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TITLE:	**Bronchial Thermoplasty for the Treatment of Severe Asthma**
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CALIFORNIA TECHNOLOGY ASSESSMENT FORUM℠

BRONCHIAL THERMOPLASTY FOR THE TREATMENT OF SEVERE ASTHMA

A Technology Assessment

INTRODUCTION

The California Technology Assessment Forum (CTAF) was asked to assess the evidence for the use of bronchial thermoplasty for the treatment of asthma. Asthma is primarily treated with therapies that reduce inflammation and relax smooth muscle. Bronchial thermoplasty is a novel therapy designed to decrease the volume of smooth muscle in the airways of the lung in patients with severe refractory asthma.

BACKGROUND

Asthma

Asthma is increasingly prevalent in the United States with approximately 8% of Americans diagnosed with the disease in 2009.[1] This represents a 12% increase from 2001.[1] Asthma typically presents with shortness of breath accompanied by a cough, chest tightness and wheezing.[2] Many patients also suffer from eczema and allergic rhinitis. The pathophysiology of asthma involves chronic inflammation of the airways, bronchial hyper-reactivity to stimuli such as cold air, allergens, or infectious organisms, and airway remodeling that leads to reversible airway obstruction.[3-5] Patients with asthma usually have an overabundance of eosinophils in their airways and elevated levels of IgE in their blood.[2]

The goals of therapy for asthma are to eliminate symptoms during both the day and night, to normalize measures of lung function, and to reduce the risk of future exacerbations. The achievement of these goals must be balanced with the costs and risks for adverse events associated with treatment. Anti-inflammatory therapy with corticosteroids is the primary treatment for asthma. Guidelines recommend a step-wise approach to the treatment of asthma.[2] The treatment for mild, persistent asthma is low-dose inhaled corticosteroids (ICS), which deliver the steroids to the airways to reduce inflammation there and minimize the adverse effects associated with systemic steroids. Most commonly long-acting beta-agonist (LABA) therapy is added to increasing doses of ICS for the treatment for moderate to severe persistent asthma. In severe asthma, when high dose ICS and LABAs are insufficient, leukotriene modifying agents (LMAs) and anti-IgE monoclonal antibodies may be added. Some patients with severe asthma require daily oral corticosteroid (OCS) treatment to control their symptoms.

Approximately 10% of patients with asthma suffer from severe or refractory asthma. [6,7] Patients with severe asthma have persistent symptoms despite adequate doses of inhaled corticosteroids and other medications including multiple courses of oral corticosteroids. Severe asthma is more common in women and is less likely to be associated with either allergies or atopy.[8,9] The evaluation of severe asthma includes ruling out other potential causes including poor inhaler technique, inadequate adherence to therapy, exposures to environmental triggers, cigarette smoking, gastroesophageal reflux disease, obstructive sleep apnea, chronic rhinitis or sinusitis, and obesity.[10,11] The American Thoracic Society (ATS) definition requires that patients meet at least one major characteristic and two minor characteristics.[12] The two major characteristics are (1) oral corticosteroids at least 50% of the year and (2) high dose ICS. The seven minor characteristics are (1) daily treatment with a controller medication in addition to ICS, (2) short acting beta-agonists on a daily basis, (3) persistent airway obstruction as measured by the forced expiratory volume in one second (FEV1 < 80% of predicted), (4) one or more urgent care visits for asthma annually, (5) three or more OCS bursts annually, (6) prompt deterioration with ≤ 25% reduction in oral or inhaled corticosteroid dose, and (7) near-fatal asthma event in the past. As suggested above, some of the measurements that indicated asthma severity include the dose of ICS and OCS required for adequate control, the pre-bronchodilator FEV1, and the provocative concentration of methacholine required to lower the FEV1 by 20% (PC20).

Bronchial Thermoplasty

Bronchial thermoplasty is a novel therapy that uses radiofrequency energy to heat the airways in order to reduce excess smooth muscle mass in the airways. Patients with chronic asthma have more airway smooth muscle than non-asthmatics.[3,13] Beta-agonist therapy temporarily reduces bronchoconstriction, but bronchial thermoplasty is the first therapeutic attempt to achieve a long-term reduction in airway smooth muscle mass and potentially reduce asthma severity. The thermal energy is hypothesized to disrupt the interaction between actin and myosin and to denature muscle proteins.[14]

The patient's asthma must be stable prior to bronchial thermoplasty. The patient receives 50 mg of prednisone daily for five days beginning three days before therapy.[15] Bronchial thermoplasty requires a series of three bronchoscopies spaced at three-week intervals. The fist session treats the right lower lobe, the second treats the left lower lobe, and the third treats the two upper lobes. The right middle lobe is not treated. Each session takes approximately 30 to 60 minutes. During each session, a specially designed catheter is inserted through the working channel of a flexible bronchoscope down to airways 3 mm in diameter. A four-electrode array 5 mm in length at the end of the catheter is expanded to contact the walls of the airway and then activated to deliver radiofrequency energy. The electrical resistance of the airway tissue converts the energy into heat. The array is then collapsed, moved, re-expanded and the process repeated to treat as much as possible of the airways 3 mm in diameter or larger. Approximately 60 activations are required each therapy session. A video of the procedure can be viewed on the website of the New England Journal of Medicine (http://www.nejm.org/doi/full/10.1056/NEJMoa064707).

During the post-treatment period, patients may experience an increase in cough, asthma exacerbations, and mucous plugging. There does not appear to be an increased risk for bronchial dilation or bronchiectasis. Airway smooth muscle is thought to function to clear mucous from the airways and promote the flow of lymph.

TECHNOLOGY ASSESSMENT (TA)

TA Criterion 1: The technology must have final approval from the appropriate government regulatory bodies.

Bronchial Thermoplasty is a procedure and the Alair® Bronchial Thermoplasty System by Asthmatx is the only device system currently used for this procedure. It is classified as a Class III device and received Premarket Approval (PMA) by the U.S. Food and Drug Administration (FDA) in April 2010 for the treatment of severe persistent asthma in patients 18 years and older not well controlled with standard of care treatment including ICS and LABA. Asthmatx will be performing a five-year post approval study per FDA requirement to assess the long-term safety and effectiveness of the system.

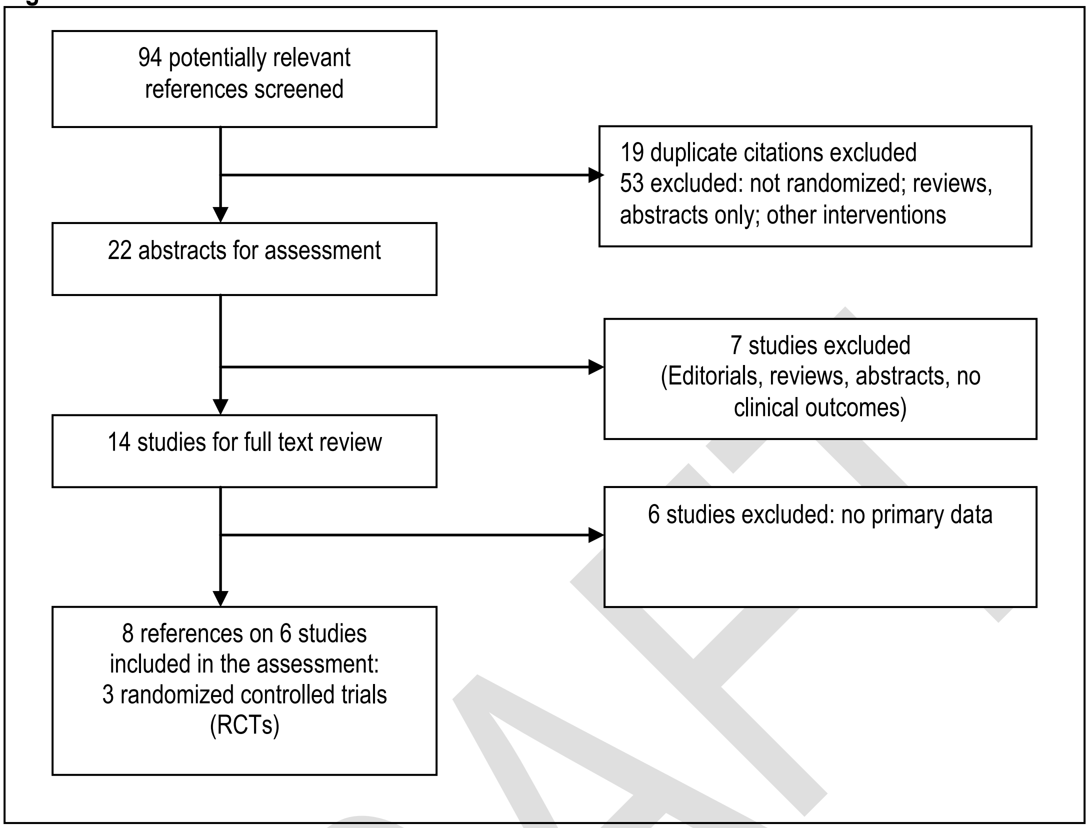
TA Criterion 1 is met.

TA Criterion 2: The scientific evidence must permit conclusions concerning the effectiveness of the technology regarding health outcomes.

The Medline database, Embase, Cochrane clinical trials database, Cochrane reviews database and the Database of Abstracts of Reviews of Effects (DARE) were searched using the key words “bronchial thermoplasty,” and “asthma.” The search was performed for the period from 1945 through September 2011. The detailed search criteria are shown in the Appendix. The bibliographies of systematic reviews and key articles were manually searched for additional references. References were also solicited from the manufacturers and local experts. The abstracts of citations were reviewed for relevance and all potentially relevant articles were reviewed in full.

The search identified 94 potentially relevant studies (Figure 1). After elimination of duplicate and non-relevant references including reviews and animal studies the search identified eight articles describing three case series[16-18] and three randomized trials.[19-23]

Figure 1: Selection of studies for inclusion in review



Level of Evidence: 1, 4, and 5.

TA Criterion 2 is met.

TA Criterion 3: The technology must improve net health outcomes.

The most important outcomes for patients would be a reduction in exacerbation of the asthma symptoms leading to unscheduled visits to their physician, ER visits, or admissions to the hospital. Other important outcomes include a reduction in the use of OCS, the number of exacerbations that require treatment with increased doses of OCS and quality of life, usually measured with the Asthma Quality of Life Questionnaire (AQLQ). The AQLQ is a well validated 32-item questionnaire in 4 domains (symptoms, activity limitation, emotional function and environmental stimuli).[24-26] Each question is answered using a seven-point Likert scale (7 = not impaired at all - 1 = severely impaired) reflecting the impact of Asthma on activities in the past two weeks. Scoring of the scale gives a number between 1 and 7 with higher scores represent better quality of life. A change of 0.5 points is the minimal important difference that would justify a change in the patient's treatment.[24-26]

Case series

The first case series was performed in dogs.[27] The investigators demonstrated that bronchial thermoplasty decreased the response of the dogs' airways to methacholine and that the effect lasted for at least three years. The reduction in airway responsiveness correlated with the reduction in airway smooth muscle and at three years, there was no evidence of smooth muscle regrowth. Adverse events included coughing and, on histology, inflammation of the airways with mucous plugging, but no inflammation of the alveoli.

The first human case series was attempted in nine patients without asthma who were scheduled for lung resection for lung cancer.[17] One patient was not treated because it was too difficult to position the catheter at the planned treatment site. The remaining eight patients were treated between five and twenty days prior to their lung resection. There were no adverse events noted between the bronchial thermoplasty and lung resection. One patient, whose lung was examined five days after treatment, had airway narrowing and retained mucus in two of the treated airways. Histologic sections of the treated airways revealed a reduction in smooth muscle in the airway and regenerating epithelial tissue. There was cartilage necrosis in half of the treated subjects and half of the specimens with necrosis had evidence of regenerating cartilage. Focal necrosis and pneumonitis was also seen frequently in the adjacent lung parenchyma.

The first case series of patients with asthma treated with asthma was published in 2006 by Cox and colleagues.[16] The investigators treated sixteen patients with stable asthma who were older than 18 years of age and had not had a recent respiratory tract infection and followed them for two years. The participants mean age was 39 and 62% were female. The study subjects did not have severe asthma: their mean FEV1 was 82% predicted, none were using OCS, only one was using high dose ICS, and 31% were using LABA. The participants reported a total of 155 device related adverse events. The majority of the patients reported cough, dyspnea, wheezing, and bronchospasm following the procedure. These tended to occur in the first 3 days following the procedure and resolved an average of 4.6 days following the procedure. None of the participants required hospitalization during the immediate period following bronchial thermoplasty and there were no serious adverse events associated with BT. The treatment had no significant effect on pre-bronchodilator FEV1 (82% at baseline to 86% at two years, p NR). There was no evidence of bronchiectasis, scarring, or other lung pathology on CT scans done two years after BT. The average morning PEF for the study subjects increased from 427 L/min at baseline to 466 L/min twelve weeks after BT ($p=0.01$) and the percentage of symptom free days increased from 47% to 73% ($p=0.015$).

Finally, there was one case report describing the first BT procedure performed in Brazil.[18] A 48 year-old man with moderate persistent asthma treated with ICS and LABA was treated with BT. At one year his FEV1 increased from 68% to 83% of predicted, his AQLQ score increased from 2.4 to 3.6, and his symptom free days increased from 0% to 64.5%. No adverse events were reported.

These case series suggest that there is an important increase in asthma-related symptoms in the week following each BT treatment session, but this is balanced by an increase in symptom free days during the one to two years following the procedure. Since there was no comparison group and it is known that asthma symptoms respond to the placebo effect, the magnitude of the long-term benefit is unclear. It appears that there are no important unexpected effects from the procedure on CT scan or clinically through two years of follow-up, but the case series only report on 16 patients through two years. Larger samples and longer follow-up are needed to rule out unexpected harms from heating the airways enough to destroy smooth muscle.

Randomized trials

Details of the randomized trials and their extended follow-up are summarized in the Tables. Table 1 summarizes the methodological quality of the trials. Table 2 summarizes the characteristics of the trials. Tables 3 and 4 summarize the major outcomes of the trials.

Table 1: Randomized trials of bronchial thermoplasty for severe asthma – Methodological Quality

Study	Randomization	Allocation concealment	Groups comparable	Outcome assessment blinded	Follow-up > 80%	Intention to treat analysis	Quality
Cox 2007 AIR	YES	YES	YES	NR	YES	YES	Fair No blinding
Thomson 2011 AIR extended follow-up	–	–	–	–	–	–	–
Pavord 2007 RISA	YES	YES	NO Symptom score higher in BT group (p=0.02), fewer symptoms free days (5.2 versus13.6)	NR	NO	YES	Poor No blinding, baseline differences in outcome, differential follow-up.
Castro 2010 AIR 2	YES	YES	YES	YES	YES	YES	Good Sham control
Castro 2011 AIR 2 extended follow-up	–	–	–	–	–	–	–

BT Bronchial thermoplasty

*All of the studies were funded by Asthmatix, the manufacturer of the Alair System for Bronchial Thermoplasty

Table 2: Randomized trials of bronchial thermoplasty for severe asthma - Study Characteristics

Study	N*	Location # sites	Inclusion criteria	Exclusion criteria	Age, years Sex, % female	OCS use, %	FEV1, % predicted	PC20, mg/ml	FU, mo	1° endpoint
Cox 2007 AIR	112R 101A	4 countries: UK, Canada, Brazil, Denmark 11 sites	18-65 years old Daily ICS ≥ 200B LABA ≥ 100S FEV1 60-85% PC20 < 8 Stable x 6 weeks Worse control with LABA withdrawal	≥ 3 lower respiratory infections requiring antibiotics in the 12 months Any respiratory tract infection in the past 6 weeks	40 56%	?0%	74%	0.30	12	Frequency of mild exacerbations when LABA withdrawn
Thomson 2011 AIR extended follow-up	69A								60	
Pavord 2007 RISA	34R 32A	3 countries: UK, Canada, Brazil 8 sites	18-65 years old Daily ICS ≥ 750F LABA ≥ 100S FEV1 ≥ 50% Airway hyper-responsiveness Uncontrolled symptoms	> 30 mg/day prednisone > 10 pack-years smoking	41 50%	47%	65%	0.25	12	NR
Castro 2010 AIR 2	297R 288A	6 countries: UK, Canada, Brazil, USA, Australia, Netherlands 30 sites	18-65 years old Daily ICS ≥ 100B LABA ≥ 100S FEV1 ≥ 60% AQLQ ≤ 6.25 Stable x 4 weeks	OCS > 10 Chronic sinus disease ≥ 10 pack-years smoking ≥ 3 hospitalizations for asthma ≥ 4 steroid pulses Life-threatening asthma	41 58%	3%	79%	0.28	12	AQLQ at 6, 9, and 12 months
Castro 2011 AIR 2 extended follow-up	166A								24	

* R = randomized, A = analyzed

Table 3: Randomized trials of bronchial thermoplasty for severe asthma - Study outcomes 1

Study	BT, n Control, n	PEF AM, L/min	PEF PM, L/min	FEV1, % predicted	Symptom-free days, %	Asthma Quality of Life (AQLQ)	Rescue medication use, puffs/7 days	Oral corticosteroid use
Cox 2007 AIR	55 54	349 to 389 372 to 381 p=0.003	360 to 397 379 to 389 p=0.006	70 to 75 71 to 72, p NS	25 to 65 32 to 49 p=0.005	4.9 to 6.2 5.2 to 5.7 p=0.003	20 to 11 16 to 15 p=0.04	NR
Thomson 2011 AIR extended follow-up	45 24			No change over 5 years				24-24-26-28-31 21-33-24 - - % with OCS use for asthma exacerbation each year of FU
Pavord 2007 RISA	15 17					+1.5 +0.4 p=0.001	-26 -6 p<0.05	4/8 stopped 1/7 stopped p=0.28
Castro 2010 AIR 2	190 98	384 to 412 386 to 409 p = 0.19		78% to 77% 80% to 79% p = 0.76	3.8 to 2.1 3.9 to 2.3 p = 0.36	4.30 to 5.66 4.32 to 5.48 p = 0.04	13 to 7 12 to 7 p = 0.19	
Castro 2011 AIR 2 extended follow-up	– 166			- No change at 2 years				

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Table 4: Randomized trials of bronchial thermoplasty for severe asthma - Study outcomes 2

Study	BT, n Control, n	ER visits, treatment period	ER visits total	Hospitalization, treatment period	Hospitalizations total	Days lost from work / school	Unscheduled MD visits	Asthma Control questionnaire (ACQ)
Cox 2007 AIR	55 54	NR	NR	6 0 p NR Number of events	9 3 p NR Number of events	NR	NR	2.5 to 1.3 2.2 to 1.7 p=0.001
Thomson 2011 AIR extended follow-up	45 24	–	4-7-5-9-5 0-12-5- - p = 1.0 % with ER visit each year of FU	–	7-7-2-2-2 0-0-5- - p NS % hospitalized for respiratory symptom each year of FU	NR	NR	NR
Pavord 2007 RISA	15 17	NR	NR	7 0 p NR Number of events	12 4 p NR Number of events	NR	NR	-1.0 -0.2 p=0.01
Castro 2010 AIR 2	190 98	NR	0.07 0.43 visits/subject/ year PPS 99.9% Post treatment period only	19 2 p NR Number of events	25 14 p NR Number of events	1.3 3.9 p = 0.007	NR	2.1 to 1.3 2.1 to 1.3 p = 0.14
Castro 2011 AIR 2 extended follow-up	– 166		– 11 patients with ER visits 6.6%		– 10 hospitalizations in 7 participants 4.2%			

The Asthma Intervention Research (AIR) Trial

The Asthma Intervention Research (AIR) trial was the first study to compare BT to usual care as a treatment for patients with moderate to severe asthma.[21] Patients with asthma stable for at least six weeks were eligible for randomization if they used ICS at a dose equivalent to 200 mcg per day of beclomethasone and LABA at a dose equivalent to 100 mcg per day of salmeterol. It is unclear if any of the participants were using OCS. Other inclusion criteria were age between 18 and 65 years, FEV1 of 60 to 85% predicted value, and airway hyper-responsiveness defined as a provocative concentration of methacholine required to lower the FEV1 by 20% (PC20) of less than 8 mg/ml. Additionally, potential participants were asked to stop their LABA for two weeks at baseline and were eligible for randomization if their score on the Asthma Control Questionnaire[28-30] (ACQ) increased at least 0.5 points or they experienced a decline of at least 5% in their morning PEF.

Participants were restarted on their LABA for the treatment period, but were asked to stop treatment with LABA at three, six, and twelve months if tolerated in order to assess outcomes. The primary outcome of the study was the rate of mild exacerbations over a two-week period during LABA withdrawal as assessed from daily symptom diaries kept by the participants. An exacerbation was defined by at least two consecutive days with at least a 20% reduction in morning PEF, the need for at least three additional puffs of rescue medication, or nocturnal awakening caused by asthma symptoms.

The investigators randomized 56 patients to BT and 56 patients to the control group. The control group received usual care except that they were treated with two days of OCS (prednisone 50 mg) treatment at three-week intervals to correspond to the treatment received by the BT group. Four patients in the BT group either withdrew consent or were lost to follow-up and eight patients in the control group withdrew consent or were lost to follow-up. The groups were comparable at baseline. Their average age was 40 years, 56% were female and 57% had severe persistent asthma while 43% had moderate persistent asthma according to the 2004 Global Initiative for Asthma guidelines.[31] At twelve months, the participants in the BT group had fewer mild exacerbations than the control group (0.18 per subject per week versus 0.31, p=0.03). The difference was also significant at 3 months, but not at 6 months. There were no significant differences between the groups in the ability to tolerate LABA withdrawal and in FEV1. At three months while on both ICS and LABA, the morning PEF improved more in the BT group (369 to 397 L/min) than in the control group (394 to 395 L/min) as did the AQLQ score (5.8 to 6.1 in BT versus 5.7 to 5.7 in controls), although the average improvement does not meet the minimal important difference warranting clinical change (0.5

points). At twelve months on ICS alone, there was no difference in FEV1. However, there was a greater improvement in morning PEF in the BT group (349 to 389) compared to the control group (372 to 380, p=0.003) and there was a trend towards greater reduction in airway responsiveness in the BT group. The BT group also used their rescue inhaler less often at 12 months (10.9 versus 14.8 puffs per week, p=0.04) and had a greater percentage of days free from asthma symptoms (65% versus 49%, p=0.005). Finally, the AQLQ score increased more in the BT group (4.9 to 6.2) than in the control group (5.1 to 5.7, p=0.003).

As was noted in the earlier case series, many adverse events occur in the period following BT. In the AIR Trial, there were 407 adverse respiratory events in the BT group during the treatment period compared with 106 in the control group. The majority of these were mild (69% in both groups), but 3% in the BT group were severe compared to 1% in the control group. Four of the participants in the BT group were hospitalized a total of six times during the treatment period (four asthma exacerbations, one lung collapse, and one case of pleurisy). The common adverse events included dyspnea (71% versus 33%, p<0.001), wheezing (62% versus 13%, p<0.001), cough (53% versus 18%, p<0.001), night awakenings (40% versus 9%, p<0.001), and productive cough (40% versus 11%, p<0.001). During the post-treatment period, there were no significant differences between the two groups in respiratory events, although there was a trend towards more upper respiratory infections (18% versus 6%, p=0.07). There were no differences in hospitalizations during the post treatment period (3 events in each group) and no one died during follow-up.

The investigators continue to follow the BT group (45/56 originally randomized = 80%) for a total of five years and the control group (24/56 originally randomized = 43%) for a total of three years.[23] The rates of respiratory adverse events were identical in the two groups (1.2 events per subject in year 2 and 1.3 events per subject in year 3). There were no significant differences in the percentage of patients admitted to the hospital or treated in the hospital for respiratory causes, though all hospitalizations in the first two years occurred in the BT group. About 25% of both groups required OCS use to treat asthma exacerbation during the first three years of follow-up. Thus BT did not reduce ER visits, hospitalizations, or OCS use. LABA use decreased for 57% of patients in the BT group and 54% of patients in the control group. About 48% of both groups discontinued use of LABA. There were no important differences in findings on annual chest x-rays, nor in pulmonary function tests.

The study is difficult to interpret because the primary outcomes were obtained during a period when the participants' LABA therapy was withheld as specified during the protocol. During that artificial period, there were fewer mild exacerbations, less use of rescue medications, and improved quality of life for the BT group. However, the withdrawal of LABA therapy was an artificial situation created by the investigators and is unlikely to be representative of the clinical response of patients in the real world. Moreover, the small increment in quality of life was not clinically significant and there was an excess of hospitalizations (9 versus 3) for respiratory causes in the BT group, primarily during the treatment period surrounding the three bronchoscopies required. It is not clear that the small benefits demonstrated in this study balance the early harms that occur from the procedure itself. During three years of follow-up there were no differences in the outcomes that matter to patients: hospitalizations, ER visits, and oral steroid bursts to treat respiratory exacerbations. Moreover, the long term effects of heating extended portions of the bronchial tree, with associated epithelial and smooth muscle damage, remain uncertain. The outcomes in the small group of patients followed through two years suggest that the benefits of BT persist and no unexpected respiratory pathologies develop, but considerable uncertainty remains.

Research in Severe Asthma (RISA) Trial

The Research in Severe Asthma (RISA) trial[22] was designed to test the efficacy of bronchial thermoplasty in patients with symptomatic, severe asthma because post hoc analyses of the AIR trial[21] suggested that the benefits of BT were greater in patients with more severe disease. Patients with asthma stable for at least six weeks were eligible for randomization if they used ICS at a dose equivalent greater than 750 mcg per day of fluticasone and LABA at a dose equivalent to at least 100 mcg per day of salmeterol. OCS therapy was allowed at doses up to 30 mg/day of prednisone. Other inclusion criteria were age between 18 and 65 years, FEV1 at least 50% of the predicted value, and airway hyper-responsiveness by methacholine challenge, and uncontrolled symptoms defined by the use of rescue medications at least 8 days in the prior two weeks or symptoms on at least 10 days in the prior two weeks No primary outcomes were specified. The participants were followed for one year with an attempt to decrease their oral or inhaled steroid dose during weeks 22 through 36 of the study.

The study randomized 34 participants to the BT group (n=17) or the control group (n=17), but there were large apparent differences at baseline. These included rescue bronchodilator use (62 versus 30 puffs per 7 days), symptom free days (5% versus 14%), AQLQ score (4.0 versus 4.7), and ACQ score (2.8 versus 2.2). In all cases, the BT group had baseline characteristics suggestive or more severe disease. All participants met the Global Initiative for Asthma criteria for severe persistent asthma and all but one met the ATS criteria for severe refractory asthma.

As in the AIR trial, there was an excess of respiratory adverse events in the BT group (total: 136 versus 57; severe: 14 versus 2) including cough, wheezing, and chest discomfort. During the treatment period there were seven hospitalizations in the BT group compared to zero in the control group. Five hospitalizations were for asthma exacerbations and the other two for partial lung collapse. In the post-treatment phase, there were five additional hospitalizations in the BT group and four in the control group.

There were no significant differences between groups in the proportion of patients who were able to wean off of OCS, all though the numbers were small and the trend favored the BT group. There were significant differences favoring the BT group for rescue bronchodilator use, improvements in quality of life, and in asthma control. However, there were large baseline differences between the groups in these three measures, so the findings may be due to regression to the mean or unmeasured confounders not accounted for in the analyses.

As in the AIR trial, there was a large excess of respiratory adverse events during the active treatment period of the RISA trial. In both trials, there were three times as many hospitalizations for respiratory causes in the BT group compared to the control group across the first year of the study. Given the small size of the RISA trial, the baseline imbalances in the two treatment groups, and the lack of blinding, it is difficult to draw meaningful conclusions from the RISA trial.

The Asthma Intervention Research 2 (AIR2) Trial

The Asthma Intervention Research 2 (AIR2) trial randomized 288 patients to either bronchial thermoplasty or a sham control.[20] It is the largest randomized trial of BT and the only one to use a sham control. To be eligible, patients were required to be between the ages of 18 and 65 years with asthma requiring daily ICS at a dose equivalent to at least 1000 micrograms of beclomethasone and daily LABA therapy at a dose equivalent to at least 100 micrograms of salmeterol. Patients were allowed to be on LMAs, omalizumab, and OCS at a dose of 10 mg/d or less. Additional inclusion criteria included stable asthma medications for at least four weeks, a baseline Asthma Quality of Life Questionnaire (AQLQ) score of 6.25 or lower (higher represents better quality of life), FEV1≥60% predicted, and airway hyper-responsiveness defined as a methacholine PC20 < 8 mg/ml. Patients were not eligible for enrollment if they had life-threatening asthma, chronic sinus disease, emphysema, three or more hospitalizations for asthma in the past year, four or more pulses of OCS in the past year, three or more lower respiratory tract infections in the past year or if they used certain medications (immunosuppressants, beta-blockers, anticoagulants).

Eligible participants were randomized by computer in a 2:1 ratio to either BT (n=190) or sham (n=98). All subjects were scheduled to have three bronchoscopy procedures three weeks apart. The participants and all staff performing follow-up and outcome assessment were blinded to the allocation status of the participants. Sham BT included conscious sedation, deployment of the electrode array, and activation of a sham RF controller. The duration of therapy and the number of sham activations matched an active treatment procedure. Participants were evaluated six weeks following the last procedure and then at 3, 6, 9 and 12 months. The primary outcome was the between group differences in the change in the AQLQ score between baseline and the average of the 6, 9, and 12 month follow-up. The minimal change in AQLQ that is clinically meaningful is 0.5 points or greater. Secondary outcomes included symptom scores, morning PEF, rescue medication use, FEV1, severe exacerbations, unscheduled physician visits, ER visits, hospitalizations and days missed from school. Bayesian statistics were used to analyze the data. The pre-specified posterior probability of superiority (PPS) that would be significant was 96.4% for their primary outcome and 95% for their secondary outcomes.

The baseline characteristics were similar in the two groups. The participants had an average age of 41 years, 59% were female, and 87% met the ATS criteria for severe refractory asthma. The median dose of ICS was 2000 micrograms in beclomethasone equivalents with less than 5% of participants using OCS and 23% using LMAs. Participants were free of all asthma symptoms on about 16% of the days prior to the intervention.

The AQLQ score increased from 4.30 at baseline to 5.66 at 12 months in the BT group and from 4.32 to 5.48 in the sham group. The score increased 1.35 points in the BT group and 1.16 points in the sham group. The difference between the two groups did not meet their pre-specified PPS and the difference between the two change scores (0.19 points) is less than the 0.5 points considered clinically significant. The percentage of participants whose AQLQ score increased at least 0.5 points was greater in the BT group (79% versus 64%, PPS 0.996).

The only secondary outcomes that differed significantly between the two groups were the number of severe exacerbations per subject per year (0.48 versus 0.70, PPS 95.5%) and the days lost from work, school, or other activities due to asthma (1.3 versus 3.9, PPS 99.3%). There were no significant differences in FEV1, PEF, symptoms scores, percent symptom free days, or rescue medication use.

During the treatment period, there were more adverse events in the BT group and more serious adverse events. Most occurred within one day of the bronchoscopy and resolved within one weak. The rate of serious adverse events was about three times higher in the BT group (.03 per bronchoscopy versus .01 per bronchoscopy). Hospitalizations during the treatment period were much more common in the BT group (19 hospitalizations in 16 patients) compared to the control group (two hospitalizations in two patients). However, in the post-treatment period there were fewer hospitalizations in in the BT group (6 hospitalizations in 5 patients) compared to the control group (12 hospitalizations in 5 patients). One patient in the control group was hospitalized nine times. There were no differences in lower respiratory infections (24% in both groups).

Over the entire follow-up period, the number of severe exacerbations was similar in the two groups: the rates were 1.02 per subject per year for the BT group compared to 0.91 per subject per year in the control group and the percentage of patients experiencing at least one severe exacerbation was 53.6% in the BT group and 45.9% in the control group.

Participants in the AIR2 trial who were randomized to the BT group continue to be followed by the investigators. The two year follow-up data have recently been published for 87% (166/190) of the participants randomized to BT.[19] These results include only events occurring more than six weeks after the final BT treatment session. The adverse events associated with the treatment period are excluded. The percentage of subjects experiencing severe exacerbations declined from 31% in the first year to 23% in the second year. The number of ER visits increased slightly (5.0% to 6.6%) as did the number of hospitalizations (3.3% to 4.2%). As in prior studies, the FEV1 remained stable. These findings suggest that the results seen during the first year will continue for at least another year, although it would have been more appropriate to compare the results of the 166 patients followed during the second year to their own results during the prior year rather than comparing them to the larger group of 181 patients with one year follow-up data in the original trial. It may be that the patients who elected not to continue in the study were less reliable with their medications and may have had more adverse events during the second year if they had remained in the study.

The AIR2 trial was the first double-blind, sham controlled trial of BT. The methodological quality of the trial appeared to be very high. The primary benefit reported in the trial was significantly fewer ER visits after the treatment period in the BT group. These results appeared stable through two years of follow-up. However, there was no reduction in hospitalizations and the rate of severe asthma exacerbations was slightly higher in the BT group. In addition, they did not meet their primary endpoint: there was not a statistically significant difference in quality of life as measured by the AQLQ and the observed difference did not meet the usual criteria for a clinically meaningful difference in the scores. As demonstrated in the prior trials, there are clear harms during the initial treatment period. Finally, despite reassuring two and five year follow-up data to date, there remains uncertainty about the long-term effects of BT on the lung itself. It is not clear that the small observed benefits from BT outweigh the early harms and ongoing uncertainty about long term benefits and harms.

TA Criterion 3 is not met.

TA Criterion 4: The technology must be as beneficial as any established alternatives.

Patients with severe refractory asthma that remains poorly controlled in spite of treatment with high dose ICS and LABA have several options. These include leukotriene modifying agents, the anti-IgE monoclonal antibody omalizumab, and daily oral corticosteroids. Many patients do not tolerate these medications and one of the potential benefits of BT would be to avoid the long-term harms of chronic OCS use. Thus, there is no clear established alternative to BT, although a randomized trial comparing BT to omalizumab would be an interesting comparative effectiveness study. However, BT has not yet been demonstrated to improve net health outcomes on its own, so TA criterion 4 is not met.

TA Criterion 4 is not met.

TA Criterion 5: The improvement must be attainable outside of the investigational setting.

No clear net benefits have been demonstrated with BT in the carefully controlled clinical trials performed to date. Given the clear harms demonstrated from use of BT in expert hands, there are significant concerns that results may be worse outside of the investigational setting. Specialty societies should consider establishing clear guidelines for training and certification in use of the technology.

TA Criterion 5 is not met.

CONCLUSION

Asthma is common in the United States and its prevalence is increasing. Most patients are able to control their symptoms with medications and self-monitoring with an action plan for intensifying therapy when their asthma worsens. However, five to 15% of patients have severe, refractory asthma. These patients have frequent, severe exacerbations leading to unscheduled doctors visits, ER care, and hospitalizations. This remains a problem despite advances in therapeutics including ICS, LABA, LMA, and anti-IgE monoclonal antibodies. Bronchial thermoplasty addresses a novel target: airway smooth muscle. It has long been appreciated that patients with severe asthma have excess airway smooth muscle and it has been hypothesized that reducing the smooth muscle volume might decrease bronchial hyper-reactivity and improve flow in the airways. Bronchial thermoplasty uses radiofrequency energy to heat the inside of the airways enough to reduce bronchial smooth muscle mass without otherwise causing long-term damage to the lungs.

Several small case series confirmed the relative safety and potential efficacy of BT in humans. Three randomized trials directly compared BT to medical therapy in patients with asthma. The AIR trial randomized 112 patients with moderate to severe asthma and an increase in symptoms when LABA therapy was withdrawn. The trial demonstrated improvements in peak expiratory flow, quality of life, and symptoms during periods when LABA was withdrawn, but there was an excess of hospitalizations in the BT group and through three years of follow-up there were no differences in the rates of ER visits and severe asthma exacerbations. The RISA trial, which enrolled patients with more severe asthma, also reported an excess of hospitalizations in the BT group. However, the results of the RISA trial may be biased because it was a small trial with large imbalances in important participant characteristics at baseline. The most important trial to consider is the AIR2 trial. It was the only trial that used a sham control to blind patients and they also ensured that staff assessing patient outcomes remained blinded to patient allocation. There was slightly greater improvement in quality of life in the BT group compared to the sham group, but it did not meet the pre-specified criteria for statistical or clinical significance. As expected, there were more respiratory adverse events in the BT group during the initial treatment period including an excess of hospitalizations. After the initial treatment period, there was a reduction in ER visits, but not in hospitalizations for the BT group compared to the sham group. In addition, the rate of severe exacerbations were similar in the two groups, though the trend favored the sham group.

There remain concerns about the long term sequelae of BT. The AIR trial followed 45 participants treated with BT for five years and did not find any worsening of lung function on spirometry or unexpected findings on chest x-ray. No cases of bronchiectasis or fibrotic damage have been reported. However the number of patients followed out five years and longer is relatively small, so there may still be some uncommon long-term harms that have yet to be identified. Given the uncertainty about long-term harms, clear early harms due to BT, and its relatively modest benefits, it remains unclear whether the technology improves net health outcomes.

CALIFORNIA TECHNOLOGY ASSESSMENT FORUM℠

RECOMMENDATION

It is recommended that use of bronchial thermoplasty for the treatment of severe, refractory asthma does not meet CTAF TA Criterion 3 through 5 for safety, effectiveness and improvement in health outcomes.

October 19, 2011

This is the first review of this technology by the California Technology Assessment Forum.

RECOMMENDATIONS OF OTHERS

Blue Cross Blue Shield Association (BCBSA)

The BCBSA Technology Evaluation Center has not conducted a review on Bronchial Thermoplasty.

Centers for Medicare and Medicaid Services (CMS)

There is not a National Coverage Determination specific to the use of this technology; reimbursement coverage is left to the discretion of local Medicare carriers.

American Academy of Allergy, Asthma, and Immunology (AAAAI)

AAAAI has been invited to provide an opinion on this technology and to send a representative to participate at the meeting.

California Society of Allergy, Asthma and Immunology (CSAAI)

CSAAI has been invited to provide an opinion on this technology and to send a representative to participate at the meeting.

American Thoracic Society (ATS)

ATS has been invited to provide an opinion and to send a representative to participate at the meeting.

American Academy of Chest Physicians (AACP)

AACP has no position statement on this technology and declined the invitation to send a representative to the meeting.

National Institute for Clinical Excellence (NICE)

NICE is developing guidelines for this technology; guideline completion date and dissemination is unknown.

National Guidelines Clearing House

No guidelines were found.

ABBREVIATIONS

CTAF	California Technology Assessment Forum
DARE	Database of Abstracts of Reviews of Effects
FDA:	US Food and Drug Administration
RCT	Randomized Controlled Trial
NS	Not significant
CI	Confidence Interval
NR	Not reported
BT	Bronchial Thermoplasty
AIR	Asthma Intervention Research
RISA	Research in Severe Asthma
ICS	Inhaled corticosteroids
OCS	Oral corticosteroids
LABA	Long acting beta-agonist
SABA:	Short-acting beta-agonist
LTRA:	Leukotriene receptor antagonist
MDI:	Metered-dose inhaler
PEF:	Peak expiratory flow
FEV1	Forced expiratory volume in one second
PC20	Provocative concentration of methacholine required to lower the FEV1 by 20%
AQLQ	Asthma quality of life questionnaire

ACQ Asthma Control Questionnaire

ER Emergency room

MD Medical doctor

COPD: Chronic obstructive pulmonary disease

EIB: Exercise-induced bronchospasm

FVC: Forced vital capacity

GERD: Gastroesophageal reflux

NAEPP: National Asthma Education and Prevention Program

NHLBI: National Heart, Lung, and Blood Institute

OSA: Obstructive sleep apnea

APPENDIX: Search strategy

PubMed:

Search	Most Recent Queries	Time	Result
#8	Search **#1 AND #2 AND #3 AND #4 NOT review[pt] NOT (animals[mh] NOT humans[mh])** Limits: **English, Publication Date from 2003**	13:51:12	20
#7	Search **#1 AND #2 AND #3 AND #4 NOT review[pt] NOT (animals[mh] NOT humans[mh])**	13:50:00	38
#6	Search **#1 AND #2 AND #3 AND #4 NOT review[pt]**	13:42:52	43
#5	Search **#1 AND #2 AND #3 AND #4**	13:42:25	63
#4	Search **random* OR clinical trial OR clinical trials OR controlled OR trial OR trials OR ((single OR double OR triple OR treble) AND (blind* OR mask*)) OR cohort OR controlled OR study OR studies OR case series OR retrospective OR prospective OR observation study* OR observational stud* OR evaluation OR follow-up OR comparative study OR comparative studies OR treatment outcome OR treatment outcomes OR systematic review**	13:41:48	9060193
#3	Search **thermoplast* OR thermal energy**	13:41:41	102171
#2	Search **bronchial OR bronchus**	13:41:33	108766
#1	Search **asthma**	13:37:00	121735

Cochrane Library - Current Search History

ID	Search	Hits	Edit	Delete
#1	(asthma) and (thermoplast* OR "thermal energy"):ti,ab,kw	18	edit	delete

Results in Clinical Trials database only (18 refs)

Embase

Search

No.	Query	Results	Date
#14	#1 AND #2 AND #11 AND [english]/lim NOT ([review]/lim OR [short survey]/lim)	56	12 Aug 2011
#13	#1 AND #2 AND #11 AND [english]/lim	77	12 Aug 2011
#12	#1 AND #2 AND #11	95	12 Aug 2011
#11	'clinical study'/de OR 'clinical trial'/de OR 'clinical trial (topic)'/de OR 'comparative study'/de OR 'control group'/de OR 'controlled clinical trial'/de OR 'controlled study'/de OR 'major clinical study'/de OR 'randomized controlled trial'/de OR 'randomized controlled trial (topic)'/de OR 'systematic review'/de OR random* OR 'clinical trial' OR 'clinical trials' OR trial OR trials OR (single OR double OR triple OR treble AND (blind* OR mask*)) OR cohort OR controlled OR study OR studies OR 'case series' OR retrospective OR prospective OR 'observation study' OR 'observational study' OR evaluation OR 'follow up' OR 'comparative study' OR 'treatment outcome' OR 'treatment outcomes'	23534591	12 Aug 2011
#2	thermoplast* OR 'thermal energy'	3191	12 Aug 2011
#1	asthma	184296	12 Aug 2011

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