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Australia and New Zealand Horizon Scanning Network

ANZHSN

AN INITIATIVE OF THE NATIONAL, STATE AND
TERRITORY GOVERNMENTS OF AUSTRALIA
AND THE GOVERNMENT OF NEW ZEALAND

Horizon Scanning Technology Prioritising Summary

Bronchial thermoplasty for asthma

August 2007



ASERNIP/S

**Australian
Safety
and Efficacy
Register
of New
Interventional
Procedures -
Surgical**



**Royal Australasian
College of Surgeons**

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PRIORITISING SUMMARY

REGISTER ID: S000046

NAME OF TECHNOLOGY: BRONCHIAL THERMOPLASTY (ALAIR® BRONCHIAL THERMOPLASTY SYSTEM)

PURPOSE AND TARGET GROUP: ASTHMA PATIENTS

STAGE OF DEVELOPMENT (IN AUSTRALIA):

- | | |
|---|---|
| <input type="checkbox"/> Yet to emerge | <input type="checkbox"/> Established |
| <input type="checkbox"/> Experimental | <input type="checkbox"/> Established <i>but</i> changed indication or modification of technique |
| <input checked="" type="checkbox"/> Investigational | <input type="checkbox"/> Should be taken out of use |
| <input type="checkbox"/> Nearly established | |

AUSTRALIAN THERAPEUTIC GOODS ADMINISTRATION APPROVAL

- | | | |
|---|-------------|-----|
| <input type="checkbox"/> Yes | ARTG number | N/A |
| <input checked="" type="checkbox"/> No | | |
| <input type="checkbox"/> Not applicable | | |

INTERNATIONAL UTILISATION:

COUNTRY	LEVEL OF USE		
	Trials Underway or Completed	Limited Use	Widely Diffused
Australia	✓		
Brazil	✓		
Canada	✓		
Denmark	✓		
Netherlands	✓		
United Kingdom	✓		
United States	✓		

IMPACT SUMMARY:

Asthmatax Inc. (California, United States) provides the Alair Bronchial Thermoplasty System with the aim of treating asthma. The technology is currently not available in Australia.

BACKGROUND

Asthma is a chronic disease characterised by wheezing, tightness in the chest, and shortness of breath. The condition is caused by widespread reversible airflow obstruction and airway hyperresponsiveness (Sims 2006).

Airflow obstruction can occur through narrowing of the airways as a result of smooth muscle contraction, mucus secretion, loss of mechanical support from surrounding parenchyma, chronic inflammation of the airways, or a combination of these (Mitzner 2006, Sims 2006). Airway narrowing can be triggered by a wide range of triggers including allergens, irritants, infection, psychological stress or other neural activation (Mitzner 2006, Sims 2006). Contraction of airway smooth muscle has been reported to often contribute to airway narrowing during exacerbations (GINA 2002). In fact, patients with asthma have been noted to have increased smooth muscle mass, which has been shown to correlate with asthma severity (Woodruff et al. 2004, Pepe et al. 2005).

There is currently no cure for asthma (Woolcock et al. 2001). Management of asthma is aimed at maintaining normal pulmonary function, reducing/preventing exacerbations and hospital visits, identifying/reducing exposure to triggers, patient education, relief of acute episodes and improving the patients' quality of life (Sims 2003, Holcomb 2004). Medication, including bronchodilators (for smooth muscle relaxation) and corticosteroids (to reduce inflammation) are usually given as maintenance medication (to control symptoms and prevent exacerbations) or for acute episodes (Sims 2006). Unfortunately, despite this, some patients will experience persistent symptoms and frequent exacerbations requiring oral corticosteroid administration which is associated with significant side effects (American Thoracic Society 2000).

Bronchial thermoplasty (BT) involves the application of controlled thermal energy directly to the airways through a bronchoscope with the aim of reducing the ability of smooth muscle to contract (Miller et al. 2005). This is achieved through a reduction in smooth muscle mass via coagulation of the bronchial tissue in airway walls where BT is applied (Miller et al. 2005). Radiofrequency energy is delivered to the airway wall heating tissue to approximately 65°C, enough to reduce smooth muscle mass but avoid tissue destruction and scarring (Danek et al. 2004). The Alair Bronchial Thermoplasty System consists of a uniquely designed bronchial catheter and radiofrequency generator. The catheter, designed to fit through the working channel of a standard bronchoscope has an expandable four electrode basket with heating and temperature sensing elements. The generator delivers 460 kHz of monopolar radiofrequency energy using active feedback to maintain target treatment temperature (Miller et al. 2005).

CLINICAL NEED AND BURDEN OF DISEASE

Asthma is a common chronic condition among Australians affecting 14% to 16% of children and 10% to 12% of adults (AIHW 2005). However, it is not a major cause of death, accounting for 314 deaths (0.3% of all deaths) in 2003 (AIHW 2005).

Asthma ranges in severity from mild, intermittent symptoms, causing few problems, to severe and persistent wheezing and shortness of breath, which may potentially be life threatening. The burden of disease rankings (based on years lost to disability) ranks asthma as number 14 for males, seven for females and nine for all persons combined (Wilson et al. 2007).

DIFFUSION

In the United States, the Alair Bronchial Thermoplasty System is approved for investigational use only. The system has also received CE Mark in Europe. The system is currently being trialled in the AIR2 Trial in Australia, Brazil, Canada, Denmark, Netherlands, United Kingdom and the United States (ClinicalTrials.gov identifier: NCT00231114). There are also two completed trials, which are reported in the following sections.

COMPARATORS

Currently, bronchial thermoplasty is the only surgical option available for the treatment of asthma. Other non-surgical treatment options for asthma are (AIHW 2005):

- Written asthma action plans (instructions on how to recognise worsening asthma and what action to take)
- Inhaled corticosteroids
- Other inhaled medications (including combination of inhaled corticosteroids with a long acting bronchodilator)

SAFETY AND EFFECTIVENESS ISSUES

The randomized, controlled Asthma Intervention Research (AIR) Trial, examined the safety and efficacy of BT as a treatment for stable moderate or severe persistent asthma (Cox et al 2007). One hundred and twelve patients requiring daily therapy with inhaled corticosteroids (ICS) and long acting β_2 -adrenergic agonists (LABA) in 11 centres across four countries participated. Patients were randomised to either BT (n = 56) or to a control group (n = 56).

The study was divided into a four week baseline period, treatment period of six to nine weeks and 12 month follow-up period. During the baseline period, patients received maintenance therapy (ICS plus LABA) for two weeks followed by ICS only for another two. During this period, it was required patients experience worsening asthma control during the ICS only period following LABA withdrawal (demonstrated by Asthma Control Questionnaire¹ or 5% decline in average morning peak expiratory flow, PEF). The treatment period was the period during which BT group patients received three BT applications (after resuming maintenance therapy) with the Alair Bronchial Thermoplasty

¹ Asthma Control Questionnaire (ACQ): Six question questionnaire and measurement of pre-bronchodilator FEV₁. Responses are rated on scale of 0-6 with higher numbers indicating lower asthma control. The minimal important change in the ACQ score is 0.5.

System. Follow-up was then undertaken for 12 months after the last treatment. Control group patients received three treatment visits at three week intervals for clinical review, spirometric assessment and administration of a systematic corticosteroid similar to that administered to the BT group. At the three month follow-up, patients discontinued LABA unless they experienced a severe exacerbation² or poor asthma control. Patients who did not resume LABA were evaluated after six and 12 months. Patients who resumed LABA were evaluated at six months and two weeks and 12 months and two weeks, following LABA withdrawal for two weeks.

Seven patients withdrew consent for the study, five were lost to follow-up and a few tests were incomplete at each stage. This left between 46 and 50 patients in each group for each follow-up analysis.

The primary outcome was the difference in change in rate of mild exacerbations from baseline between the two groups. After 12 months, the mean number of mild exacerbations³ experienced per patient per week in the BT group declined. These patients experienced a drop from 0.35 ± 0.32 to 0.18 ± 0.31 mild exacerbations per patient per week, while control patients experienced a small increase from 0.28 ± 0.31 to 0.31 ± 0.46 mild exacerbations per patient per week. At three and 12 months (but not six months) the difference between groups in change from baseline was statistically significant ($p = 0.03$). The average number of exacerbations during the two week ICS only periods at three, six and 12 months (compared to baseline) was significantly ($p = 0.005$) reduced in the BT group but not the control group (-0.16 ± 0.37 versus 0.04 ± 0.29 mild exacerbations per subject per week). Further statistical analysis revealed a significant difference between the groups ($p = 0.001$). This translated to approximately 10 fewer mild exacerbations per patient each year in the BT group.

The mean number of severe exacerbations in the BT group was reduced at 12 months. However unlike mild exacerbations, control group patients also experienced a reduction. Bronchial thermoplasty did not significantly reduce the number of severe exacerbations when compared to maintenance therapy alone.

Various other secondary outcomes were also measured in this study. Table 1 demonstrates all secondary outcomes evaluated at three months while patients were receiving ICS and LABA (Table 1). The change at three months was significantly greater for morning PEF, percentage of symptom free days⁴, symptom score⁵, Asthma Quality of

² Severe exacerbation: event requiring treatment with oral corticosteroids, or decrease in morning PEF for 1 or more days of >30% below average baseline morning PEF (recorded during week immediately preceding withdrawal from LABA).

³ Exacerbation: at least 1 of the following events on 2 consecutive days: reduction in morning PEF of $\geq 20\%$ below average value (based on PEF recorded during week immediately preceding withdrawal of LABA), need for >3 additional puffs of rescue medication exceeding average use during week immediately preceding the withdrawal of LABA, or nocturnal awakening caused by asthma symptoms.

⁴ Symptom free day: day during which symptom score is 0 and there is no night time awakening.

⁵ Symptom score: total of individual scores (on 0-3 scale with higher number indicating more frequent or severe symptoms or both) for night time wheezing and cough and day time wheezing, cough, breathlessness and sputum production. Maximum score is 18.

Life Questionnaire (AQLQ)⁶ score and Asthma Control Questionnaire (ACQ) score in the BT group. However it is notable that there was a major baseline imbalance between the groups for morning PEF and so there was little difference between the mean PEFs at three months. No significant change for, percent change in pre-bronchodilator FEV₁ (% predicted), post-bronchodilator FEV₁ (% predicted) and use of rescue medication.

Table 1: Secondary outcomes at 3 months in patients on ICS + LABA

Outcome	BT group		Control group		p value*
	Baseline Mean (\pm sd)	3 months Mean (\pm sd)	Baseline Mean (\pm sd)	3 months Mean (\pm sd)	
Morning PEF (L/min)	369.4 \pm 97.9	397.4 \pm 100.7	394.0 \pm 98.2	395.4 \pm 88.6	0.003
Pre-bronchodilator FEV₁ (%predicted)	72.0 \pm 9.9	74.3 \pm 14.3	75.8 \pm 9.0	75.7 \pm 10.1	NS
Post-bronchodilator FEV₁ (%predicted)	83.7 \pm 12.4	83.3 \pm 14.1	84.6 \pm 9.7	84.3 \pm 11.4	NS
Rescue medication usage (no. puffs per week)	10.3 \pm 14.0	6.6 \pm 11.7	6.6 \pm 10.1	7.5 \pm 10.9	NS
Symptom free days (%)	36.9 \pm 35.3	59.5 \pm 39.8	47.6 \pm 38.2	53.7 \pm 38.6	0.03
Symptom score	2.49 \pm 2.31	1.31 \pm 1.86	1.97 \pm 2.67	1.64 \pm 1.87	0.05
AQLQ score	5.58 \pm 1.05	6.06 \pm 1.02	5.72 \pm 0.94	5.72 \pm 1.23	0.01
ACQ score	1.43 \pm 0.67	1.13 \pm 0.83	1.39 \pm 0.81	1.38 \pm 0.93	0.05

Note: p values are for comparisons of mean change from baseline between BT and control groups; NS: not significant.

Table 2 demonstrates all secondary outcomes evaluated at twelve months while patients were receiving ICS only (Table 2). The change at 12 months was significantly greater for morning PEF, afternoon PEF, use of rescue medication, percentage of symptom free days (which translated into 148 additional symptom free days per year in the BT group, compared to 62 in control), total symptom score, AQLQ score and ACQ score. As previously, the PEFs were not balanced between the groups at baseline. No significant change for, percent change in pre-bronchodilator FEV₁ (% predicted), post-bronchodilator FEV₁ (% predicted) and airway responsiveness.

⁶ AQLQ: Quality of Life questionnaire with 32 items covering asthma related symptoms and limitations during the 2 weeks preceding questionnaire administration. Responses scored on scale of 1-7 with higher numbers indicating better quality of life. Minimal important change in score considered to be 0.5.

Table 2: Secondary outcomes at 12 months on ICS alone

Outcome	BT group		Control group		p value*
	Baseline Mean (\pm sd)	12 months Mean (\pm sd)	Baseline Mean (\pm sd)	12 months Mean (\pm sd)	
Morning PEF (L/min)	349.3 \pm 90.6	388.6 \pm 105.0	372.4 \pm 99.9	380.9 \pm 92.9	0.003
Pm PEF (L/min)	359.7 \pm 88.4	397.4 \pm 102.8	379.1 \pm 98.7	389.0 \pm 93.9	0.006
Pre-bronchodilator FEV₁ (%predicted)	70.4 \pm 12.1	75.2 \pm 13.9	70.7 \pm 10.5	72.4 \pm 12.6	NS
Post-bronchodilator FEV₁ (%predicted)	83.5 \pm 12.0	83.7 \pm 13.4	81.2 \pm 11.0	81.6 \pm 11.4	NS
Airway responsiveness (geometric mean (95% CI) PC₂₀ [mg/ml])	0.24 (0.15, 0.40)	0.61 (0.36, 1.03)	0.32 (0.20, 0.51)	0.5 (0.31, 0.80)	NS
Rescue medication usage (no. puffs per week)	19.8 \pm 17.2	10.9 \pm 15.0	16.0 \pm 18.8	14.8 \pm 21.2	0.04
Symptom free days (%)	24.7 \pm 30.5	65.4 \pm 40.4	32.3 \pm 34.3	49.4 \pm 41.3	0.005
Symptom score	3.16 \pm 2.21	1.25 \pm 1.97	2.65 \pm 2.55	2.00 \pm 2.23	0.01
AQLQ score	4.91 \pm 1.23	6.18 \pm 0.88	5.15 \pm 1.19	5.72 \pm 1.11	0.003
ACQ score	2.50 \pm 0.92	1.32 \pm 0.85	2.16 \pm 0.86	1.69 \pm 0.99	0.001

Note: p values are for comparisons of mean change from baseline between BT and control groups; NS: not significant.

A post hoc analysis of a more severe subset of patients requiring high maintenance doses (> 1000 μ g) of the corticosteroid beclomethasone or an equivalent was also performed. Analysis of 16 BT and 16 control patients showed greater improvements than the full cohort following BT for airflow (morning PEF, $p = 0.05$), airway hyperresponsiveness ($p = 0.03$), AQLQ score ($p = 0.002$) and ACQ score ($p = 0.004$). Unexpectedly however, changes in the use of rescue medication, percentage of symptom free days and total symptom score, which all demonstrated significant improvements following BT at 12 months in the full cohort, did not demonstrate statistically significant improvements at 12 months. Pre bronchodilator FEV₁ values were not statistically significant at 12 months.

There was an increase in adverse respiratory events in BT group patients immediately after the procedure with return to baseline values during the post treatment period (three months onwards). During the treatment period, 407 adverse respiratory events were reported (69% mild, 28% moderate and 3% severe). Control group patients reported 106 adverse respiratory events (69% mild, 30% moderate and 1 % severe), while BT group patients reported 301 adverse respiratory events. During the treatment period the most common adverse respiratory adverse events included dyspnea (19.9%), wheezing (17%), cough (16%), chest discomfort (10.3%), night awakenings (9.8%) and productive cough (8.6%), in the BT group. In the control group, the most common adverse respiratory events during the treatment period included dyspnea (21.7%), chest discomfort (18.9%),

cough (11.3%), nasal congestion (10.4%), productive cough (8.5%) and wheezing (7.5%). Dyspnea, wheezing, cough, chest discomfort, night awakening and productive cough all occurred statistically significantly more in the BT group ($p \leq 0.004$). Dry mouth also occurred significantly more often in the BT group ($p = 0.03$). In the BT group, most adverse events occurred within one day after the procedure and resolved within seven days after onset. Four patients required six hospitalisations (four for asthma exacerbation, one for partial collapse of lower left lobe and one for pleurisy) in the BT group compared to two hospitalisations in the control group. One additional hospitalisation for an adverse respiratory event not related to BT (abscess in left upper lobe requiring resection) occurred at 14 months in a BT patient who had completed the trial without complications. The reasons for the large difference in adverse respiratory events were not reported. However, given that the greatest difference in adverse events between groups occurred during the treatment period it is a possibility that application of bronchial thermoplasty was involved.

During the post treatment periods the proportion of subjects with adverse respiratory events was low and similar in the two groups. Three patients in the BT group were hospitalised for chest infection ($n = 1$) and asthma exacerbation ($n = 2$). This compared to three hospitalisations in two patients in the control group for increased asthma symptoms. There were no deaths reported during study.

Cox et al. (2006) reported the application of BT in 16 patients with stable, moderate to mild asthma. Patients at two investigational sites underwent BT of intra parenchymal airways with the Alair System. Patients were generally treated in three bronchoscopy sessions scheduled at least three weeks apart (one session for each lower lobe and another session for accessible airways in both upper lobes). The right middle lobe was not treated.

Intra procedurally BT was performed with no major complications or post procedure hospital admissions. Two patients required four BT sessions (reasons not stated) and one patient received two sessions due to concern regarding need for antibiotics for management of respiratory symptoms after the second treatment. Out of 312 adverse events reported over two years, 155 were classified as related to the device or procedure. All adverse events, which included 130 mild and 25 moderate events, occurred within one week from BT application and either resolved spontaneously (42%) or were managed with medications (42%). This is a similar finding to that reported by Cox et al. 2007. The most common adverse events were increased cough, dyspnea, wheezing, bronchospasms, fever, chest discomfort and mucus production. Neither the incidence nor the severity of the adverse events increased following subsequent treatment sessions. No emergency department visits, hospitalisations or deaths attributed to treatment or asthma exacerbations were reported.

At baseline, 5/16 patients required LABA and 15/16 required ICS. Medication use was reported in two periods: prior to the 12 week follow-up, and at, or after the 12 week follow-up. Prior to the 12 week follow-up, two patients were prescribed LABA for control of increased symptoms. During the second period (at or after the 12 week follow-up), one patient was prescribed LABA, one increased ICS dosage, two increased ICS and

LABA, two decreased ICS dosage, two decreased LABA and ICS (one discontinued LABA completely), and the remaining six patients remained unchanged. No significant changes in the use of rescue medication were reported up to the 12 week follow-up.

CT scans were also performed at baseline, one and two years post treatment and were reviewed by both a radiologist and pulmonologist. No clinically significant findings including evidence of bronchiectasis, bronchial wall thickening or other parenchymal changes were found as a result of BT.

Although the study was designed as a safety and feasibility study and was not powered to detect efficacy outcomes, they were nonetheless reported.

Both pre-bronchodilator FEV₁ (% predicted) and post-bronchodilator FEV₁ (% predicted) did not significantly change from baseline to the two year follow-up, although pre-bronchodilator FEV₁ (% predicted) experienced significant increases at 12 weeks (p = 0.043) and one year (p = 0.030). Similarly, no significant changes in mean post-bronchodilator FEV₁/FVC ratios were detected.

Peak morning and afternoon expiratory flow showed statistically significant improvement at 12 weeks. Morning PEF increased from 427.1 ± 108.1 to 465.9 ± 111.8 L/min (p = 0.010). Evening PEF increased from 435.3 ± 96.0 to 476.4 ± 114.5 L/min (p = 0.007).

The mean percentage of symptom free days also significantly improved from a baseline of 47 ± 33 to 73 ± 27 at 12 weeks (p = 0.015).

Airway hyperresponsiveness also improved, with the geometric mean value of the provocative concentration of methacholine causing a 20% fall in FEV₁ (PC₂₀) improving from 0.92 mg/ml (95% CI, 0.42 – 1.99) at baseline to 4.75 mg/ml (95% CI, 2.51 - 8.85) at 12 weeks, 5.45 mg/ml (95% CI, 1.54 - 19.32) at one year and 3.40 mg/ml (95% CI, 1.35 - 8.52) at two years. Some patients did not experience a 20% drop in FEV₁ even with the highest concentration of methacholine (16 mg/ml). These patients were given value of 16 for purposes of analysis thus making the results somewhat conservative.

COST IMPACT

The cost of bronchial thermoplasty for the treatment of asthma was not revealed in the searches conducted.

ETHICAL, CULTURAL OR RELIGIOUS CONSIDERATIONS

No issues were identified from material.

OTHER ISSUES

No issues were identified from the retrieved material.

SUMMARY OF FINDINGS

Bronchial Thermoplasty has the potential to provide relief of symptoms, better asthma control and decrease the level of airway hyperresponsiveness in patients who continue or have discontinued daily use of LABA. The technology has the potential of being used in conjunction with current medications to provide increased benefit to the patient. Studies to determine the severity of asthma that would benefit most from this therapy and that evaluate the most suitable airways to provide the safest and most effective treatment are required.

The long term consequences of the procedure are not known at this stage. The potential for disorders such as permanent widening of airways, chronic infections with ensuing bronchiectasis, or increased collapsibility of the airway wall exists and should be investigated in future studies.

HEALTHPACT ACTION:

Based on the low level of evidence currently available and the potential risks associated with the use of this technology, bronchial thermoplasty will be monitored for 12 months.

NUMBER OF STUDIES INCLUDED

Total number of studies	2
Level II intervention evidence	1
Level IV intervention evidence	1

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SOURCES OF FURTHER INFORMATION:

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SEARCH CRITERIA TO BE USED:

Asthma/surgery*

Asthma/therapy*

Bronchi/surgery*

Catheter ablation

Thermography/methods*

Bronchi thermoplasty