Bedfordshire and Hertfordshire Priorities Forum statement
Number: 62
Subject: Temperature-controlled laminar airflow device for the treatment of chronic allergic asthma
Date of decision: March 2014
Date of review: March 2017

Guidance

Recommendations

There is currently insufficient evidence of effectiveness of temperature-controlled laminar airflow for the treatment of chronic allergic asthma to support NHS funding. In particular there is limited evidence in terms of objective outcome measures. There are also no specific studies on the safety of this device.

Patients are able to purchase this device directly but if clinicians wish to recommend TCLA it should only be funded via research and development funds, as part of an approved clinical trial. Patients purchasing this device directly should be aware of the lack of safety data available.

The Human Rights Act has been considered in the formation of this guidance statement.

Appendix 1 - Literature Review

It is well documented that the inhalation of allergens can trigger asthmatic symptoms[i,ii,iii] Temperature controlled laminar airflow (TCLA) technology has been developed to try and remove allergens in the air whilst patients sleep at night, in order to reduce asthmatic symptoms[iv,v]. A new device has been developed that delivers TCLA and the evidence around the effectiveness of this device is presented in this document.

In the UK, BTS guidelines[iv] recommend a stepped approach for asthma management, with moderate persistent asthmatics recommended to receive optimised treatment with inhaled corticosteroids and inhaled long acting beta-2 agonists. If control is still inadequate leukotriene receptor antagonists or aminophylline can be considered. For patients with persistent poor control it is advised that they receive an increased dose of ICS and the use of oral corticosteroids should be considered. If, despite optimised treatment asthmatic symptoms are still not adequately controlled, patients may be eligible for add-on therapy with omalizumab.

In one TCLA study significant improvements were documented in some patients who received TCLA and who had *poor symptom control*[iv] However these participants had only moderately persistent asthma according to the British Thoracic Society (BTS) guidelines. They had not had their treatment stepped-up according to BTS guidelines as study inclusion criteria stated daily inhaled corticosteroid ≥200 micrograms/day, but those with inhaled corticosteroid (ICS) doses >1200 micrograms per day were excluded. Also patients who had received treatment for omalizumab in the previous 2 years were excluded.

It is advised that patients should continue along the BTS pathway, stepping-up treatment, until standard therapy is optimised and control of symptoms is adequate. It is not clear what dose of inhaled corticosteroid patients were receiving e.g. low dose/high dose. None of the patients in the TCLA studies were using high dose ICS, oral steroids or omalizumab. Any of these treatments may have optimised the management of the patients' asthma. It is therefore advised that asthmatic patients in England are managed following the BTS guidelines and their management stepped up, according to individual need.

Further research is required on the effectiveness of TCLA for patients with allergic asthma, in particular as add-on therapy, for patients with persistent poor control. Objective outcomes such as medication reduction, frequency and severity of asthma exacerbations and hospital admissions need to be assessed.

Evidence

Effectiveness information of TCLA in the treatment of chronic allergic asthma is based on relatively few studies; 3 randomised controlled trials, 1 before-after study and 1 cost-effectiveness study. The sample size for 3 of the studies was very small (7, 9, 22). The remaining study enrolled 312 patients. Two of the studies included

adults and children. One study included only adults and one study included only children. The duration of treatment ranged from 4 weeks to 1 year.

Change in quality of life score was the predominant measure of outcome. Quality of life was assessed by the Mini Asthma Quality of Life Questionnaire (see appendix 2), or in children ≤12 years, the Paediatric Asthma Quality of Life Questionnaire (appendix 3).

In one study by Boyle et al[v] 312 patients (aged 7 – 70 years) with inadequately controlled persistent atopic asthma were recruited from 19 European centres, for 1 year treatment with nocturnal TCLA device (n=207) or an identical placebo device (n=105). They found that participants in the intervention group were 1.92 times more likely to have a clinically significant increase in quality of life score (>0.5) at the end of 1 year (OR 1.92 95%CI 1.09, 3.38. P-value 0.02). Participants who were receiving high treatment intensity but who had poor symptom control were 4.74 times more likely to have a clinically significant increase(>0.5) in quality of life score (OR 4.74 95%CI 1.48, 15.19. P-value 0.009). Secondary outcome measures included airway inflammation (proxy: fractional nitric oxide measurement-FENO), systemic allergy (IgE levels to indoor aeroallergens and blood eosinophil count) and airflow obstruction (forced expiratory volume in 1 second). It was found that participation in the intervention group was associated with a greater decrease in FENO levels compared to placebo; mean difference between placebo and active treatments -7.1ppb (95%CI -13.6, -0.7. P-value 0.03). Participants who had the highest baseline FENO level had the greatest decrease in FENO levels; mean difference between placebo and active treatments -29.7 (95%CI -47.2, -12.2). Importantly no significant difference between the groups was seen in total IgE level change nor change in lung function (FEV1). Furthermore, supplementary data tables showed that by the end of the trial there was no significant difference between groups in asthma exacerbation rates.

Overall, there is some evidence to support the asthma device but the primary outcome measure is subjective and some aspects of the trial are questionable e.g. after 3 months the study states that treatment regimes of some of the patients may have been changed but no information provided on who this affected and what the changes entailed. Changes in QOL score may therefore have been due to adjustment and optimisation of medication and not due to the TCLA device. Participants with 'high treatment intensity and poor symptom control' showed the greatest improvement in QOL score[i], however it must be noted that participants in this category are more likely to show bigger improvements anyway as they have more room for improvement. It must also be noted that this study was funded by Airsonnett AB, manufacturers of the TCLA device.

Pedroletti et al[vi] conducted a double-blind placebo-controlled crossover trial. 28 patients were recruited from two university hospitals in Linkoping and Stockholm (mean age 18.8 years) with mild to moderate allergic asthma. Participants were initially randomized to receive 10 weeks 'add-on' active or placebo treatment with a nocturnal TCLA device followed by a 2-week 'wash-out period' followed by use of the

alternative treatment for 10 weeks. Participants were excluded if they were on allergen specific immunotherapy (such as omalizumab). The primary outcome measure was change in quality of life score, measured using the mini-AQLQ. Secondary outcomes included; exhaled nitric oxide (FENO) measured by spirometry.

Only 20 patients were included in the analysis. Some details of patients not included in the analysis and reasons for exclusion were provided (2 pregnancy-related, 2 non medical reason, 4 breached protocol). The study found that compared to placebo, active treatment improved mini-AQLQ score (mean score difference 0.54, $p<0.05$). Compared to placebo, active treatment lowered exhaled nitric oxide (-6.4 ppb, $p<0.05$). However lung function did not significantly change in either group.

There were a number of limitations associated with this study. Firstly the small sample size (n=20) and short time to follow up for each treatment group (10 weeks). No information was provided on the randomisation process so it is difficult to deduce if this was done appropriately. No information is provided on group demographics so it cannot be deduced if groups were similar at the outset. Analysis was carried out by per-protocol procedures and not intention to treat therefore effect of randomisation was lost and potential confounders may have accounted for results seen. NB. 2 of the authors are associated with the manufacturer, Airsonnett.

Quality of study methodology was assessed using the Effective Public Health Practice Project (EPHPP) quality assessment tool for quantitative studies. Both RCTs were assessed as 'moderate' quality. Component ratings included selection bias, study design, confounders, blinding, data collection methods and withdrawals.
Two other studies have also been conducted but only poster presentations are available. In the first study[vii] 9 children (aged 7-12 years) who had lived in a dust mite-free environment for more than 3 months were randomized to start with TCLA (n=4) or a control (n=5) when returned home. Outcome measures included: asthma symptoms, exhaled nitric oxide levels, eosinophil count in sputum and lung function which were measured at the start of returning home and after a period of 2-3 months. The authors state that compared to the control group, the TLA group had well-controlled inflammation markers (exhaled nitric oxide levels and sputum eosinophils). They also state that no difference in asthma symptoms or lung function was observed between the control and intervention group.
In the second study[viii] 7 TCLA devices were installed in the bedrooms of 7 adult patients with allergic asthma for 4 weeks. Outcome was assessed using the mini-AQLQ. It was stated that patients reported an improvement of more than 20 percent in their quality of life. Authors also stated that medication was not changed during the trial.

It must be noted that e*xtremely limited* details were provided on *both* poster presentations in terms of the study design, methods and results and based on this the small sample sizes used and the short length of follow up, particularly for poster 2, the evidence is not sufficient as a basis for recommendations. Both studies were assessed by the EPHPP quality assessment tool as 'weak'.

The use of TCLA in the treatment of chronic allergic asthma has predominately been evaluated using quality of life questionnaires but limited evidence of effectiveness has been demonstrated with regards to more objective outcomes such as airway inflammation and in particular, lung function. No evidence has been provided on the effectiveness of TCLA on reducing other objective outcomes such as asthma exacerbations, reducing medication use or reducing hospital admissions.

Cost Effectiveness

One study looked at the cost-effectiveness of adding TCLA treatment to optimise standard therapy for adolescents with atopic asthma compared to placebo[ix]. The costs and effects are from a Swedish health-care perspective and the main outcome of interest was cost per QALY gained.

The paper reported that TCLA provided a mean gain of 0.25 QALY per patient, but the data that went into the QALY calculation is not provided in the paper or in another referenced paper, so it is difficult to determine whether this value is accurate.

It is also reported that the cost per QALY gained was 35,000 euros (~£28,000), when the cost of the TCLA is valued under *8200 euros* (~£6600). *Importantly it must be noted that the cost of the TCLA device has not yet been determined and it may cost considerably more than 8200 euros*. In comparison, the cost per QALY gained for inhaled corticosteroids at various dosage levels (as per BTS guidelines) has been estimated to be between £4800 and £18,300[x]. However NICE have queried the generalisability of these values to the UK and concluded that their use may be limited due to the pooling of results from a number of countries. Despite this, the values still give an indication of estimated cost per QALY and provide a comparison for TCLA.

To account for the unknown cost of the TCLA device in the economic analysis, the researchers performed their analyses over a range of costs. Only direct costs of using TCLA were included, no societal costs were taken into consideration during the calculations. Also, only 20 patients were included in the study that this economic analysis is based on.

Appendix 2: Mini-AQLQ[xi]

In general how much of the time during the last 2 weeks did you:

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	Hardly Any of the Time	None of the Time
1. Feel short of breath							
2. Feel bothered by or have to avoid dust in the environment?							
3. Feel frustrated as a result of your asthma?							
4. Feel bothered by coughing?							
5. Feel afraid of not having your asthma medication available?							
6. Experience a feeling of chest tightness or chest heaviness?							
7. Feel bothered by or have to avoid cigarette smoke in the environment?							
8. Have difficulty getting a good night's sleep as a result of your asthma?							
9. Feel concerned about having asthma?							
10. Experience a wheeze in your chest?							
11. Feel bothered by or have to avoid going outside because of weather or air pollution?							
How limited have you been during the last 2 weeks doing these activities as a result of your asthma?							
	Totally Limited	Extremely Limited	Very Limited	Moderate Limitation	Some Limitation	A Little Limitation	Not at all Limited
12. Strenuous activities e.g. running							
13. Moderate activities e.g. walking							
14. Social activities e.g. talking							
15. Work-related activities							

Appendix 3: PAEDIATRIC ASTHMA QUALITY OF LIFE QUESTIONNAIRE[vi]

We want you to tell us how much you have been bothered doing these things **during the last week because of your asthma.**

HOW BOTHERED HAVE YOU BEEN DURING THE LAST WEEK?

	Extremely bothered	Very bothered	Quite bothered	Somewhat bothered	Bothered a bit	Hardly bothered	Not bothered	Activity not done
1. Playing								
2. Running								
3. Sleeping								
4. Coughing								
In General how often during the last week did you:								
	All of the time	Most of the time	Quite often	Some of the time	Once in a while	Hardly any of the time	None of the time	
5. Feel frustrated because of your asthma?								
6. Feel tired because of your asthma?								
7. Feel worried, concerned or troubled because of your asthma?								
HOW BOTHERED HAVE YOU BEEN DURING THE LAST WEEK BY?								
8. Asthma attacks?								
9. Feel ANGRY because of your								

asthma?								
HOW BOTHERED HAVE YOU BEEN DURING THE LAST WEEK BY?								
10. Wheezing ?								
IN GENERAL, HOW OFTEN DURING THE LAST WEEK DID YOU:								
11. Feel IRRITABLE / grumpy because of your asthma?								

References

[i] Custovic A et al. Allergen avoidance in the treatment of asthma and atopic disorders. Thorax 1998; 53:63-72

[ii] Platts-Mills TA et al. The role of intervention in established allergy: avoidance of indoor allergens in the treatment of chronic allergic disease. J Allergy Clin Immunol 2000;106(5):787-804

[iii] Tunnicliffe WS et al. Sensitivity and exposure to indoor allergens in adults with differing asthma severity. Eur Respir J 1999;13:654-9

[iv] British Guideline on the Management of Asthma http://www.brit-thoracic.org.uk/Portals/0/Guidelines/AsthmaGuidelines/sign101%20Jan%202012.pdf Last accessed 05/03/2013

[v] Boyle RJ, Pedroletti C, Wickman M, Bjermer L, Valovirta E, Dahl R, von Berg A, Zetterström O, Warner JO. (2011) Nocturnal temperature controlled laminar airflow for treating atopic asthma: a randomised controlled trial. Thorax. 67:215-221

[vi] Pedroletti C, Millinger E, Dahlén B, Söderman P, Zetterström O. (2009) Clinical effects of purified air administered to the breathing zone in allergic asthma: A double-blind randomized cross-over trial. Respiratory Medicine. 103(9): 1313-1319.

[vii] Ragazzo V, Costella S, Kantar. Temperature controlled Laminar Airflow (TLA) treatment controls inflammation during summer leave after a long-term, high-altitude stay in asthmatic children with a dust mite allergy. Poster presentation.

[viii] Svensson, P. Influence of clean air directly in to the breathing zone on allergy and asthma patients during night-time. Poster presentation.

[ix] Brodtkorb TH, Zetterström O, Tinghög G. (2010) Cost-effectiveness of clean air administered to the breathing zone in allergic asthma. Clinical Respiratory Journal. 4(2): 104-10.

[x] Inhaled corticosteroids for the treatment of chronic asthma in adults and in children aged 12 years and over; NICE. Last accessed 05/03/2013 http://www.nice.org.uk/nicemedia/pdf/TA138Guidance.pdf

[xi] Measurement of health-related quality of life and asthma control http://www.qoltech.co.uk/miniaqlq.html Last accessed 05/03/2013