

Bronchial Thermoplasty for Asthma

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Rationale: Bronchial thermoplasty (BT) reduces the potential for smooth muscle-mediated bronchoconstriction by reducing the mass of smooth muscle in the walls of conducting airways.

Objectives: This study was conducted to examine the safety and impact on lung function and airway responsiveness of BT over 2 yr.

Methods: The safety of BT was studied in 16 subjects with mild to moderate asthma. Baseline and 12-wk post-treatment measurements included spirometry, methacholine challenge, daily diary recordings of peak flow, symptoms, and medication usage. Subjects completed follow-up evaluations at 12 wk, 1 yr, and 2 yr.

Measurements and Main Results: The procedure was well tolerated; side effects were transient and typical of what is commonly observed after bronchoscopy. All subjects demonstrated improvement in airway responsiveness. The mean PC₂₀ increased by 2.37 ± 1.72 ($p < 0.001$), 2.77 ± 1.53 ($p = 0.007$), and 2.64 ± 1.52 doublings ($p < 0.001$), at 12 wk, 1 yr, and 2 yr post-procedure, respectively. Data from daily diaries collected for 12 wk indicated significant improvements over baseline in symptom-free days ($p = 0.015$), morning peak flow ($p = 0.01$), and evening peak flow ($p \leq 0.007$). Spirometry measurements remained stable throughout the study period.

Conclusions: BT is well tolerated in patients with asthma and results in decreased airway hyperresponsiveness that persists for at least 2 yr.

Keywords: airway smooth muscle; asthma; bronchoscopy; radiofrequency energy

One feature of asthma is the presence of airway hyperresponsiveness (AHR), which is usually associated with chronic airway inflammation and may arise from an abnormality of airway smooth muscle (1, 2). An increase in the mass of airway smooth muscle is evident in patients with asthma (3, 4), and this increase has been shown to correlate with asthma severity (5). Contraction of the smooth muscle, whether in response to an allergen, an irritant, psychologic stress, or other neural activation, leads to airway narrowing and airflow obstruction (6). Therapies that prevent or reduce the ability of airway smooth muscle to contract have the potential to reduce airway responsiveness, the severity and frequency of asthma symptoms, the medications required by patients, and perhaps to improve baseline lung function (7).

Bronchial thermoplasty (BT) is one therapy designed to reduce the contractile ability of airway smooth muscle (8). BT is the delivery of radiofrequency energy to the airway wall, which

heats the tissue in a controlled manner and aims to reduce smooth muscle mass. Consequently, there is decreased potential for bronchoconstriction and possibly decreased frequency and severity of asthma symptoms (9).

BT targets for treatment the intraparenchymal airways distal to the mainstem bronchi down to airways 3 mm in diameter (8). Although the relative contribution of central and peripheral airways to airflow obstruction in asthma is uncertain, there is potential for therapeutic effect from treating the more central airways (10–12). The major source of resistance to airflow in the normal bronchial tree is in the conducting airways at about the fourth generation (13). Furthermore, because resistance to airflow in the lungs is additive, reducing obstruction in the central airways reduces overall resistance to airflow so that treatment of central airways is expected to provide a clinical benefit (12, 14).

BT is performed using the Alair System. The Alair System has been used safely in animals (9) and in subjects without asthma (15) and in those with asthma (8). Data from animal studies showed that treatment with the Alair System significantly reduced the responsiveness of airways (distal to the main bronchi and > 3 mm in diameter) to local methacholine challenge for at least 3 yr (9). Histologic evidence from these studies suggested that BT reduces airway responsiveness by altering airway smooth muscle (16). Histologic studies of airways from patients who underwent scheduled pulmonary resection after BT demonstrated that the response to treatment in human airways was similar to that in canine airways. In this study, BT was not associated with any clinically significant adverse events (15). The extent of the treatment was confined to the wall of airways and to the immediate peribronchial region. These data indicate that BT may provide therapeutic benefit for patients with asthma. This study was designed to examine the safety of performing BT, using the Alair System, in adult subjects with asthma. Some of the results of this study have been reported in the form of abstracts (17–19).

METHODS

Study Design

This was a nonrandomized, prospective study in which 16 subjects with stable asthma were enrolled at two investigational sites between October 2000 and June 2002 and followed through October 2004. The protocol was approved by the institutional review boards of St. Joseph's Healthcare, Hamilton, Ontario (site A), and Vancouver General Hospital, Vancouver, British Columbia (site B). Written, informed consent was obtained from all subjects before their participation in the study.

Study Participants

All subjects were 18 yr of age or older and had stable asthma, as indicated by no change in their asthma condition or medication needs in the previous 6 wk. Baseline subject characteristics are listed in Table 1. Primary exclusion criteria included respiratory tract infection within the last 6 wk; a history of two or more lower respiratory tract infections per year requiring antibiotic treatment; and the use of more than four puffs in a 24-h period of a short-acting β_2 -adrenergic agonist, such as albuterol 100 μ g/puff or equivalent, except for exercise.

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TABLE 1. PATIENT DEMOGRAPHICS AND BASELINE ASTHMA CHARACTERISTICS

Parameter	Patient Population
No. subjects	16
Age, yr	Mean: 39; range: 24–58
Sex, n (%)	
Male	6 (37.5)
Female	10 (62.5)
Race, n (%)	
White	15 (93.8)
East Indian	1 (6.2)
Height, cm (mean $\pm$ SD)	165.24 $\pm$ 8.02
Bronchial responsiveness, geometric mean (95% confidence interval), PC ₂₀	0.92 (0.42–1.99)
Prebronchodilator FEV ₁ , % predicted (mean $\pm$ SD)	82.28 $\pm$ 13.97
Inhaled corticosteroid use, n (%)*	
None	1 (6.3)
Low dose (< 250 μ g/d)	1 (6.3)
Medium dose (250–500 μ g/d)	13 (81.3)
High dose (> 500 μ g/d)	1 (6.3)
Long-acting bronchodilator use, n (%)	5 (31.3)
Rescue medication use, puffs/d (mean $\pm$ SD)	1.0 $\pm$ 1.14

* Corticosteroid dose severity determined by the Global Initiative for Asthma (GINA) guidelines (1) and stratified by micrograms of fluticasone or equivalent.

Study Treatment

Baseline spirometry was performed at enrollment according to American Thoracic Society criteria (20) and was reevaluated before bronchoscopy on the day of each treatment. Systemic steroids were given to minimize potential side effects of bronchoscopy, such as edema and inflammation. In site A, all subjects received 50 mg oral prednisone the day before treatment and 40 mg methylprednisolone IV on the day of treatment. In site B, all subjects received 30 mg prednisone the day before, the day of, and the day after treatment.

BT was performed during bronchoscopy with general anesthesia (site A) or local anesthesia with conscious sedation (site B). Intraparenchymal airways were treated under bronchoscopic vision using adjacent activations of the device, moving from distal to proximal, as described previously (8, 9). Airways beyond the lobar bronchi, accessible with a bronchoscope, and larger than 3 mm in diameter were treated. Typically, one treatment session was required to treat each lower lobe, and the accessible airways in both upper lobes were treated at another session. The right middle lobe was not treated (8). Treatment sessions were scheduled at least 3 wk apart. After the first treatment session, previously treated airways were evaluated by bronchoscopy before proceeding with further treatment.

Post-Treatment Monitoring and Evaluation

Subjects were monitored during treatment and for a minimum of 6 h after treatment before being discharged and were contacted daily via telephone for the week after treatment. Safety was evaluated by assessment of adverse events after each study treatment and by objective measurements made at follow-up visits up to 2 yr. All adverse events were determined by the investigator to be a side effect of the procedure or not and rated as mild, moderate, or severe. Mild was defined as easily tolerated, transient, causing the patient no loss of time from normal activities; moderate was defined as discomfort severe enough to cause interference with the patient's usual activities and for which symptomatic treatment was possible; severe was defined as incapacitating with the inability to do work or usual activities and requiring medical intervention and/or treatment.

Follow-up visits consisted of physical examination; review of symptoms, exacerbations, and adverse events; review of daily diary; spirometry; and pulse oximetry. Subjects recorded peak expiratory flows and asthma symptoms twice daily in a diary out to 12 wk post-treatment. Clinically significant symptoms were managed according to usual clinical practice (e.g., increase maintenance dose or frequency, oral steroids, or antibiotics). After the final treatment was performed, subjects returned

for short-term follow-up examinations at 6 wk. This completed the treatment period. Post-treatment evaluations were made at office visits scheduled at 12 wk, 1 yr, and 2 yr. Additional annual follow-up visits are planned out to 5 yr. The 12-wk visit also included resting EKG, chest X-ray, and AHR measured by methacholine (MCh) challenge (21). Each annual visit also included a computed tomography (CT) scan using a General Electric High Speed Advantage single detector scanner in site A and a multitrack Siemens Sensation 16 detector CT scanner in site B to look for changes such as bronchiectasis, consolidation, bronchiolitis obliterans, bronchial wall thickening, gas trapping, or parenchymal changes.

Statistics

This study was designed to evaluate safety and feasibility of BT in patients with asthma. The study was not powered to detect efficacy outcomes. Statistical analyses of efficacy measures were performed for information. Data are presented as mean $\pm$ SD. Subject baseline values were matched to treatment follow-up data using a paired *t* test. Parametric tests of group means (QST Consultations, Allendale MI) are presented except where indicated.

RESULTS

Patient Demographics

Ten subjects were enrolled at site A, and eight subjects were enrolled at site B. Of these, 16 were treated (two subjects withdrew consent before receiving BT). There were 6 men and 10 women, with a mean age of 39 $\pm$ 8.58 yr. Subject demographics are shown in Table 1.

BT Treatment

Forty-nine bronchoscopic procedures were performed on 16 subjects. All treatments were completed in 30 min or less. Treatment was completed in three sessions in 13 subjects and in four sessions in two subjects. One subject received two treatments but did not undergo a third based on the investigator's concern about the need for two courses of antibiotics for management of respiratory symptoms after the second treatment. The macroscopic appearance of the bronchi immediately after treatment was relatively unchanged. Acutely, blanching of the airway wall was occasionally observed during the treatment bronchoscopy, but no visible changes to the shape, size, or structure of the airways were observed. At subsequent bronchoscopies, the blanching had resolved, and it was nearly impossible to discern that the airways had been treated. All subjects tolerated the procedure well, and all subjects were discharged at the end of the planned 6-h observation period. No subject required post-procedure admission to the hospital.

Safety of BT

All symptoms were recorded for safety analysis. A total of 312 adverse events were reported over the 2-yr period. Of these, 230 (74%) were "mild," 79 (25%) were "moderate," and 3 (1%) were "severe." All three severe adverse events (allergic reaction to peanuts, ovarian cyst and fibroid removal, and partial mastectomy) involved hospitalization and were considered not related to the procedure.

Of the 312 adverse events, 155 were considered device and/or procedure related or "side effects" of the procedure. The profile of these side effects that occurred exclusively during the treatment period is presented in Table 2. The most frequently reported side effects were related to airway irritation and were recorded by the investigators as increased cough, dyspnea, wheeze, and bronchospasm. The mean time to onset was 1.7 d, and the mean time to resolution was 4.6 d after the most recent bronchoscopic procedure. The incidence or severity of side effects did not increase after subsequent treatment sessions. The

TABLE 2. SUMMARY OF DEVICE-RELATED ADVERSE EVENTS DURING THE TREATMENT PERIOD (TREATMENT THROUGH 6-WK FOLLOW-UP)

Adverse Event	Adverse Event Frequency	Subject* Frequency
Cough	33 (21%)	15 (94%)
Dyspnea	19 (12%)	11 (69%)
Wheeze	17 (11%)	8 (50%)
Bronchospasm	16 (10%)	10 (63%)
Fever	14 (9%)	7 (44%)
Chest discomfort	12 (8%)	9 (56%)
Mucus production	11 (7%)	8 (50%)
Throat irritation	8 (5%)	4 (25%)
Headache	5 (3%)	4 (25%)
Congestion	4 (3%)	2 (13%)
Hemoptysis	4 (3%)	3 (19%)
Localized heat	3 (2%)	1 (6%)
Retained mucus	3 (2%)	2 (13%)
Bronchitis	2 (1%)	2 (13%)
Hypoxemia	2 (1%)	1 (6%)
Hoarseness	1 (1%)	1 (6%)
Lower back pain	1 (1%)	1 (6%)

A total of 155 events were reported. Sixteen subjects experienced one or more reported events.

* Count reflects the number of subjects cited as having one or more adverse events.

majority of side effects in this study were mild (130/155), with the remaining events being moderate (25/155). No severe side effects were reported. The data show no evidence of a relationship between the number or severity of side effects and the anesthesia used, baseline medication use, or baseline AHR.

All of these device- and/or procedure-related side effects presented within 1 wk of BT, and 90 of 155 (58%) resolved spontaneously. Sixty-five of 155 (42%) were managed with a total of 78 uses of medications; in decreasing frequency these were inhaled albuterol (55%), over-the-counter medication such as acetaminophen (31%), antibiotic (15%), inhaled corticosteroid (ICS; 6%), long-acting β -agonist (5%), oral corticosteroid (3%), supplemental oxygen (< 6 h post-procedure; 3%), and anticholinergic medications (2%).

Before the 12-wk visit, two subjects were prescribed long-acting β -agonists (LABA) for control of increased symptoms. All other changes occurring at or after 12 wk were as follows: one subject added LABA, one subject increased ICS, two subjects increased ICS and LABA, two subjects decreased their dose of ICS, two subjects decreased ICS and LABA (one of whom discontinued LABA altogether), and six subjects had no change. No patient required the addition of oral steroids to their maintenance medication, and there were no emergency room visits or hospitalizations related to treatment or to asthma exacerbation. There were no patient deaths during the study.

A radiologist at each site reviewed CT scans of each patient, and no significant findings were reported. In addition, a blinded independent radiologist reviewed CT scans of all subjects in the study at baseline and at 1 and 2 yr post-treatment. This was performed first without knowledge of which were baseline and post-treatment scans and repeated unblinded to this timeframe. No clinically significant findings were observed as a result of BT, including no evidence of bronchiectasis or bronchial wall thickening or parenchymal changes. The CT scans and the findings of the radiologist were reviewed by a pulmonologist not involved in the execution of the study.

Efficacy Outcomes

Pulmonary function tests. Prebronchodilator FEV₁ (% predicted) was maintained after BT, with no significant change from

baseline (82.2 ± 14.0 , $n = 16$) at the 2-yr follow-up (85.7 ± 13.1 , $n = 15$; Figure 1). There were significant increases observed at 12 wk (88.6 ± 16.1 , $n = 15$, $p = 0.043$) and 1 yr (88.3 ± 17.1 , $n = 16$, $p = 0.030$). Post-bronchodilator FEV₁ (% predicted) was maintained throughout the period, with no significant change from baseline. The prebronchodilator FEV₁/FVC ratio was statistically significantly higher at 1 yr (75.8%) than at baseline (72.7%; $p = 0.049$). This change was not significant at 12 wk (72.8%) or 2 yr (74.5%) post-treatment. There was no significant increase in the mean postbronchodilator FEV₁/FVC ratios after treatment.

Peak expiratory flow. Compared with baseline, there were statistically significant improvements in morning and evening peak flows at 12 wk post-treatment, which is the latest time data were collected by diary (Table 3).

In the days after treatment, 10 of 16 subjects (62%) experienced no change in morning peak flow outside of baseline variability. Transient decreases in morning peak flows outside of baseline variability were reported by 6 of 16 subjects (38%). The largest decrease recorded was 29% from a baseline of 496 ml/min. By Day 3, this subject had a morning peak flow within 5% of baseline. The peak flow for all six subjects returned to within 5% of baseline 1 wk post-treatment.

Symptom-free days. The increase in the mean percentage of symptom-free days between baseline (50%) and 12 wk after treatment (73%) was statistically significant ($p = 0.015$). During the 12-wk follow-up period, 67% (10/15) of subjects experienced an increase in percentage of symptom-free days.

AHR. At baseline, the geometric mean value for PC₂₀ was 0.92 mg/ml (95% confidence interval [CI], 0.42–1.99). After BT, mean PC₂₀ increased to 4.75 (95% CI, 2.51–8.85) at 12 wk, 5.45 (95% CI, 1.54–19.32) at 1 yr, and 3.40 (95% CI, 1.35–8.52) at 2 yr. Individual data contributing to these means are shown in Figure 2. At follow-up, several subjects did not experience a 20% drop in FEV₁ with the highest concentration of MCh (16 mg/ml), so for purposes of analysis, these subjects were attributed a value of 16, as shown in the Figure 2. Five subjects met this criterion at 12 wk post-treatment, four subjects met this criterion at 1 yr post-treatment, and three subjects met this criterion at 2 yr post-treatment. One site did not perform PC₂₀ measurements at 1 yr on their subjects due to a minor protocol difference. This was corrected at subsequent annual follow-ups. The improvements observed throughout the study period represented approximately 2.4 doublings at 12 wk, 3.0 doublings at 12 mo, and 2.3 doublings at 2 yr.

Rescue medication. The use of rescue medication was low for most subjects, with a mean of 1 puff/d at baseline. Of the 15 subjects with baseline and 12-wk follow-up data, five subjects required less rescue medication, one subject increased their use, and nine subjects were unchanged. These changes were not statistically significant ($p > 0.05$ sign test).

DISCUSSION

The primary objective of this study was to evaluate the safety of performing BT in patients with mild to moderate persistent asthma. The study also examined a number of outcomes commonly used in asthma clinical trials. These measurements were especially important for the design of subsequent randomized controlled trials of BT. BT may provide clinical benefit by reducing the contractile function of airway smooth muscle (8, 9, 15), which reduces the ability of stimuli to induce airway smooth muscle contraction and exacerbation of asthma.

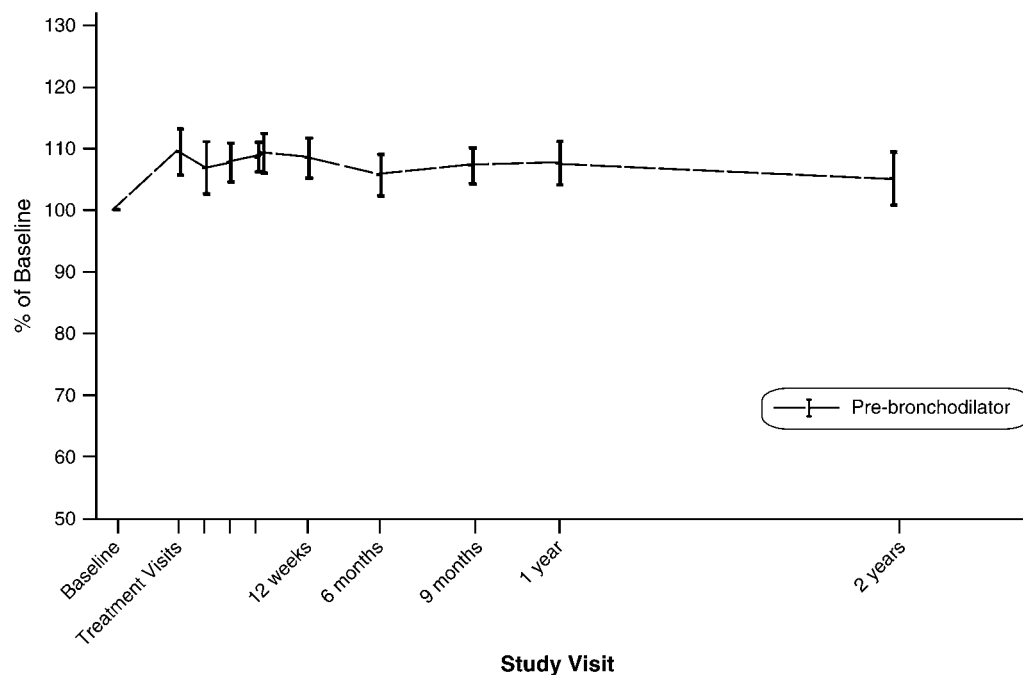


Figure 1. Prebronchodilator FEV₁% of baseline for individual subjects over the 2-yr study period.

The safety data reported in this study indicate that BT was well tolerated. All adverse events related to the procedure occurred within 1 wk of BT. The majority of these events were those commonly encountered after bronchoscopic procedures in subjects with asthma (22–24) and resolved spontaneously or with antibiotics or temporary increase in asthma drug therapy.

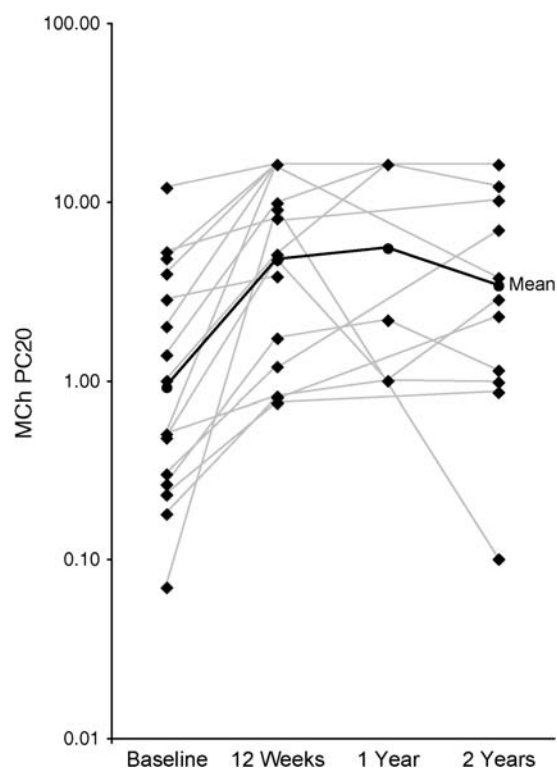


Figure 2. Individual and geometric mean methacholine (MCh) PC₂₀ values at baseline, 12 wk, 1 yr, and 2 yr after Bronchial thermoplasty.

Long-term safety assessment at 2 yr showed no deterioration in respiratory health status. There was no change in FEV₁ at 2 yr after BT (Figure 1) and no new findings on CT scans. Furthermore, subjects reported satisfaction with the procedure in a survey done 1 yr after the last treatment in which all subjects indicated they would undergo the procedure again (19).

This study reports a statistically and clinically significant improvement in AHR after BT. This effect persisted for at least 2 yr after treatment. The improvement reported would have been greater had the bronchial challenge continued to determine the PC₂₀ for patients who did not experience a 20% fall in FEV₁ at 16 mg/ml. In a controlled study, Sont and colleagues (25) reported that patients whose inhaled steroids were adjusted according to their PC₂₀ had fewer mild exacerbations and greater improvement in FEV₁ than patients who were managed based on symptoms, bronchodilator use, peak expiratory flow measurements, and FEV₁. Furthermore, they reported a direct relationship between AHR and rates of mild exacerbations in the control group. Because AHR is a key component of asthma, it is reasonable to hypothesize that the observed reduction of AHR after BT might be associated with improvements in asthma symptoms (26). In this study, we found a significant increase in the percentage of symptom-free days at 12 wk (Table 3). These findings support additional studies to determine the potential of BT as a treatment for asthma.

TABLE 3. MORNING AND EVENING PEAK EXPIRATORY FLOWS AND SYMPTOM-FREE DAYS

	Evaluation Period		
	Baseline	12 wk after Bronchial Thermoplasty	p Value
Morning PEF, L/min (n)	427.1 ± 108.1 (15)	465.9 ± 111.8 (13)	0.010
Evening PEF, L/min (n)	435.3 ± 96.0 (16)	476.4 ± 114.5 (12)	0.007
Symptom-free days, % (n)	47 ± 33 (16)	73 ± 27 (15)	0.015

* Peak flows were collected for 12 wk after Bronchial thermoplasty.

Limitations of this study include the lack of a control group and the small number of subjects studied. This study was designed to evaluate the feasibility and safety of BT, not its efficacy. However, the results revealed significant improvements in peak expiratory flow, symptom-free days, and airway responsiveness. These findings are encouraging and provide important direction for the design of further studies examining whether BT, in combination with standard medications, can provide benefits to patients with asthma that are not obtained with current strategies. During this study, an attempt was made to maintain consistent medical management of the patients. However, certain subjects required medication adjustments during this study. A randomized, controlled study is required to examine whether BT changes requirements for asthma medication. In addition, because the inclusion criteria specified that subjects had stable asthma, our study design limited the opportunity to detect improvements in asthma control. We did not study patients with suboptimal control of their asthma, who could potentially derive more benefit from BT than those studied here. Finally, this study does not rule out the possibility of longer term safety concerns, such as bronchiectasis or chronic or recurrent bronchitis, beyond the 2-yr follow-up. These issues are being addressed through continued follow-up of the study subjects out to 5 yr.

Conflict of Interest Statement: G.C. has received \$266,601 from Asthmatx Inc. for participating in multicenter clinical research studies relating to Bronchial Thermoplasty, between 2002 and 2005, and he will participate in the AIR-2 trial of Bronchial Thermoplasty in asthma in 2006–2009. J.D.M. has been corecipient of a research grant of \$266,601 from Asthmatx Inc. for participating in multicenter research, and will participate in further studies evaluating efficacy of Bronchial Thermoplasty in asthma 2006–2009. A.M. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. J.M.F. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. S.L. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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