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Time to onset of improvements in Quality of Life from Temperature-controlled Laminar Airflow (TLA) in severe allergic asthma

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ABSTRACT

Background: Allergen avoidance is important in allergic asthma management. Nocturnal treatment with Temperature-controlled Laminar Airflow (TLA; Airsonett®) has been shown to provide significant reduction of exposure to allergens in the breathing zone, leading to long-term reduction in airway inflammation and improvement in quality of life. Allergic asthma patients uncontrolled on GINA step 4 were found to benefit the most. A frequently asked question from clinicians and funders is related to time to onset (TTO) of improvements for patients using TLA.

Methods: Asthma Quality of Life Questionnaire (AQLQ) scores were collected in a previous study. TTO of improvements in Quality of Life was analysed for difference (TLA-placebo) in Area-under-Curve using backwards deletion from 12, 9, 6, 3 down to 1 month for the AQLQ total score, the four individual domains and specifically the sleep question.

Results: Patients with uncontrolled asthma on GINA step 4 (n = 87)) reported a statistically significant and clinically relevant (≥0.5 point) improvement in total AQLQ score (0.57; p = 0.009) after 3 months treatment for TLA over placebo. The shortest TTO was within 1 month for the environmental domain (0.68; p = 0.016) and the sleep question (0.771; p = 0.037). TTO for the emotional and symptom domains was 3 months (0.66; p = 0.020 and 0.64; p = 0.014 respectively) and for the activity domain 6 months (0.47; p = 0.036).

Conclusion: Nocturnal avoidance of allergens using TLA provided a statistically significant and clinically relevant improvement in total AQLQ score within 3 months in patients in the GINA 4 + ACT < 18 group. Questions related to sleep quality may provide the first signal of response already within a month after commencing treatment.

1. Introduction

Patients with severe, uncontrolled asthma treated according to Global Initiative for Asthma (GINA) step 4/5 [1] account for ca 3% of all patients with persistent asthma according to recent population-based studies using administrative and prescribing databases [2,3], but account for a much larger share of asthma-related healthcare resource use and costs [4–6]. Treatment alternatives for such patients include high-dose inhaled corticosteroids (ICS) plus a second controller such as long-acting β2-antagonists (LABAs) and/or long-acting muscarinic antagonists (LAMAs) and/or systemic corticosteroids [1]. During the last decade several new drugs for treatment of severe asthma have been developed and some of these drugs, such as anti-immunoglobulin E- and anti-interleukin-5-treatments, have been included in Step 5 in the latest GINA recommendations [1,7]. The costs for treatment with these biologics are however very high.

A new alternative to treat patients with severe, uncontrolled asthma is temperature-controlled laminar airflow (TLA) [8,9]. TLA controls nocturnal exposure to particles by delivering slightly cooled and filtered air from above the head of the patient during sleep. The greater density of the cooled air reverses the convection current, which otherwise brings allergen-bearing and irritant particles into the breathing zone of the patient. Placebo-controlled trials with TLA have demonstrated significant improvements in Quality of Life and reductions on airway inflammation as monitored by exhaled nitric oxide levels (FENO) [10,11]. The use of TLA has shown cost-effectiveness according to the National Institute for Health and Care Excellence (NICE) standards [8,12].

The time to onset (TTO) of improvements in Quality of Life during

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treatment with TLA has not been fully explored, though the results from the study by Boyle et al. [11] indicate that an effect can be seen around 3–6 months for total AQLQ, though patient feedback has indicated that the effect can occur earlier. We wanted to investigate this more thoroughly by re-analysing data from that study by applying specific statistics to look at TTO for improvements in total AQLQ-score, but also for the individual domains (Symptoms, Activity, Emotional and Environment) and the specific question about Sleep. The main focus will be the symptomatic more severe asthma population.

2. Materials and methods

2.1. Patients

The present study is a post-hoc analysis of data from the 4A Asthma study by Boyle et al. [11] (ClinicalTrials.gov NCT00986323). Patients had atopic asthma (diagnosis ≥1 year prior to study), age 7–70 years, AQLQ-score ≤ 5,5 at inclusion, allergic sensitisation to a pet allergen (cat and/or dog) and/or house dust mite demonstrated by specific IgE level or positive skin prick test, daily use of inhaled corticosteroids (budesonide/beclomethasone ≥200 μg/day or fluticasone ≥100 μg/day) for the last 6 months, and features of incompletely controlled asthma according to GINA 2006.

2.2. Study design

The study was a phase III multicentre, double-blind, placebo-controlled, parallel-group trial. Patients were randomised to receive add-on treatment with TLA (Airsonett®) or a placebo device for 1 year. Asthma medications were kept unchanged for the first 3 months, and thereafter adjusted to optimise asthma control by local investigators according to GINA guidelines. Patients were monitored by medical assessments after 1, 3, 6, 9 and 12 months of treatment, and via completion of a diary [11]. ACT score was not collected at the 1-month visit.

2.3. Outcome measures

In the study by Boyle et al., the primary outcome measure was quality of life assessed by the mini-AQLQ (Mini Asthma Quality of Life Questionnaire) or in children 7–11 years, the Paediatric AQLQ (PAQLQ). The term "total AQLQ" was used in combination for mini-AQLQ and PAQLQ. Secondary outcomes included AQLQ score changes and objective measures of airway inflammation (fractional exhaled nitric oxide; FENO) [11].

In the current study, the primary outcome measure is TTO of a statistically significant difference (based on $p < 0.05$) and clinically important difference (based on the minimally important difference (MID) > 0.5) between TLA and placebo for the total AQLQ total score and the four individual domains and the sleep question. Secondary outcome measures are TTO for reduction in FENO and TTO for changes in Asthma Control Test (ACT) score.

For AQLQ and ACT, TTO were calculated for a) all patients and b) three pre-specified sub-groups (ACT score < 18; GINA classification equal to 4; ACT score < 18 plus GINA classification equal to 4). These sub-groups will be referred to as ACT < 18, GINA 4 and GINA 4 + ACT < 18. FENO analyses were performed for a) all patients and b) patients with abnormally raised FENO (> 45 ppb) at baseline. This cut-off was used in the study by Boyle et al. [11].

It should be noted that the results are presented in the same order of asthma severity as in the paper by Boyle et al. [11], starting with the entire population, followed by ACT < 18, GINA 4 and GINA 4 + ACT < 18. The main conclusions will be drawn from the latter group, which is recommended population for treatment with TLA.

2.4. Statistical analyses

In the study by Boyle et al., the difference in outcome variables between active and placebo groups at the end of the 12-month treatment period were examined [11].

In the current study, the difference in average AQLQ between TLA and placebo were assessed for the sequence 0–12, 0–9, 0–6, 0–3 and 0–1 months (ΔTLA-PLA$_{0\text{-}x}$). The TTO is defined as the shortest time the treatment difference resulted in a positive outcome by the backward deletion testing procedure. A positive outcome was defined as Statistical TTO, equals $p < 0,05$ and Clinical Important TTO, equals MID > 0,5 for AQLQ [13] and MID > 3,0 for ACT [14]. The analysis model was an ANOVA with a factor for treatment, and with the baseline value as covariate. Missing data was not imputed in the analysis.

The ITT population was utilized for the calculations on all patients and for the sub-groups. It should be noted that number of patients decrease by sub-grouping (see Table 2) and that the number of data points decrease through the backward deletion analysis, which by default decreases the power.

Children have only three domains in AQLQ since Environment is not collected in the PAQLQ. The PAQLQ has two sleep questions while the mini-AQLQ has one. The average of the two sleep questions were used in the analyses for the children.

A descriptive analysis was performed among the TLA-treated patients for the differences between AQLQ-scores at different timepoints vs the baseline AQLQ-value for total AQLQ, the different domains and the sleep question for children vs adults.

3. Results

3.1. Patient population

The primary efficacy population in the study by Boyle et al. included all 282 patients who had a TLA or placebo device installed in their bedroom. Treatment groups had similar baseline demographic and clinical characteristics (Table 1). For further details and patient flow in the study, see Boyle et al. [11].

The efficacy population in the current study includes different numbers of patients for the different domains due to missing data. Table 2 specifies the number of patients for each domain for all patients and the sub-groups ACT < 18, GINA 4 and GINA 4 + ACT < 18.

3.2. Time to onset for improvements in total AQLQ score in different severities of asthma

Fig. 1 and Table 2 presents the difference in total AQLQ score based on AUC between TLA and placebo for all patients and for the three sub-groups. The treatment difference for total AQLQ score increased with increasing asthma severity, in agreement with the results presented by Boyle et al. [11] for the whole 12 months study period.

Table 1
Characteristics of study patients at baseline, presented as mean (SD) unless otherwise stated (ITT-population).

	TLA (N = 189)	Placebo (N = 93)
Age (years)	24,7 (16,1)	24,9 (16,0)
Age < 12, n (%)	46 (24%)	22 (24%)
Male sex, n (%)	107 (57%)	44 (47%)
Duration of asthma (years)	14,8 (12,9)	11,7 (10,6)
AQLQ	4,21 (0,82)	4,25 (0,97)
FEV1 (% predicted)	89,9 (17,6)	91,2 (15,3)
FENO (ppb)	38,5 (38,6)	34,5 (33,3)
ACT score	15,8 (3,7)	15,9 (3,5)
Inhaled corticosteroid dose[a]	576 (368)	616 (376)

[a] Inhaled corticosteroid dose is beclomethasone dipropionate equivalent daily dose.

Table 2
Magnitude of and p-value (in parenthesis) for differences in AUC between TLA and placebo at different time points.

	N TLA	N PLA	1 month	3 months	6 months	9 months	12 months
			ΔAUC (p-value)				
ITT AQLQ	184	89	−0,162 (0,207)	−0,147 (0,210)	−0,176 (0,121)	−0,185 (0,095)	−0,196 (0,077)
ITT Symptoms	176	86	−0,266 (0,074)	−0,222 (0,099)	−0,252 (0,050)*	−0,255 (0,039)*	−0,263 (0,029)*
ITT Activity	176	86	−0,080 (0,577)	−0,072 (0,583)	−0,086 (0,488)	−0,097 (0,422)	−0,110 (0,362)
ITT Emotional	176	86	−0,262 (0,112)	−0,224 (0,145)	−0,259 (0,082)	−0,249 (0,085)	−0,268 (0,059)
ITT Environmental	134	67	−0,293 (0,081)	−0,232 (0,127)	−0,274 (0,056)	−0,309 (0,029)*	−0,320 (0,025)*
ITT Sleep	175	86	−0,040 (0,829)	−0,048 (0,770)	−0,154 (0,317)	−0,170 (0,248)	−0,228 (0,113)
ACT < 18 AQLQ	121	57	−0,231 (0,169)	−0,227 (0,126)	−0,272 (0,063)	−0,317 (0,026)*	−0,350 (0,014)*
ACT < 18 Symptoms	111	55	−0,307 (0,126)	−0,273 (0,123)	−0,326 (0,058)	−0,378 (0,020)*	−0,412 (0,010)**
ACT < 18 Activity	111	55	−0,174 (0,343)	−0,139 (0,395)	−0,176 (0,258)	−0,239 (0,110)	−0,281 (0,061)
ACT < 18 Emotional	111	55	−0,416 (0,057)	−0,435 (0,028)*	−0,479 (0,014)*	−0,493 (0,008)**	−0,527 (0,004)**
ACT < 18 Environmental	87	45	−0,381 (0,058)	−0,337 (0,063)	−0,363 (0,040)*	−0,422 (0,016)*	−0,443 (0,012)*
ACT < 18 Sleep	114	55	−0,201 (0,429)	−0,202 (0,372)	−0,352 (0,098)	−0,392 (0,052)	−0,476 (0,016)*
GINA 4 AQLQ	79	47	−0,322 (0,087)	−0,407 (0,017)*	−0,454 (0,006)**	−0,451 (0,005)**	−0,427 (0,008)**
GINA 4 Symptoms	77	46	−0,470 (0,029)*	−0,540 (0,006)**	−0,595 (0,001)**	−0,567 (0,002)**	−0,530 (0,002)**
GINA 4 Activity	77	46	−0,236 (0,285)	−0,324 (0,101)	−0,323 (0,079)	−0,329 (0,071)	−0,311 (0,089)
GINA 4 Emotional	77	46	−0,245 (0,297)	−0,381 (0,085)	−0,482 (0,022)*	−0,476 (0,020)*	−0,454 (0,023)*
GINA 4 Environmental	63	39	−0,491 (0,034)*	−0,488 (0,020)*	−0,471 (0,021)*	−0,518 (0,010)*	−0,491 (0,014)*
GINA 4 Sleep	76	46	−0,568 (0,032)*	−0,546 (0,017)*	−0,613 (0,004)**	−0,591 (0,005)**	−0,594 (0,005)**
GINA 4 + ACT < 18 AQLQ	54	30	−0,471 (0,059)	−0,566 (0,009)**	−0,652 (0,002)**	−0,672 (0,001)***	−0,675 (0,001)***
GINA 4 + ACT < 18 Symptoms	52	30	−0,536 (0,072)	−0,637 (0,014)*	−0,748 (0,002)**	−0,754 (0,001)**	−0,732 (0,002)**
GINA 4 + ACT < 18 Activity	52	30	−0,371 (0,189)	−0,449 (0,062)	−0,466 (0,036)*	−0,509 (0,022)*	−0,533 (0,018)*
GINA 4 + ACT < 18 Emotional	52	30	−0,455 (0,143)	−0,655 (0,020)*	−0,798 (0,003)**	−0,810 (0,002)**	−0,792 (0,002)**
GINA 4 + ACT < 18 Environmental	45	24	−0,681 (0,016)*	−0,672 (0,008)**	−0,669 (0,009)**	−0,733 (0,004)**	−0,721 (0,004)**
GINA 4 + ACT < 18 Sleep	51	30	−0,771 (0,037)*	−0,763 (0,014)*	−0,906 (0,002)**	−0,913 (0,001)**	−0,930 (0,001)***

For all patients (N = 273), a treatment difference for total AQLQ score between TLA and placebo in the range 0,15–0,20 was observed during the study, with no statistical significance reached i.e. no statistical nor clinical important TTO were found.

For uncontrolled patients (ACT < 18), a significant difference was observed after 9 months with a treatment difference of 0,32 (p = 0,026), i.e. a statistical TTO but not a clinical important TTO were found.

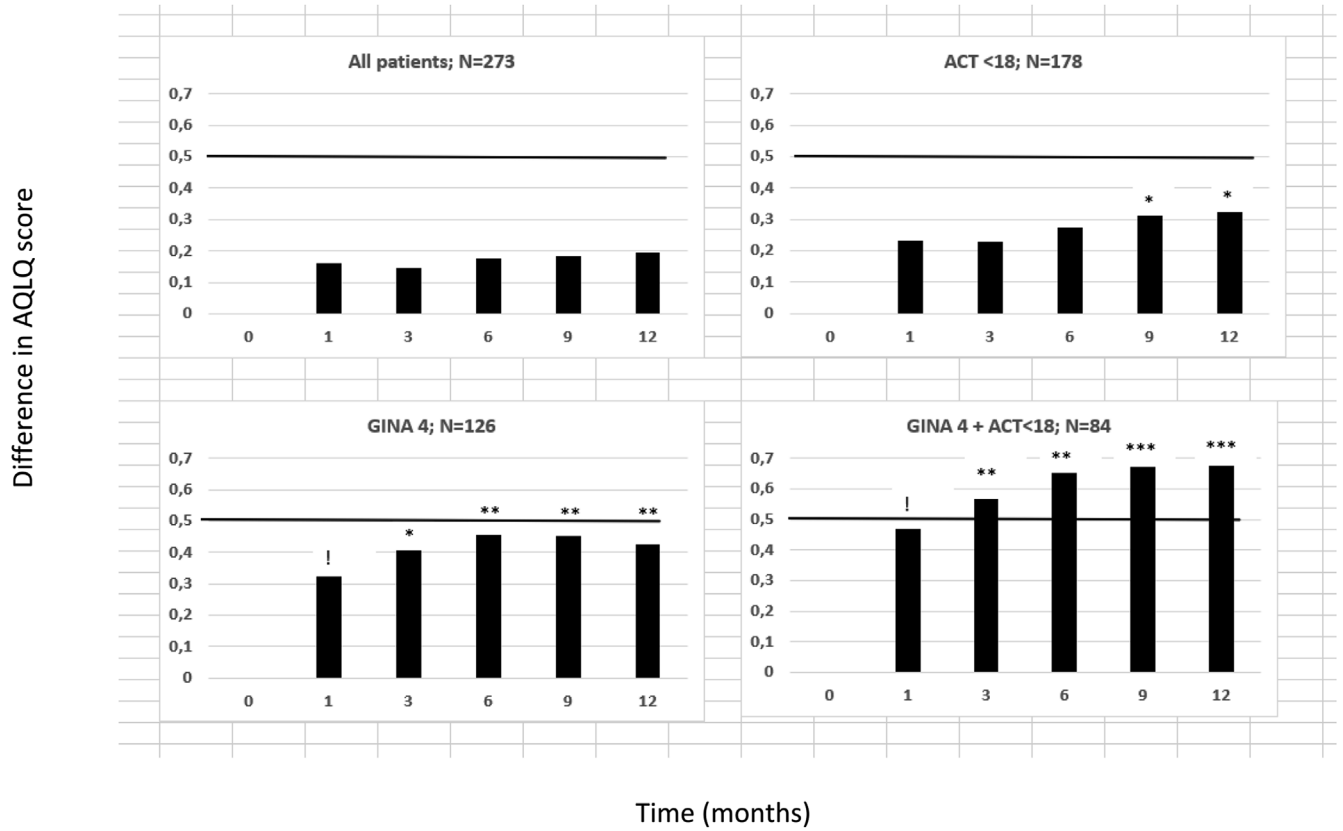
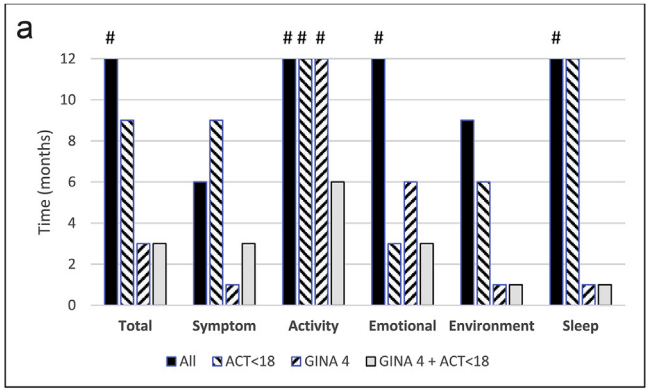
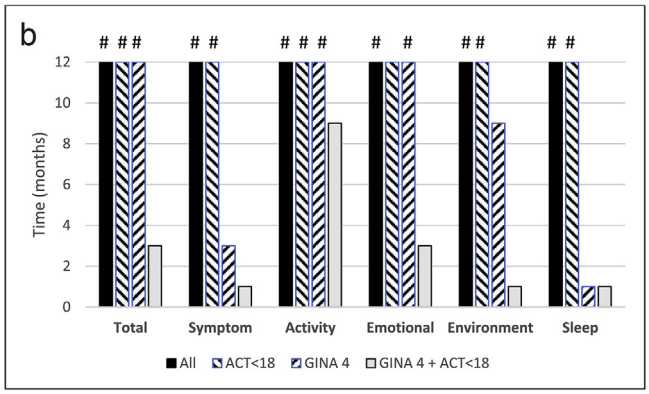


Fig. 1. Treatment difference between TLA and placebo in total AQLQ over time for different severities of asthma. MID = 0,5 inserted as a solid line.



= no significance at 12 months



= no treatment difference ≥ MID at 12 months

Fig. 2. a. Statistical time to onset for total AQLQ and the different domains and sleep for different severities of asthma. **b**. Clinical time to onset for total AQLQ and the different domains and sleep for different severities of asthma.

For patients with severe, persistent asthma (GINA 4), a significant treatment difference was observed after 3 months (treatment difference 0,41; p = 0,017). The outcome for TTO was similar to the previous group but achieved statistical TTO earlier.

Symptomatic GINA 4 patients (GINA 4 + ACT < 18) reached a statistically significant treatment difference after 3 months (treatment difference 0,57; p = 0,009). After 1 month the treatment difference was 0,47 (p = 0,059). For this symptomatic GINA 4 group both statistical and clinical important TTO were achieved at 3 months.

Fig. 2a and b also illustrate how statistical and clinical important TTO descriptively correlates.

Regarding the number and percentage of responders defined as patients with improvement in AQLQ > 0,5 vs baseline at different time points, for symptomatic GINA 4 patients (GINA 4 + ACT < 18) treated with TLA a 69% response rate was observed at 3 months, compared to 76% at 6 months and 78% at 12 months. The placebo response was approximately 50%.

3.3. Time to onset of improvements in the different AQLQ domains and sleep in different severities of asthma

Fig. 2a, b and 3 and Table 2 presents TTO for the different domains and sleep in different severities of asthma.

For all patients, statistical TTO was reached for the Symptoms domain (0.255, p = 0.039) and the Environment domain after 9 months (0,309 p = 0,029), while no significance was reached for the other domains and the sleep question. No clinical important TTOs were detected.

For uncontrolled patients (ACT < 18), statistical TTOs were observed for all domains except activity. The sleep question reached significant difference at 12 months. No clinical important TTOs were detected with one exception; the emotional domain at 12 months.

For the GINA 4 patients statistical TTOs were observed for all domains except activity, but TTO was shorter than that observed for the ACT < 18 sub-groups, most notably for Symptoms, Environment and Sleep (all three with a TTO of 1 month). Clinical important TTOs were detected for symptoms at 3 months, environment at 9 months and sleep at 1 month.

For the GINA 4 + ACT < 18 subgroup statistical TTOs were observed for all domains and the sleep question, with TTO as low as 1 month for Environment and Sleep. Clinical important TTOs were detected for all domains and for sleep; Symptoms, environment and sleep already at 1 month, emotional at 3 months and activity at 9 months.

3.4. Time to onset of improvements in the different AQLQ domains and sleep in children and adults

Fig. 4 presents the mean improvements in AQLQ-scores for the TLA-treated patients from the baseline visit, split by adults and children as defined by the use of the mini-AQLQ or the PAQLQ questionnaire. For symptoms, emotional and total AQLQ, no differences between children and adults were observed. Numerical improvements in activity were observed earlier for the children, while for the sleep question numerical improvements were larger among the adults. For placebo, the results were more varying due to the low number of patients.

3.5. Time to onset for decreases in FENO

Patients with abnormally high values for FENO at baseline (> 45 ppb; N = 77) had a statistically significant decrease in FENO (0,32; p = 0,024) already after 1 month of treatment with TLA compared to placebo (Table 3, upper part). The treatment difference persisted at 12 months ((0,24; p = 0,038)).

3.6. Time to onset for improvements in ACT score

The lower part of Table 3 presents the difference in ACT score based on AUC between TLA and placebo for all patients and for the three subgroups. The treatment difference for ACQ score increased with increasing asthma severity.

For all patients (N = 273), a treatment difference for ACT score between TLA and placebo in the range 0,2–0,5 was observed during the study, with no statistical significance reached. For uncontrolled patients (ACT < 18 at baseline), a significant difference was observed after 9 months with a treatment difference of 1,1 (p = 0,025), while for patients with severe, persistent asthma (GINA 4), a significant treatment difference was observed after 6 months (treatment difference 1,44; p = 0,011). Symptomatic GINA 4 patients (GINA 4 + ACT < 18) reached a statistically significant treatment difference after 6 months (treatment difference 1,88; p = 0,010). Clinical important TTOs were not detected for ACT score.

4. Discussion

The study by Boyle et al. demonstrated descriptively an increased difference in change from baseline for total AQLQ score between TLA and placebo in the more severe and poorly controlled asthma patients. The treatment effect was greatest in the GINA 4 + ACT < 18 group, who represent a significant area of unmet need [11]. Symptomatic GINA 4–5 is also the recommended indication for TLA [15–17].

The current study further demonstrates that nocturnal treatment with TLA improves Quality of life for patients with severe and uncontrolled asthma, with a rapid onset of the effects. For the patients in the GINA 4 + ACT < 18 group, statistically significant changes in TTO of improvements for the Sleep question and the Emotional domain occurred already after one month, while TTO was 3 months for total

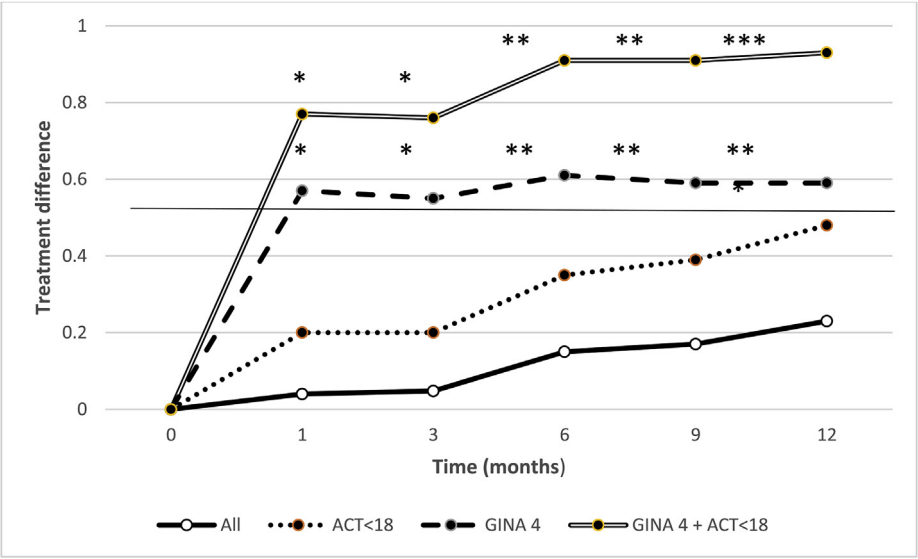


Fig. 3. Treatment difference between TLA and placebo over time for the sleep question. MID = 0,5 inserted as solid line.

AQLQ score and the Symptoms and Environmental domains. The activity domain had the longest TTO, becoming statistically significant after 6 months. Similar results were obtained for clinical TTO. After 3 months of treatment with TLA, the percentage of responders based on improvement in total AQLQ score vs baseline in the GINA 4 + ACT < 18 group was 69% compared to 78% after 12 months. As the placebo response is included a true response should be based on more than one asthma response indicator.

Allergen exposure produces an immediate response within 10–15 min and is commonly followed by a late phase more prolonged response commencing 4 h later [18]. The late response is associated with neutrophilic and eosinophilic airway inflammation. It enhances non-specific bronchial hyperresponsiveness (BHR) [19] for many days. The early effects of TLA will reduce acute allergen reactions, but it will take much longer to improve BHR [20]. The observation that an intervention used exclusively at night eventually improves day-time symptoms is likely due to a progressive reduction in BHR which is primarily being perpetuated by nocturnal exposures. The concentration of particulates inhaled when recumbent in bed is likely many orders of magnitude higher than during up-right postures in the day.

The avoidance of nocturnal trigger factors reduces inflammation. This has been shown using FENO as a marker for inflammation [21,22]. As TLA is indicated for use during bed-time this reduced inflammation will initially lead to beneficial effects during night, possibly by improving night-time symptoms, as manifested by improvements in sleep and in the emotional domain. After 3 months effects are possibly spilling over to morning and later whole day improvements shown by improvements in total AQLQ score and the symptoms and environmental domains. After 6–9 months effects are also present later during day-time, as shown by the statistically significant and clinically important improvements in the Activity domain. Another plausible explanation of the time-lag for activity could be that activity changes need more substantial improvements to be recorded by the patients. Our data on delayed onset for improvements in activity is consistent with Chupp et al. from the 12-months MUSCA trial, where symptoms and impact preceded the activity domain [23]. The more rapid appreciation of improvement in the activity domain in children is likely due to children being much more likely to participate in physical activities than adults.

In patients with increased levels of FENO (> 45 ppb) at baseline, reductions in airway inflammation, manifested by statistically significant decreases in FENO-levels for TLA vs placebo, occurred already after 1 month. This decrease in FENO persisted throughout the study and may be correlated with the early onset of improvements in sleep and emotional status.

Improvements in ACT score had a longer statistical TTO compared to the findings using the AQLQ instrument. ACT did not reach a clinical important TTO (MID > 3.0) over 12 months for any of the sub-groups, which AQLQ did. This finding of a clinically important difference for AQLQ score but not for ACT-score parallels the findings by Chupp et al. [23]. In this trial, the difference in mean change from baseline in ACQ-5 scores between the mepolizumab group and the placebo group was less than the MCID at all time points, while the improvements in SGRQ score exceeded the MCID already after 3 months.

One of us has earlier reported that, based on UK health-service costs, the use of TLA falls well below the National Institute for Health and Care Excellence (NICE) threshold for the incremental cost effectiveness ratio per quality adjusted life year. Health economic considerations brings up TLA as an attractive alternative to treatment of patients with severe, uncontrolled asthma with very expensive treatments such as anti-immunoglobulin E-treatments (omalizumab) [8,12].

A limitation of this exploratory study is the post-hoc nature of the analysis. Also, many multiple analyses were performed, but the testing strategy for each test was conservative as testing started with all data, followed by, if significant, removing the last value, and then repeating as long as the significance level was preserved. In addition, the main focus of this work answers the question on TTO in the recommended in symptomatic patients with severe asthma. The other groups can be regarded as complementary, giving information about TTO in these groups.

A further limitation is the existence of missing data. However, the amount of missing data was low and since we calculated area-under-curve rather than using individual data points, the effects of this indirect imputation were likely to reduce the bias introduced by withdrawals. The assumption is that the missing data for placebo patients, on average, is not better than the corresponding missing data for the active group.

In conclusion, nocturnal avoidance of allergens using TLA provides a clinically relevant improvement in total AQLQ score within 3 months in patients in the GINA 4 + ACT < 18 group. Questions related to sleep quality may provide the first signal of response already within a month after treatment start.

Funding

Airsonett AB, Sweden was the sponsor of the study. However, the paper was written without any influence from the sponsor and

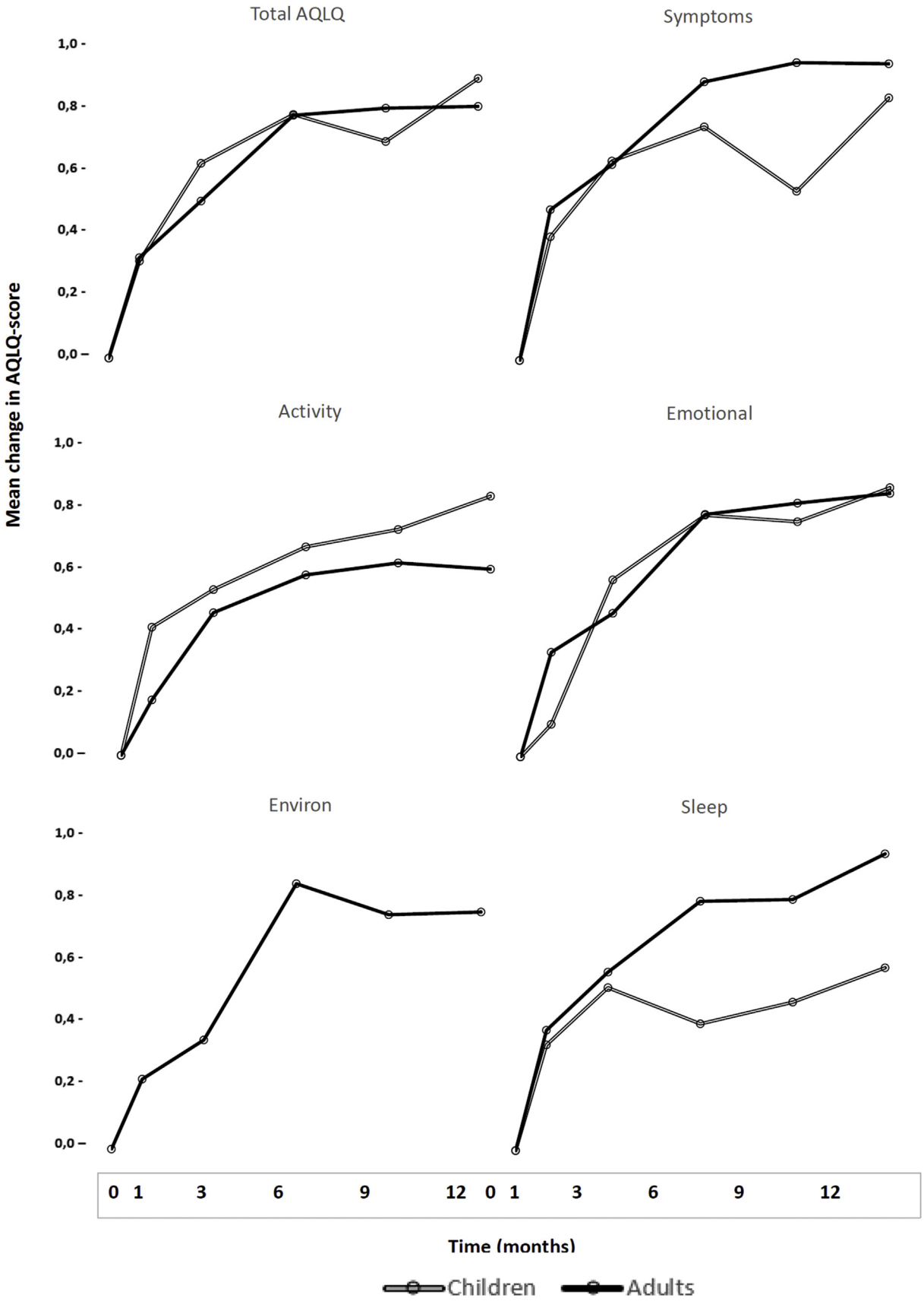


Fig. 4. Mean change in AQLQ-scores for TLA-treated adults and children over time.

Table 3
Magnitude of and p-value (in parenthesis) for differences in FENO and reported score at Asthma Control Test between TLA and placebo at different time points.

	N TLA	N PLA	1 month	3 months	6 months	9 months	12 months
			ΔAUC (p-value)				
ITT FENO	178	85	0,013 (0,86)	−0,016 (0,81)	0,007 (0,91)	0,003 (0,96)	0,024 (0,68)
FENO > 45 ppb at baseline	54	23	0,322 (0,024) *	0,23 (0,084)	0,229 (0,078)	0,189 (0,106)	0,237 (0,038) *
ITT ACT	175	84		−0.209 (0.647)	−0.364 (0.358)	−0.448 (0.228)	−0.512 (0.157)
ACT < 18 ACT	115	54		−0.352 (0.558)	−0.788 (0.133)	−1.097 (0.025)*	−1.269 (0.007)**
GINA 4 ACT	76	45		−1.256 (0.058)	−1.440 (0.011)*	−1.498 (0.006)**	−1.256 (0.017)*
GINA 4 + ACT < 18 ACT	52	30		−1.355 (0.106)	−1.882 (0.010)*	−2.268 (0.001)**	−2.066 (0.002)**

represent the author's views alone.

Conflicts of interest

LBJ was on the scientific advisory board and an investigator on the 4A trial. He has given paid lectures during Airsonett symposia at international conferences. GE consults for Airsonett, ALK, Almirall, AstraZeneca, MVIC and Novartis. FR has no conflicts of interest to report. SP consults for Airsonett, AstraZeneca and MVIC. JOW was on the scientific advisory board and an investigator on the 4A trial. He has given paid lectures during Airsonett symposia at international conferences. He was also the author of a paper on the health/economic value of TLA.

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