Convection and flow of warm air transport particle-laden air towards the breathing zone, contributing to potentially higher personal exposure overnight compared with usual daily activities.⁴⁵ This process is reversed by the TLA device.¹⁵ Although we do not know enough about the effect of overnight exposures on disease activity, one might hypothesize that allowing a break from exposure to allergens and/or other particles for part of the 24-hour period may allow some recovery, and facilitate immunological changes. Bräuner et al have shown that reduction of particle exposure using air filtration improved microvascular function.⁴⁶ In addition, the contribution of circadian rhythm cannot be excluded.⁴⁷

Our cluster analysis suggested that approximately two-thirds of the study participants have responded to the intervention, with no evidence of benefit in the remaining third. Non-responders reported significantly more pruritus and sleep disturbances than responders. Clinically, it appeared that non-responders had more severely affected hands and feet, but this observation would have to be confirmed in a larger study. Also, much higher use of oral antibiotics among non-responders may indicate that patients with infection-induced exacerbations of AE may not respond to TLA treatment.

In conclusion, our findings suggest that the addition of TLA device to the standard pharmacological treatment may be an effective add-on to the management of children with difficult-to-treat, severe atopic eczema. We observed improvements in both objective and subjective eczema control measures, which were accompanied by a reduction in medication use. The estimations of the range of possible responses using confidence intervals provided evidence of clinically meaningful differences and support the efficacy of the intervention. Unlike some pharmacological treatments, the use of TLA device is not associated with any side-effects. This is important, as these severely affected patients were already treated with very high doses of currently available topical medications, as well as systemic immunosuppression, and oral corticosteroids. However, our analyses should be considered as predominantly exploratory, providing an indication of preliminary evidence, and should not be used as a tool for verifying or confirming the effectiveness of the intervention. In this context, our study generated a hypothesis, which will require randomized placebo-controlled trials to verify it, both in patients with severe AE and in those with more moderate disease.

CONFLICT OF INTEREST

CG has acted as a paid consultant to Airsonett and has received speaker fees. RG has previously received research funding from Airsonett A.B. AC reports personal fees from Novartis, personal fees from Regeneron/Sanofi, personal fees from ALK, personal fees from Bayer, personal fees from ThermoFisher, personal fees from

GlaxoSmithKline, personal fees from Boehringer Ingelheim, outside the submitted work.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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Temperature-controlled laminar airflow (TLA) device in the treatment of children with severe atopic eczema: Open-label, proof-of-concept study

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SUPPLEMENTARY APPENDIX

METHODS

The mode of action of the TLA device

The Airsonett TLA device is designed to displace the body convection which leads to persistent exposure to particles and allergen in bed. Ambient room air is filtered, cooled by 0.5-0.8°C and distributed to the breathing zone by the TLA – the reduced temperature allows the filtered air to descend slowly in a steady laminar stream, displacing particulate and allergen rich air from the breathing zone. The method is able to break body convection without creating draught or dehydration, and thereby reduces and controls particle and aeroallergen exposure in the breathing zone.^{1,2}

Statistical analysis

Statistical learning

Missing values imputation

Due to the small proportion of missing values and the nature of the data, we applied median trajectory imputation method. This longitudinal imputation method considers only non-missing data for the same subject, i.e., the missing values for subject i are replaced by the median of the values of the i -th trajectory, independent of the data from other individuals. Missing data were imputed by using the median trajectory.

KmL: cluster analysis

KmL technique belongs to the class of partitional clustering³. The main advantages of these methods are that no distributional assumptions within clusters are required, no assumptions regarding the shape of the trajectories are made, and they are independent from time-scaling. This algorithm is a 2-step iterative procedure, which requires the initialization of a random partition. In the first step, the mean trajectories per cluster are computed. The second step updates the partition on the basis of the distance between each individual trajectory and each mean trajectory. Here, we used the Manhattan distance, which is more robust to outliers⁴. The algorithm iterates between these two steps and convergence is reached when there are no more changes in the partition.

Formally, consider a set S of n subjects and let x_{it} be the value of variable X measured for each subject i at time t . The sequence $\mathbf{x}_i = (x_{i1}, x_{i2}, \dots, x_{it})$ is then called a *trajectory*. The aim of KmL is, then, to divide S into g homogeneous sub-groups. Several distance measures can be chosen to assign trajectories to clusters. We used the Manhattan distance, which is more robust to outliers³. The optimal number of clusters is assessed using the Calinski and Harabatz criterion, which evaluates cluster validity based on the average between- and within-cluster sum of squares.

RESULTS

The effect of TLA on overnight breathing zone particulate exposures

Table E1. The effect of TLA on overnight breathing zone particulate exposures in among 12 study subjects

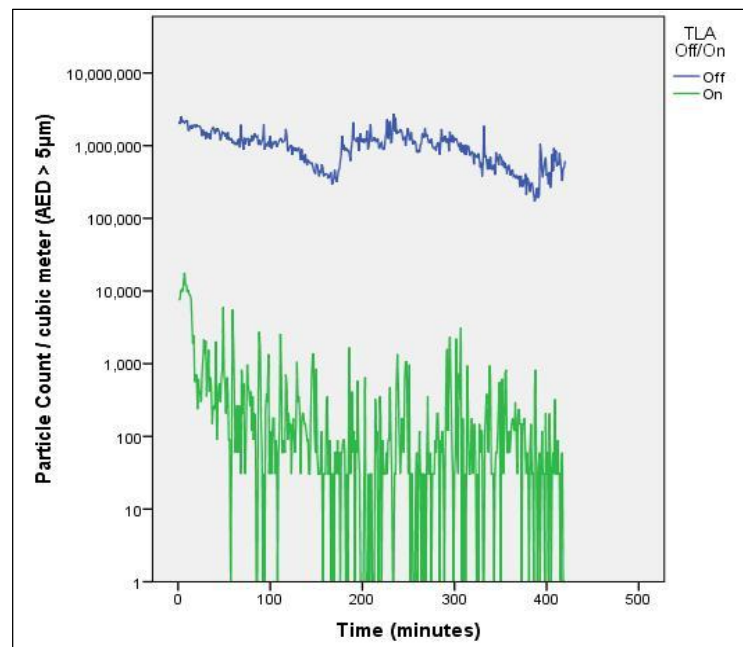
[‡] Geometric estimated marginal mean counts/m³ (95% CI); TLA-ON vs TLA-OFF: p<0.001 for each size class

AED: Aerodynamic Equivalent Diameter

Particle size (AED)	Counts [‡] ; TLA OFF	Counts [‡] ; TLA ON
>0.5 µm	5.9x10 ⁶ (5.3 x 10 ⁶ , 6.4 x 10 ⁶)	400 (370, 440)
>5 µm	6900 (6400, 7300)	2.6 (2.4, 2,7)
>10 µm	82 (74, 90)	1.6 (1.5, 1.8)

Figure E1. TLA reduces overhead particle counts (AED >5µm)

Data: Mean of untransformed particle counts/m³



Primary and secondary end points

Table E2 shows the results for Friedman test for primary and secondary end points. There were significant differences for all outcomes except for POEM and CDLQI.

At visit 12, we observed a positive effect of TLA on all outcomes (Table E3). Changes in resource consumptions were significant only for potent steroids and hospital contacts (Table E4).

Table E2. Results of Friedman test for primary and secondary end points (*significant at $p < 0.1$, **significant at $p < 0.05$, ***significant at $p < 0.01$, ****significant at $p < 0.001$)

	Friedman test p-values
PRIMARY END POINTS	
SCORAD total	0.000****
Investigator Global Assessment (IGA)	0.000****
SECONDARY END POINTS	
SCORAD Objective	0.000****
SCORAD Subjective	0.003***
SCORAD Subjective Pruritus/Itch	0.018**
SCORAD Sleep Loss	0.037**
CDLQI	0.129
POEM	0.604
FDLQI	0.000****
DFI	0.000****

Table E3. Results of Wilcoxon signed rank test for eczema outcomes (*significant at $p<0.1$, **significant at $p<0.05$, ***significant at $p<0.01$, ****significant at $p<0.001$); BL – baseline; There were no significant differences in CDQLI and POEM

Wilcoxon signed rank test p-values										
	Run in period		TLA Device Intervention period							
	BL -5 to -10 weeks	V2 -3 days	V4 +3 days	V6 1 month	V7 2 months	V8 3 months	V9 4 months	V10 6 months	V11 9 months	V12 12 months
Primary end points										
SCORAD total	0.532	0.363	0.041**	0.069*	0.048**	0.191	0.008***	0.027**	0.012**	0.015**
Investigator Global Assessment	0.852	0.614	0.013**	0.017**	0.008**	0.038**	0.002**	0.085*	0.001***	0.001****
Secondary end points										
SCORAD Objective	0.460	0.394	0.036**	0.088*	0.026**	0.156	0.003***	0.050**	0.015**	0.012**
SCORAD Subjective	0.754	0.826	0.875	0.069*	0.495	0.615	0.073*	0.092*	0.050**	0.009***
SCORAD Subjective (Pruritus/Itch)	0.636	0.382	0.292	0.135	0.864	0.666	0.088*	0.082*	0.196	0.043**
SCORAD Sleep Loss	0.861	0.711	0.615	0.059*	0.310	0.314	0.141	0.157	0.016**	0.027**
FDLQI	0.019**	0.964	0.208	0.467	0.042**	0.028**	0.019**	0.047**	0.013**	0.023**
DFI	0.269	0.801	0.157	0.513	0.150	0.124	0.090*	0.030**	0.099*	0.011**

Figure E2. Mean difference in SCORAD total scores between Visit 1 and Visit 12 with confidence intervals.

x axis: the differences between SCORAD at visit 1 vs visit 12; Positive value indicated improvement.

y axis: different levels for the confidence intervals (70%-95%)

Note: The hypothesis that intervention is effective is rejected if the lower limit of the CIs lies below the lower bound of the zone of MCID. Evidence of the efficacy is demonstrated if the mean treatment difference is above zero and if the CI of a certain length includes (or is above) the MCID⁵.

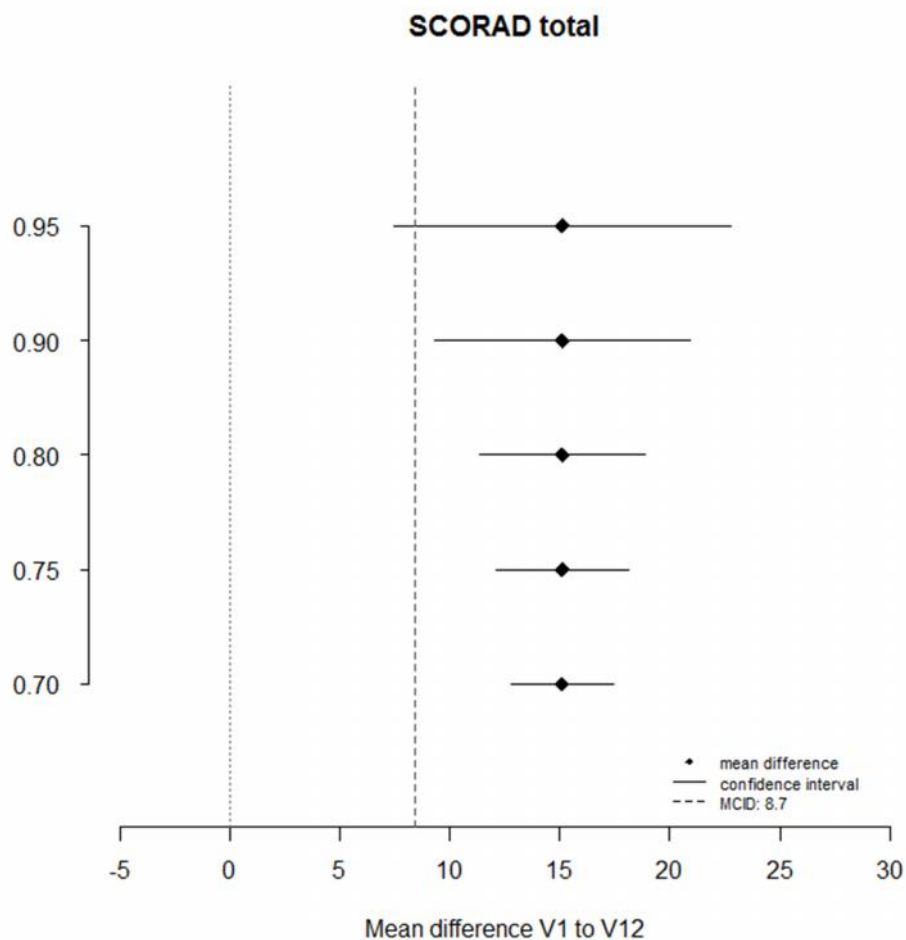


Figure E3. Differences in medication and healthcare usage at different time points.

Quantities of topical treatments = grams, quantity of antibiotic treatment = days, healthcare contacts = counted as x1 for each prescription pick-up, consultation, ambulatory care attendance, day spent as in-patient.

Analysis at +/-12 months is based on 13 subjects, due to missing information for 2 patients

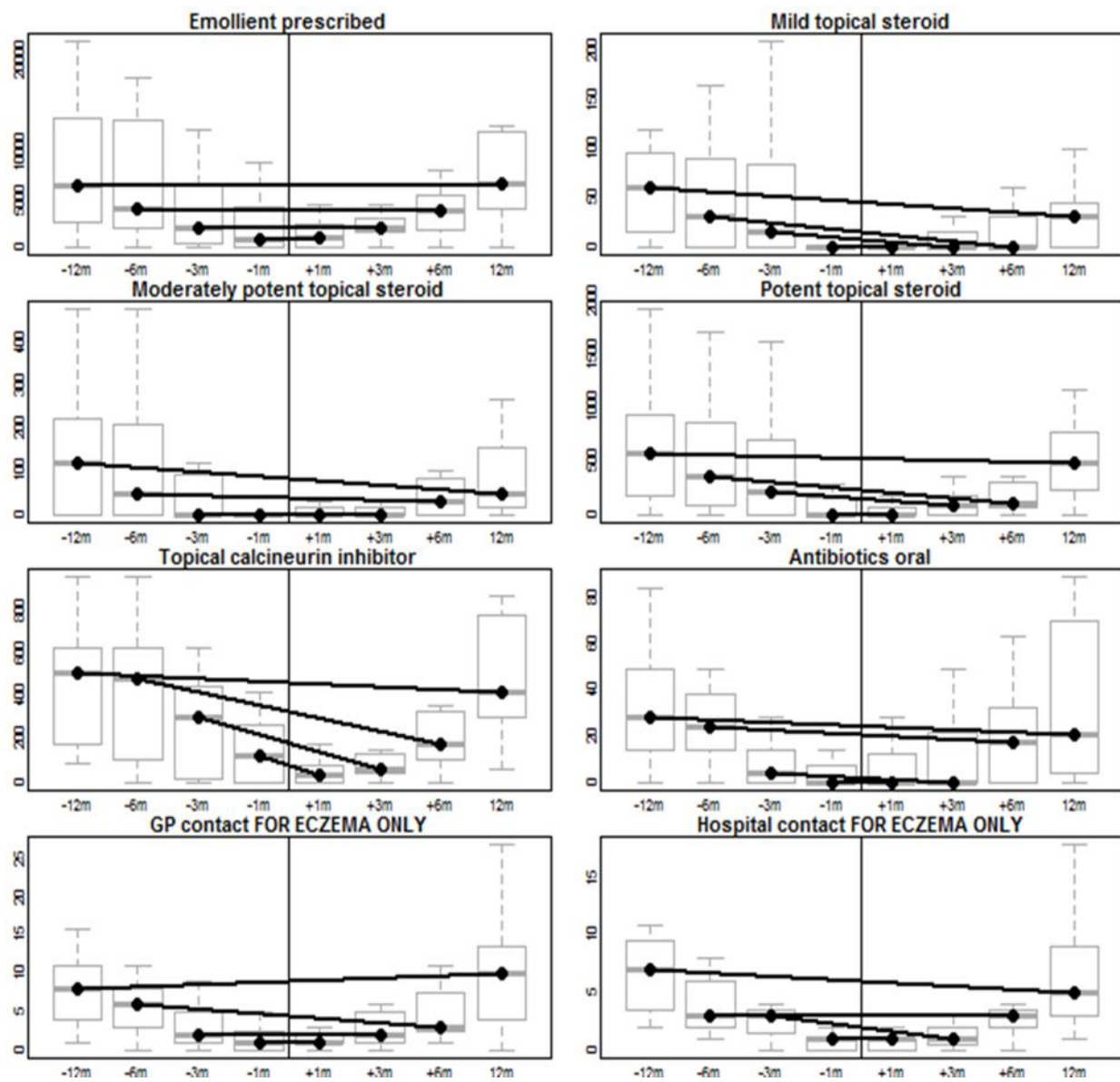


Table E4: Descriptive statistics for resource consumptions before and after 6 of TLA treatment for all patients. All topical treatments reported in grams prescribed. Green cells = reduction, yellow = no change

		6 months before TLA treatment				6 months after TLA treatment				Difference in median
		Median	Q1	Q3	Range	Median	Q1	Q3	Range	
Medication										
Mild topical steroid	All	30.00	0.00	90.00	0-680	0.00	0.00	30.00	0-180	-30.00
Moderately potent topical steroid	All	50.00	0.00	210.00	0-480	30.00	0.00	85.00	0-500	-20.00
Potent steroid	All	360.00	90.00	870.00	0-1720	100.00	75.00	85.00	0-730	-260.00
Topical calcineurin inhibitor	All	480.00	105.00	630.00	0-960	180.00	105.00	85.00	0-1320	-300.00
Days of antibiotics	All	24.00	14.00	38.50	0-182	17.00	0.00	85.00	0-139	-7.00
Healthcare utilization										
GP contact for eczema	All	6.00	3.00	8.00	0-11	3.00	2.50	85.00	1-11	-3.00
Hospital contact for eczema	All	3.00	2.00	6.00	1-28	3.00	2.00	85.00	0-11	0.00

Table E5. Results of Wilcoxon signed rank test for primary and secondary outcomes (in green p-values significant for False Discovery Rate (FDR)=0.05, in orange additional p-values significant for FDR=0.1, in red additional p-values significant for FDR=0.20)

		Wilcoxon signed rank test: Benjamini-Hochberg P-value									
		Treatment period									
		BL	V2	V4	V6	V7	V8	V9	V10	V11	V12
Primary end points											
IGA	Visit 1	0.852	0.682	0.026	0.028	0.020	0.054	0.007	0.106	0.005	0.005
SCORAD total		0.532	0.403	0.080	0.099	0.080	0.239	0.050	0.068	0.050	0.050
Secondary end points											
SCORAD Objective		0.460	0.438	0.072	0.126	0.065	0.195	0.030	0.083	0.050	0.050
SCORAD Subjective		0.875	0.875	0.875	0.183	0.825	0.875	0.183	0.184	0.183	0.090
SCORAD Subjective											
Pruritus/Itch		0.740	0.546	0.487	0.338	0.864	0.740	0.293	0.293	0.392	0.293
SCORAD Sleep Loss		0.861	0.790	0.769	0.197	0.449	0.449	0.314	0.314	0.135	0.135
FDLQI		0.056	0.964	0.260	0.519	0.067	0.056	0.056	0.067	0.056	0.056
DFI		0.336	0.801	0.224	0.570	0.224	0.224	0.224	0.150	0.224	0.110

Table A6. Results of Wilcoxon signed rank test for resource consumption (in green p-values significant for False Discovery Rate (FDR) =0.05, in orange additional p-values significant for FDR=0.1, in red additional p-values significant for FDR=0.20)

	Wilcoxon Signed Rank Test: Benjamini-Hochberg P-value		
	-1month vs +1month	-3month vs +3month	-6month v +6month
Medication			
All emollients	0.582	0.573	0.573
Mild topical steroid	0.159	0.159	0.159
Moderately potent topical steroid	0.564	0.515	0.515
Potent steroid	0.349	0.050	0.050
Very potent topical steroid	0.317	0.317	0.317
Topical calcineurin inhibitor	0.123	0.294	0.315
Days of antibiotics	0.654	0.673	0.674
Healthcare utilization			
GP contact	0.794	0.293	0.293
GP contact for eczema	0.886	0.886	0.886
Hospital contact	0.879	0.135	0.434
Hospital contact for eczema	0.523	0.030	0.122

Confidence intervals for SCORAD total, SCORAD objectives and FDQLI at different time points show how the positive effect of TLA grows over time and results seem to support a one year treatment. The mean of the considered indices is equal or above the MCID only after visit 12.

Figure E4. Differences in all outcomes apart from SCORAD total stratified by cluster
(Cluster A, red = responders; Cluster B, blue = non-responders)

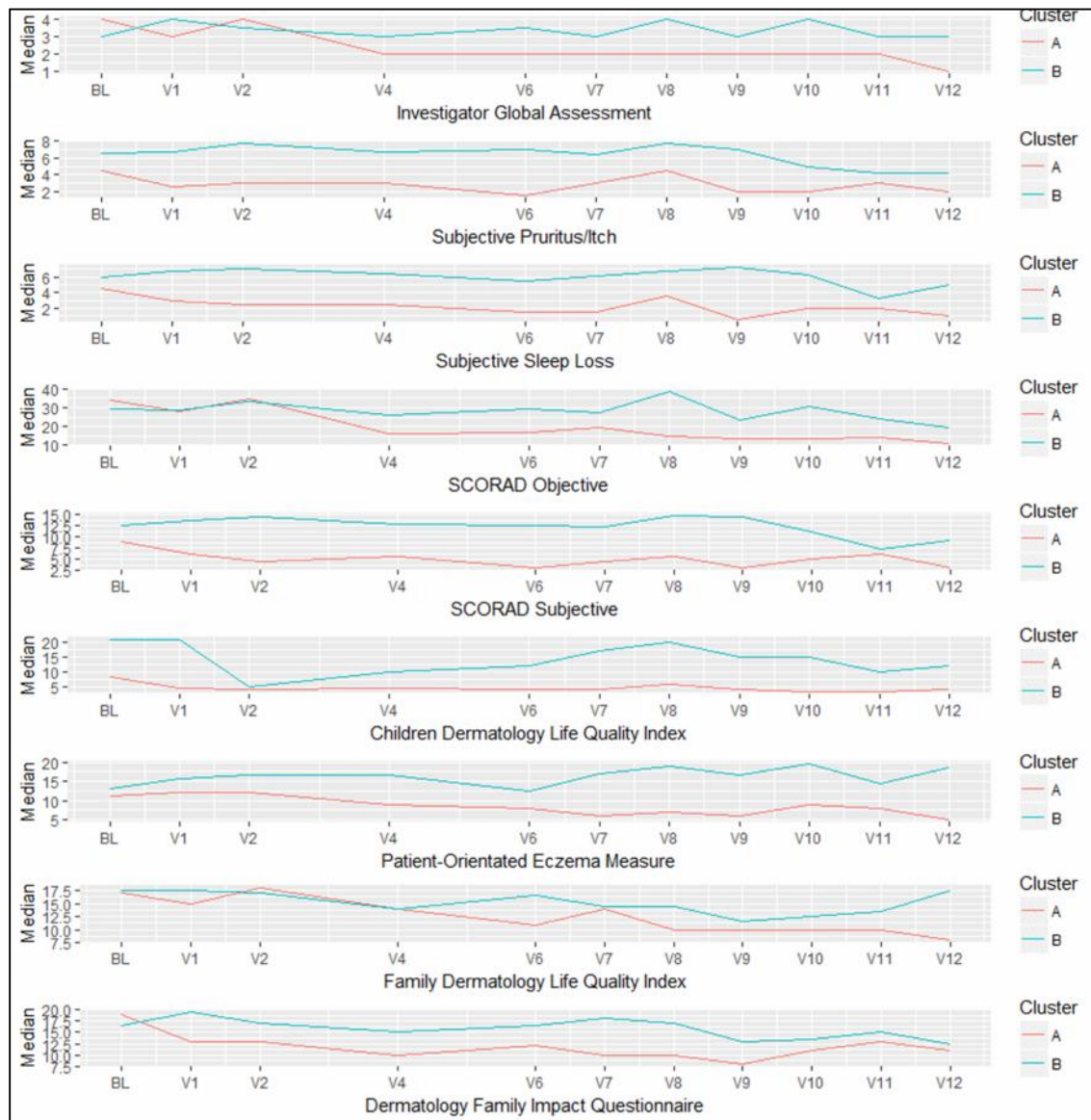
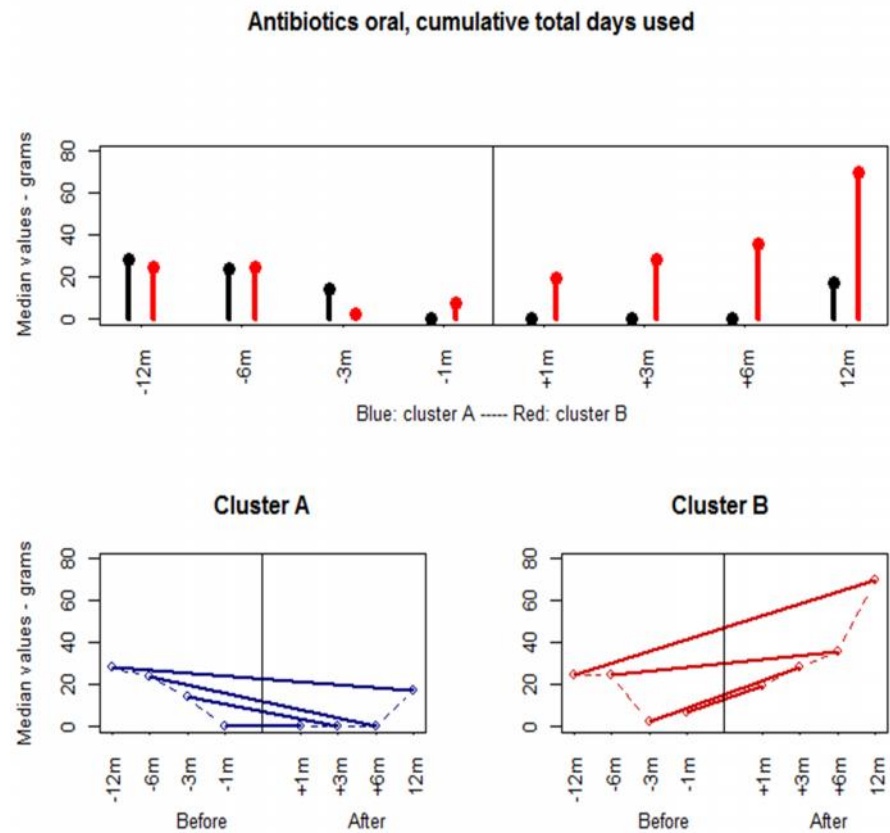


Table E8. Differences in baseline characteristics stratified by clusters

	CLUSTER							
	A				B			
	Median	Q1	Q3	IQR	Median	Q1	Q3	IQR
Age (in months)	141.00	116.25	160.50	44.25	108.00	79.00	119.00	40.00
Weight	40.60	28.08	43.44	15.36	29.50	23.55	31.25	7.70
Height	144.50	127.95	151.55	23.60	131.55	115.05	133.10	18.05
Medical history - atopic dermatitis age of onset	6.00	3.00	7.50	4.50	2.25	1.50	4.50	3.00
Medical history - allergic rhinoconjunctivitis, age of onset	30.00	24.00	60.00	36.00	36.00	31.50	36.00	4.50
Medical history - asthma age of onset	29.00	18.50	41.00	22.50	27.00	24.00	30.00	6.00
Medical history - food allergy IgE mediated, age of onset	48.00	24.00	60.00	36.00	1.50	1.25	3.38	2.13
Medical history - food allergy non-IgE mediated, age of onset	12.00	6.00	28.50	22.50	1.50	1.50	1.50	0.00
Medical history - allergic gut disease, age of onset	6.00	6.00	6.00	0.00	3.25	1.88	4.63	2.75
Duration atopic dermatitis	133.00	92.00	158.73	66.73	104.25	75.25	117.25	42.00
Duration allergic rhinoconjunctivitis	117.00	69.00	128.75	59.75	62.00	42.50	63.50	21.00
Duration Asthma	120.00	83.00	141.50	58.50	31.00	26.00	36.00	10.00
Duration food allergy IgE mediated	102.00	36.00	129.00	93.00	116.50	109.63	117.25	7.63
Duration food allergy non-IgE mediated	135.00	60.75	154.25	93.50	102.75	89.00	116.50	27.50
Duration allergic gut disease	144.00	135.00	153.00	18.00	105.75	98.88	112.63	13.75

Figure E5. Differences in oral antibiotic use stratified by clusters.

Descriptive statistics for resource consumptions at ± 12 months are based only on 13 subject, due to missing information for 2 patients



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