

Safety and Efficacy of Bronchial Thermoplasty in Symptomatic, Severe Asthma

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Rationale: Bronchial thermoplasty (BT) is designed to reduce airway smooth muscle and improve asthma control.

Objectives: This study was conducted to determine the safety and efficacy of this procedure in subjects with symptomatic, severe asthma.

Methods: Adults who were symptomatic despite treatment with fluticasone or equivalent at more than 750 µg/day, a long-acting β₂-agonist, and other medications, which could include 30 mg or less of oral prednisolone/day, were randomized to BT or to a control group. After treatment, subjects entered a 16-week steroid stable phase (Weeks 6–22), a 14-week steroid wean phase (Weeks 22–36), and a 16-week reduced steroid phase (Weeks 36–52).

Measurements and Main Results: BT resulted in a transient worsening of asthma symptoms. Seven hospitalizations for respiratory symptoms occurred in 4 of 15 BT subjects during the treatment period. Five hospitalizations were within 3 days of treatment. Two subjects had segmental collapse involving the most recently treated lobe; one required bronchoscopy and aspiration of a mucus plug. There were no hospitalizations during this period in the 17 control subjects. The rate of hospitalizations was similar in both groups in the post-treatment period. At 22 weeks, BT subjects had significant improvements versus control subjects in rescue medication use (-26.6 ± 40.1 vs. -1.5 ± 11.7 puffs/7 d, $P < 0.05$), prebronchodilator FEV₁% predicted (14.9 ± 17.4 vs. $-0.94 \pm 22.3\%$, $P = 0.04$), and Asthma Control Questionnaire scores (-1.04 ± 1.03 vs. -0.13 ± 1.00 , $P = 0.02$). Improvements in rescue medication use and Asthma Control Questionnaire scores remained significantly different from those of controls at 52 weeks.

Conclusions: BT is associated with a short-term increase in asthma-related morbidity. However, there is preliminary evidence of long-lasting improvement in asthma control.

Clinical trial registered with www.clinicaltrials.gov (NCT 00214539).

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

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All authors were investigators in the Research in Severe Asthma (RISA) trial. This is the first clinical study to evaluate the effects of bronchial thermoplasty in symptomatic severe asthma.

*A list of the participants in the RISA Trial Study Group may be found at the end of this article.

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AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Bronchial thermoplasty is a technique for reducing airway smooth muscle mass and bronchoconstriction.

What This Study Adds to the Field

Bronchial thermoplasty was associated with a short-term increase in asthma-related symptoms but a longer term improvement in symptoms, lung function, and rescue bronchodilator use in patients with symptomatic severe asthma.

Asthma is an increasingly prevalent disease that adversely impacts the lives of millions of subjects and caregivers. Much of the morbidity, mortality, and health care expense attributed to asthma occur in patients with more severe disease, and the need for better therapeutic options in this important group of patients is widely acknowledged (1–6).

Some of the variable symptoms of asthma are due to airway smooth muscle (ASM) contraction, which results from a variety of stimuli (7). The application of bronchial thermoplasty (BT) to the airways is an innovative treatment approach to reduce the bronchoconstrictor response in asthma. Preclinical studies have shown that BT results in reduction of ASM (8, 9). Animal studies have shown that this is associated with a long-lasting reduction in airway responsiveness to methacholine (8). In a feasibility study to determine the safety of BT in subjects with mild to moderate asthma ($n = 16$), there were no severe adverse events in the 2-year study period (10). Although the study was not powered to evaluate efficacy, BT resulted in significant improvements in symptom-free days and PEF at 3 months, and a reduction in airway hyperresponsiveness that persisted for at least 2 years (10). In the Asthma Intervention Research (AIR) trial, which evaluated the effects of BT in subjects with moderate to severe asthma, treatment significantly reduced mild exacerbations and use of rescue medication. It also improved morning PEF, Asthma Quality-of-Life Questionnaire (AQLQ) scores, Asthma Control Questionnaire (ACQ) scores, and symptom scores compared with the control group (11). A *post hoc* analysis suggested that the benefits of treatment were particularly marked in subjects with more severe disease.

The primary objective of this study, the Research in Severe Asthma (RISA) trial, was to determine the safety of BT in subjects with symptomatic, severe asthma. Secondary objectives included evaluation of the effect of BT on asthma symptoms and daily medication requirements. Some of the results of this study have been previously reported in the form of abstracts (12, 13).

METHODS

Subject Selection

Key inclusion criteria were as follows: subjects with asthma aged 18 to 65 years; requirement of high-dose inhaled corticosteroid (ICS) (>750 μ g fluticasone propionate per day or equivalent) and long-acting β_2 -agonist (LABA) (at least 100 μ g salmeterol per day or equivalent), with or without oral prednisone (≤ 30 mg/d), leukotriene modifiers, or theophylline; prebronchodilator FEV₁ $\geq 50\%$ of predicted; demonstrable airway hyperresponsiveness by challenge with methacholine (methacholine challenge not performed in subjects with prebronchodilator FEV₁ $< 60\%$ predicted or FEV₁ less than the lower limit defined by individual hospital protocol) or reversible bronchoconstriction during prior 12 months as demonstrated by an increase in FEV₁ of at least 12% 30 minutes after four puffs of a short-acting β_2 -agonist; uncontrolled symptoms despite taking maintenance medication (demonstrated by the use of rescue medication on at least 8 of the 14 days before enrollment, or daytime symptoms on at least 10 of the 14 days before enrollment); and abstinence from smoking for 1 year or greater and past smoking history of less than 10 pack-years.

Study Design and Intervention

This trial was conducted at eight investigational sites (three countries) using a protocol approved by the respective ethics committees. All

subjects provided prior written, informed consent. Enrollment began in April 2004 and 1-year follow-up was completed by February 2006. An independent data and safety monitoring board oversaw the study.

After a 2-week run-in period, subjects were randomized either to the control group or to treatment (BT group) with the Alair Bronchial Thermoplasty System (Asthmatx, Inc., Mountain View, CA) using randomization envelopes based on a computer-generated code (blocks of 4 per site). BT group subjects underwent three procedures at least 3 weeks apart (11). All subjects maintained baseline asthma medications.

After the treatment period, subjects entered a 16-week steroid stable phase (Weeks 6–22), followed by a 14-week steroid wean phase (Weeks 22–36), and a 16-week reduced steroid phase (Weeks 36–52) (Figure 1). During the steroid wean phase, investigators attempted to wean subjects, following a prospectively defined protocol, from oral corticosteroids (OCS) or ICS. OCS dose was reduced by 20 to 25% of the baseline dose in steps of 2 weeks each. For subjects successfully weaned to OCS daily doses of 5–7.5 mg, further attempts to reduce the OCS dose were per investigator discretion. For subjects taking only ICS+LABA, the ICS dose was tapered in three stages by 20 to 25% of the baseline dose every 4 weeks to a minimal dose of 100–600 μ g/day of fluticasone propionate or equivalent (12). Investigators were not blinded to treatment.

The weaning process was stopped and medications were adjusted to the previous tolerable dose if a subject experienced a mild exacerbation (lasting more than 7 d), or experienced a severe exacerbation, or if

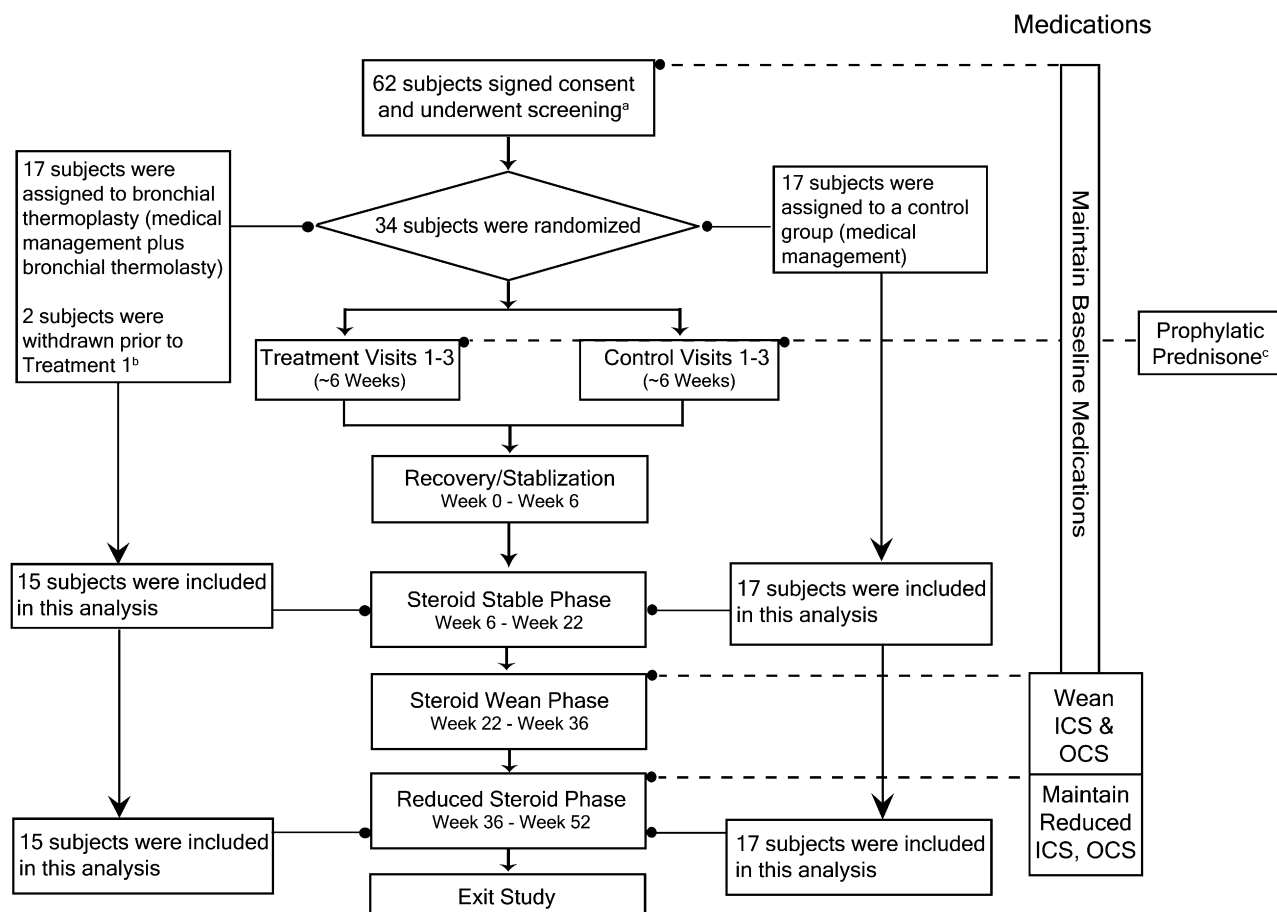


Figure 1. Schematic of RISA (Research in Severe Asthma) trial study design: flow chart outlining the various stages of the study, medical status during each stage, and participant flow. The number of subjects with data at each evaluation is shown. ^aReasons for screen failure include the following: FEV₁ or methacholine criteria not met (5 subjects), DLCO too low (2 subjects), smoking criterion not met (3 subjects), medications not stable, exacerbation (4 subjects), comorbidity (4 subjects), subject withdrew, study closed, or reason not noted (10 subjects). ^bReasons for study withdrawal: possible Churg-Strauss syndrome (1 subject), post-bronchodilator FEV₁ $< 55\%$ predicted before treatment 1 visit and on several subsequent attempts, resulting in data and safety monitoring board recommendation not to treat (1 subject). ^cAll subjects (both treated and control) were given 50 mg prednisone/day for 5 days, beginning 3 days before each treatment or control visit. ICS = inhaled corticosteroid; OCS = oral corticosteroid.

the investigator determined that a deterioration in asthma control required a change in asthma medication. Mild and severe exacerbation definitions were as previously described (11). During the reduced steroid phase, subjects continued those medications prescribed at the end of the steroid wean phase for as long as possible.

Measurements

The safety of BT was assessed by monitoring adverse events and pulmonary function. Subjects were asked by trained medical professionals at every visit and by phone call about potential adverse events, and their diaries were examined by study personnel to ensure complete event reporting. Adverse events were designated as respiratory- or non-respiratory-related, and were reported for treatment and post-treatment periods. Investigators reported the severity of adverse events using the following definitions:

Mild: Awareness of signs or symptoms, but easily tolerated; causing no loss of time from normal activities; symptoms would not require medication (other than short-acting bronchodilators) or a medical treatment; signs and symptoms are transient.

Moderate: Discomfort severe enough to cause interference with patient's usual activities. Symptomatic treatment is possible.

Severe: Incapacitating with inability to do work or usual activities; signs and symptoms may be of systemic nature or require medical intervention and/or treatment.

In addition, an adverse event could also be classified as a serious adverse event. According to protocol, a serious adverse event was pre-defined as any event that was fatal, required or prolonged hospitalization, caused substantial risk of dying at the time of the event, resulted in permanent or significant disability/incapacity, or required intervention to prevent permanent impairment.

Additional endpoints included change in OCS and ICS, use of rescue medication, morning and evening PEF, FEV₁, PC₂₀ (provocative concentration causing a 20% fall in FEV₁), asthma symptom score, symptom-free days (11), or AQLQ (15) and ACQ scores (16). Further details of the outcome measures are supplied in the online supplement.

Statistical Analyses

Adverse event frequencies were compared using Fisher's exact test. Statistical significance for continuous variables was determined using Student's *t* test and Wilcoxon rank sum test. The Cochran-Mantel-Haenszel test was used for categorical variables, with statistical significance at *P* < 0.05. The perceived imbalance at baseline in rescue medication use, AQLQ, and ACQ was additionally analyzed with baseline values as a covariant. The database was managed by and all analyses were performed by QST Consultations Ltd. (Allendale, MI).

RESULTS

Thirty-two subjects completed this study (15 in the BT group, 17 in the control group) (Figure 1); all subjects met the Global Initiative for Asthma (GINA) criteria for severe persistent asthma (17) and all but one (one subject had one major but only one minor criterion) met the American Thoracic Society (ATS) criteria for refractory asthma (1). The mean FEV₁ percent predicted was 63% in the BT group and 66% in the control group. Approximately half of the subjects in each group were taking OCS in addition to their ICS+LABA. Baseline parameters were similar between groups except for symptom score (5.6 for the BT group and 3.4 for controls, *P* = 0.02; Table 1). In the 12 months before study entry, the BT group reported more hospitalizations for respiratory adverse events than the control group, although the difference in the proportion of subjects reporting a hospitalization was not statistically significant (10 in 6 subjects vs. 5 in 2 subjects, respectively; *P* = 0.11; Table 1).

Safety

All adverse events were recorded for safety analysis. After BT, there was an increase in respiratory adverse events in the treatment period (Table 2), but there was no increase in the frequency of adverse events with successive treatments. There

TABLE 1. PATIENT DEMOGRAPHICS AND BASELINE ASTHMA CHARACTERISTICS ON ALL MEDICATIONS

Parameter	BT	Control
No. of subjects	15	17
Age, yr	39.1 ± 13.0	42.1 ± 12.6
Sex, male/female, n (%)	6 (40)/9 (60)	10 (59)/7 (41)
White race, n (%)	15 (100)	17 (100)
No. of subjects who performed MCh challenge	9	9
PC ₂₀ , mg/ml* (95% CI)	0.19 (0.05, 0.76)	0.31 (0.08, 1.26)
Prebronchodilator FEV ₁ , % predicted	62.9 ± 12.2	66.4 ± 17.8
No. of subjects receiving OCS	8	7
OCS dose, mg/d† (median)	14.4 ± 6.2 (15)	18.6 ± 9.8 (20)
ICS, fluticasone equivalent, µg/d‡ (median)	1,166.7 ± 408.3 (1,000)	1,058.9 ± 336.9 (1,000)
Long-acting β ₂ -agonist, µg/d§	125.0 ± 60.5	136.7 ± 45.5
Rescue bronchodilator use, puffs/7 d (median)	62.3 ± 58.5 (56)	30.1 ± 17.6 (29)
Morning PEF, L/min	355.9 ± 93.4	350.4 ± 91.0
ACQ score	2.83 ± 1.02	2.23 ± 0.75
AQLQ score	3.96 ± 1.34	4.72 ± 1.06
Symptom-free days, %	5.2 ± 13.6	13.6 ± 24.3
Night awakenings, per wk	3.3 ± 2.5	1.9 ± 2.0
Symptom score	5.6 ± 3.0	3.4 ± 1.8
Seasonal allergies	10 (67%)	9 (53%)
History of hospitalizations in year prior to study (total no. of events/total no. of subjects with an event)*¶	10 (6)	5 (2)

Definition of abbreviations: ACQ = Asthma Control Questionnaire; AQLQ = Asthma Quality-of-Life Questionnaire; BT = bronchial thermoplasty; CI = confidence interval; ICS = inhaled corticosteroids; MCh = methacholine; OCS = oral corticosteroids.

Values are means ± SD unless otherwise stated.

* Geometric mean for those that performed the MCh challenge test.

† Mean for those that were on OCS at baseline.

‡ Dose of fluticasone. All other ICS doses were converted to their equivalent doses of fluticasone.

§ Dose of salmeterol. All other long-acting β₂-agonist doses were converted to their equivalent doses of salmeterol.

|| *P* = 0.02 versus BT group.

¶ Self-reported by subjects at time of enrollment.

TABLE 2. RESPIRATORY ADVERSE EVENTS DURING THE TREATMENT AND POST-TREATMENT PERIODS*

Adverse Event	Treatment Period						Post-Treatment Period					
	BT		Control		P Value		BT		Control		P Value	
	AE Frequency (%)	Subject Frequency (%)	AE Frequency (%)	Subject Frequency (%)			AE Frequency (%)	Subject Frequency (%)	AE Frequency (%)	Subject Frequency (%)		
					AE [†]	Subject [‡]					AE [†]	Subject [‡]
Wheezing	17.6	73.3	7.0	23.5	0.072	0.012	15.6	66.7	15.4	64.7	1.000	1.000
Cough	16.9	73.3	17.5	35.3	1.000	0.042	10.7	40.0	8.9	47.1	0.674	0.735
Chest discomfort	15.4	40.0	5.3	5.9	0.057	0.033	3.3	26.7	12.2	35.3	0.015	0.712
Dyspnea	15.4	60.0	15.8	41.2	1.000	0.480	20.5	73.3	25.2	82.4	0.447	0.678
Productive cough	11.8	53.3	17.5	29.4	0.355	0.280	13.9	66.7	11.4	47.1	0.570	0.308
Sputum discolored	5.1	33.3	0.0	0.0	0.107	0.015	0	0	0	0	1.000	1.000
Nasal congestion	2.9	20.0	5.3	17.6	0.423	1.000	4.1	33.3	4.9	29.4	1.000	1.000
Nasopharyngitis	2.2	20.0	7.0	17.6	0.198	1.000	5.7	26.7	4.9	29.4	0.784	1.000
Pharyngolaryngeal pain	2.2	20.0	1.8	5.9	1.000	0.319	1.6	13.3	0.8	5.9	0.622	0.589
Atelectasis	1.5	6.7	0.0	0.0	1.000	0.469	0	0	0	0	1.000	1.000
Bronchial irritation	1.5	13.3	0.0	0.0	1.000	0.212	0	0	0	0	1.000	1.000
Lower respiratory tract infection	1.5	13.3	8.8	29.4	0.025	0.403	7.4	46.7	4.9	17.6	0.439	0.128
Upper respiratory tract infection	1.5	6.7	5.3	17.6	0.154	0.603	8.2	40.0	6.5	23.5	0.634	0.450

Definition of abbreviations: AE = adverse event; BT = bronchial thermoplasty.

* AE frequency $\geq 1.0\%$ in the BT group.

[†] P value from Fisher's exact test, comparing the proportion of adverse events.

[‡] P value from Fisher's exact test, comparing the proportion of subjects reporting an adverse event.

was no difference between groups during the post-treatment period (Table 2). The most frequently observed respiratory adverse events in the treatment period for BT subjects were wheezing, cough, chest discomfort, dyspnea, productive cough, and discolored sputum (Table 2). Most of these adverse events occurred within 1 day of the bronchoscopy procedure and resolved on average within a week.

During the treatment period, the BT group had 136 respiratory adverse events: 49% were mild, 41% were moderate, and 10% were severe. The control group had 57 respiratory adverse events: 49% were mild, 47% were moderate, and 4% were severe. There were no subject deaths and no permanent or significant disability/incapacity in any patient in the study. All of the respiratory adverse events that met the definition of serious adverse events involved a hospitalization and are described in Table 3.

During the treatment period, there were seven hospitalizations for respiratory adverse events involving four subjects in the BT group and none in the control group (Table 3). Five of the seven hospitalizations in the BT group were for exacerbations of asthma and two were for partial collapse of a lower lobe of the lung. In one case, a left lower lobe segment collapsed 2 days after treatment of the same area and the lung segment reinflated after physiotherapy plus standard medical therapy. In the other case, the lung segment collapse occurred the day after treatment of the area, and was due to a mucus plug; aspiration of the mucus plug resulted in reflation of the lung segment. The median length of stay for the hospitalizations in the BT group during this period was 2 days. In addition, two subjects in the BT group had five severe respiratory adverse events (chest infection, increased wheeze, cough, shortness of breath on exertion) and two subjects in the control group had two severe respiratory adverse events (dyspnea, chest infection) that were medically treated and did not result in hospitalization. In the post-treatment period, five hospitalizations occurred in three subjects in the BT group and four hospitalizations occurred in one subject in the control group (Table 3). This difference was not statistically significant ($P = 0.32$). No BT subjects required intubation or treatment in the intensive care unit (ICU); one control subject had an exacerbation on Day 42 that resulted in management in the ICU (respiratory failure). In addition, in the post-treatment period, two subjects in the BT group had five

severe respiratory adverse events (increased wheeze, chest tightness, increased breathlessness, nocturnal wheeze, and chest infection) and one subject in the control group had one severe respiratory adverse event (flu-like syndrome), all of which were medically treated and did not result in hospitalization.

Efficacy

Steroid stable phase (Weeks 6–22). Subjects treated with BT significantly reduced short-acting β_2 -agonist use from baseline compared with the control group (-26.6 ± 40.1 vs. -1.5 ± 11.7 puffs/7 d, $P < 0.05$ at 22 wk) (Figure 2A, left panel). There were significant improvements in the percentage change from baseline in the prebronchodilator FEV₁% predicted in the BT group compared with the control group at 22 weeks (14.9 ± 17.4 vs. $-0.9 \pm 22.3\%$, $P = 0.04$) (Figure 2B, left panel). There were no significant differences between groups in the change from baseline in post-bronchodilator FEV₁% predicted ($5.7 \pm 8.6\%$ for the BT group vs. $-0.8 \pm 16.8\%$ for the control group, $P = 0.2$). Significant improvements from baseline to 22 weeks were also observed in AQLQ and ACQ scores: in the BT group, AQLQ scores improved by 1.21 ± 1.05 compared with 0.15 ± 0.75 for the control group ($P = 0.003$) (Figure 2C, left panel); ACQ scores improved (noted by a decrease in the score) by -1.04 ± 1.03 versus -0.13 ± 1.00 in the control group ($P = 0.02$) (Figure 2D, left panel).

There were no significant differences in morning or evening PEF, symptom-free days, symptom scores, or methacholine PC₂₀ (see the online supplement).

Reduced steroid phase (Weeks 36–52). Four of eight BT subjects and only one of seven control subjects receiving OCS were able to completely wean off OCS and stay off through 52 weeks ($P = 0.28$). The mean reduction in OCS dose was $63.5 \pm 45.4\%$ in BT subjects and $26.2 \pm 40.7\%$ in control subjects ($P = 0.12$) and the overall reduction in ICS dose was $28.6 \pm 30.4\%$ in the BT group compared with $20.0 \pm 32.9\%$ in the control group ($P = 0.59$).

After the reduced steroid phase at 52 weeks, BT subjects compared with control subjects continued to show a significantly better improvement in short-acting β_2 -agonist use (-25.6 ± 31.2 vs. -6.1 ± 12.4 puffs/7 d, $P < 0.05$; Figure 2A, right panel), AQLQ (1.53 ± 0.79 vs. 0.42 ± 0.82 , $P = 0.001$; Figure 2C, right

TABLE 3. HOSPITALIZATIONS FOR RESPIRATORY ADVERSE EVENTS DURING THE TREATMENT AND POST-TREATMENT PERIODS

Patient #	AE Description	Days Since Most Recent Treatment	Treatment (BT) or Control (C) Group	Duration of Hospitalization (d)*	Treatment of AE while in Hospital
Treatment Period					
1	Wheeze and breathlessness	1 d after treatment 1	BT	2	Co-dydramol and 2.5mg albuterol
1	Shortness of breath and wheeze	1 d after treatment 3	BT	4	40 mg prednisolone, nebulized bronchodilators and IV hydrocortisone
2	Chest tightness	0 d after treatment 1	BT	2	50 mg prednisolone for additional 3 d beyond the 5 d specified in the protocol
2	Dyspnea	45 d after treatment 2 [†]	BT	4	IV aminophylline
2	Cough and Dyspnea	66 d after treatment 2 [†]	BT	5	Antibiotics and 60 mg prednisolone for 8 d
3	Left lower lobe collapse	2 d after treatment 2	BT	2	Nebulizer, antibiotics, chest physiotherapy; lung spontaneously reinflated
4	Increased breathlessness; lower lung lobe collapse	1 d after treatment 2	BT	1	Medical therapy and interventional bronchoscopy to remove a small mucus plug
Post-Treatment Period					
1	Cough, wheeze, and shortness of breath	48 d after treatment 3	BT	2	40 mg prednisolone, nebulized bronchodilators, and magnesium
2	Dyspnea and wheeze	73 d after treatment 3	BT	9	Antibiotics, prednisolone, and nebulizers
2	Dyspnea, wheeze, cough	183 d after treatment 3	BT	14	Prednisolone, aminophylline, terbutaline, and antibiotics; negative sputum cultures
5	Asthma exacerbation/ chest infection	119 d after treatment 3	BT	3	Increased ICS dose, OCS, and antibiotics
5	Asthma exacerbation	268 d after treatment 3	BT	6	IV hydrocortisone, aminophylline, followed by OCS; doxycycline for chest infection; normal chest X-ray and ECG
6	Respiratory failure	42 d after treatment 3	C	7	Intubated for ventilation, treated with nebulizers and hydrocortisone, aminophylline, magnesium, and terbutaline via IV
6	Shortness of breath	224 d after treatment 3	C	3	Oxygen sat 92%, treated with 40 mg prednisolone and cyclazine, negative chest X-ray
6	Wheeze and shortness of breath	287 d after treatment 3	C	3	IV steroids and nebulizers
6	Wheeze and shortness of breath	358 d after treatment 3	C	6	Chest X-ray hyperinflated with no focal consolidation; treated with IV magnesium, IV hydrocortisone, and oxygen

Definition of abbreviations: AE = adverse event; BT = bronchial thermoplasty; ICS = inhaled corticosteroids; IV = intravenous; OCS = oral corticosteroids.

* Duration of hospitalization was calculated as the day of discharge minus the day of admission.

[†] Treatment sessions were planned approximately 3 weeks apart. However, subsequent treatment sessions were to be delayed per protocol if the subject experienced an asthma exacerbation or infection.

panel), and ACQ (-0.99 ± 0.83 vs. -0.22 ± 0.78 , $P = 0.01$; Figure 2D, right panel). There were no significant differences between groups in the change from baseline and the end of this reduced steroid phase in the other efficacy measures.

Post hoc analysis of covariance. The possible influence of differences in baseline values between groups on outcome measures was explored using a *post hoc* analysis of covariance. The baseline value did have a statistically significant relationship to ACQ at 22 weeks, resulting in a loss of statistical significance for this one measure. Analysis of covariance was either not applicable, not indicated, or did not change statistical significance in all other measures.

DISCUSSION

This is the first randomized clinical trial to evaluate BT in the treatment of symptomatic, severe asthma. All subjects met the GINA criteria for severe persistent asthma, and all but one subject met the criteria established by the ATS Workshop on Refractory Asthma, indicating a severe patient population that is not well controlled by current therapy (1). We found that, in this population, BT was associated with a short-term increase in asthma-related morbidity around the time of treatment but showed a potential for a longer term improvement in rescue medication use, lung function, asthma control, and quality of life.

Consistent with previous observations, treatment with BT was associated with adverse events, some requiring hospital-

ization, that were primarily related to worsening of asthma symptoms in the period immediately after treatment (10, 11). Subjects in the AIR study were less symptomatic than subjects in the current study, and had a mean FEV₁% predicted of 73% and a mean daily beclomethasone equivalent inhaled steroid dose of approximately 1,350 μ g. In that study, there were six hospitalizations in 4 subjects out of 55 treated subjects during the treatment period; there were no hospitalizations in the 18 BT subjects with mild-moderate asthma and relatively normal lung function studied by Cox and colleagues (10, 11). Thus, as has been shown before for bronchoscopy and bronchial biopsy in asthma, the severity and frequency of the adverse events appear to be greater in subjects with severe asthma compared with those with less severe asthma (18–20). In keeping with the AIR study, respiratory adverse events were similar between 6 weeks and 12 months in BT-treated subjects and control subjects, suggesting that longer term adverse effects related to BT do not occur and that subjects with more severe asthma are not at increased risk for these effects. However, longer and larger studies of subjects with different asthma severity are required before we can be sure that there are not delayed adverse effects.

The adverse events that were reported after BT included episodes of lobar segmental collapse in two subjects, one of whom required a bronchoscopy with aspiration of a mucus plug. A partial lobar collapse occurred 2 days after treatment in the AIR study (11). All reported cases have involved the most recently treated lobe, suggesting that BT was at least partly responsible for the complication. Further work is required to

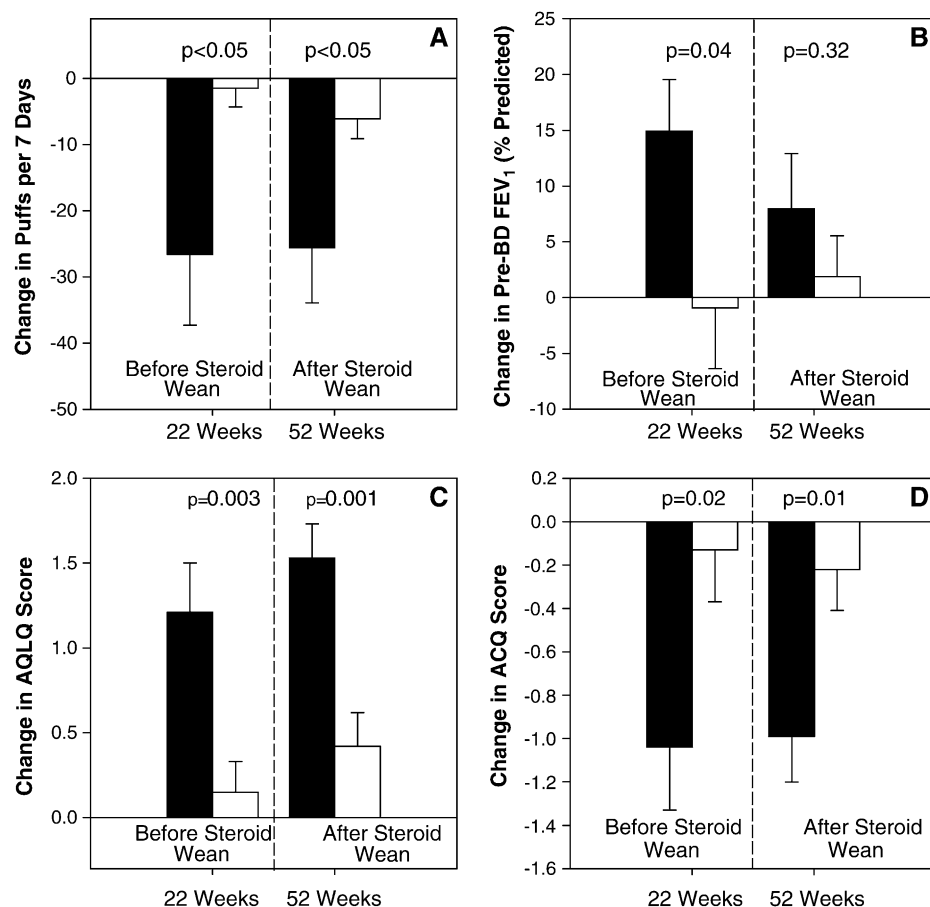


Figure 2. Change in efficacy outcomes at 22 weeks (steroid stable phase) and 52 weeks (reduced steroid phase). Mean change from baseline values are shown for all subjects with data at the given time points. (A) Rescue bronchodilator use (number of puffs/7 d); (B) % predicted FEV₁, prebronchodilator (pre-BD); (C) Asthma Quality-of-Life Questionnaire (AQLQ) score (the response scale is from 1 to 7, with higher scores indicating better quality of life); (D) Asthma Control Questionnaire (ACQ) score (the response scale is from 0 to 6, with lower scores indicating better asthma control). Solid bars, bronchial thermoplasty group; open bars, control group.

determine whether there is an increase in lobar segmental collapse associated with BT. If so, a better understanding of the mechanism and risk factors for this complication may allow the development of effective preventive strategies.

In considering the potential long-term role for BT in the treatment of severe asthma, the increased short-term risk of procedure-related adverse events needs to be weighed against the preliminary evidence of improvement in a range of measures of asthma control. In the stable steroid phase of this study (6–22 wk), treated subjects had clinically and statistically significant improvements over baseline in rescue medication use, prebronchodilator FEV₁% predicted, and AQLQ and ACQ scores. Given the increase in hospitalizations in the treatment period, we considered whether the timing of the last OCS dose resulting from these hospitalizations could have influenced the 22-week evaluation. One BT subject completed his/her OCS dose 25 days before the 22-week evaluation, and all other subjects completed their OCS dose more than 2 months before the 22-week evaluation. Therefore, it is unlikely that the increased steroid use due to hospitalization contributed to the outcomes observed. The net improvement in FEV₁ of 16% seen in our study was larger than that seen in the AIR trial (11), perhaps because the effect of BT is more readily observed in a more severe patient population because of greater room for improvement.

The changes from baseline compared with the control group in the questionnaire scores (+1.1 and -0.9 for AQLQ and ACQ, respectively) were significantly higher than the reported clinically important differences in these measures, and the reduction in puffs per week equates to almost seven fewer canisters of rescue medication per year (21, 22). Changes in bronchodilator use, AQLQ, and ACQ remained statistically significant at 52

weeks, after an attempt had been made to reduce corticosteroid treatment, providing further evidence of a sustained beneficial effect of BT (11). The changes in corticosteroid requirements were not statistically significant, but the power of the study to demonstrate such an effect was low. Future appropriately powered studies should address this important question.

Our results show that most subjects with symptomatic, severe asthma were able to safely tolerate BT. There were seven short-term hospitalizations for respiratory adverse events involving four subjects in the BT group during the treatment period. In the post-treatment period, treated subjects had an adverse event profile similar to their baseline and the control group, but with improvements in their rescue medication use, lung function, asthma control, and quality of life. Some caution is required in interpreting these results as this was a small study with a high potential for placebo effect and there were differences in baseline values, which although not statistically significant, could have influenced the response to treatment. However, a *post hoc* analysis of covariance suggests that the baseline differences did not account for the improvements observed with the exception of one measure. The magnitude of the positive effects, their persistence to 52 weeks, the similar findings in the AIR study (11), and the significant improvements observed in measures like FEV₁, which are less susceptible to bias, provide further reassurance that the results are real. However, appropriately powered studies with blinded sham treatment are critical. Only then will it be possible to interpret the real risk-benefit balance of this novel procedure.

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References

1. American Thoracic Society. Proceedings of the ATS workshop on refractory asthma. *Am J Respir Crit Care Med* 2000;162:2341–2351.
2. Wenzel S. Severe asthma in adults. *Am J Respir Crit Care Med* 2005;172:149–160.
3. Strek ME. Difficult asthma. *Proc Am Thorac Soc* 2006;3:116–123.
4. Busse W, Banks-Schlegel S, Noel P, Ortega H, Taggart V, Elias J; NHLBI Working Group. Future research directions in asthma: an NHLBI working group report. *Am J Respir Crit Care Med* 2004;170:683–690.
5. Holgate ST, Polosa R. The mechanisms, diagnosis, and management of severe asthma in adults. *Lancet* 2006;368:780–793.
6. Moore WC, Peters SP. Severe asthma: an overview. *J Allergy Clin Immunol* 2006;117:487–494.
7. Hogg JC. The pathology of asthma. *APMIS* 1997;105:735–745.
8. Danek CJ, Lombard CM, Dungworth DL, Cox PG, Miller JD, Biggs MJ, Keast TM, Loomas BE, Wizeman WJ, Hogg JC, *et al.* Reduction in airway hyperresponsiveness to methacholine by the application of RF energy in dogs. *J Appl Physiol* 2004;97:1946–1953.
9. Miller JD, Cox G, Vincic L, *et al.* A prospective feasibility study of bronchial thermoplasty in the human airway. *Chest* 2005;127:1999–2006.
10. Cox G, Miller JD, McWilliams A, *et al.* Bronchial thermoplasty for asthma. *Am J Respir Crit Care Med* 2006;173:965–969.
11. Cox G, Thomson NC, Rubin AS, Niven R, Corris P, Siersted HC, *et al.* Asthma control during the year after bronchial thermoplasty. *N Engl J Med* 2007;356:1327–1337.
12. Niven R, Pavord I, Laviolette M, Thomson N, Corris P, Cox G, Chung KF, Rubin AS. Bronchial thermoplasty in refractory asthma: interim results in severe asthma population. Research in Severe Asthma (RISA) trial. *J Allergy Clin Immunol* 2007;119:S1.
13. Thomson NC, Pavord I, Laviolette M, Corris P, Rubin AS, Niven R, Chung KF, Cox G. Bronchial thermoplasty improves asthma control in refractory asthma: research in severe asthma (RISA) trial. *Am J Respir Crit Care Med* 2007;175:A812.
14. National Institutes of Health; National Heart, Lung, and Blood Institute. Expert panel report 2: guidelines for the diagnosis and management of asthma. Bethesda, MD: National Institutes of Health, National Heart, Lung, and Blood Institute; 1997. NIH Publication No. 97-4051.
15. Juniper EF, Guyatt GH, Ferrie PJ, Griffith LE. Measuring quality of life in asthma. *Am Rev Respir Dis* 1993;147:832–838.
16. Juniper EF, O'Byrne PM, Guyatt GH, *et al.* Development and validation of a questionnaire to measure asthma control. *Eur Respir J* 1999;14:902–907.
17. Global Initiative for Asthma. Global strategy for asthma management and prevention. Updated 2004. Bethesda, MD: National Institutes of Health; 1995. NIH Publication No. 02-3659.
18. Jarjour NN, Peters SP, Djukanovic R, Calhoun WJ. Investigative use of bronchoscopy in asthma. *Am J Respir Crit Care Med* 1998;157:692–697.
19. Humbert M, Robinson DS, Assoufi B, Kay AB, Durham SR. Safety of fiberoptic bronchoscopy in asthmatic and control subjects and effect on asthma control over two weeks. *Thorax* 1996;51:664–669.
20. Busse WW, Wanner A, Adams K, Reynolds HY, Castro M, Chowdhury B, Kraft M, Levine RJ, Peters SP, Sullivan EJ. Investigative bronchoprovocation and bronchoscopy in airway diseases. *Am J Respir Crit Care Med* 2005;172:807–816.
21. Juniper EF, Svensson K, Mork A-C, Stahl E. Measurement properties and interpretations of three shortened versions of the Asthma Control Questionnaire. *Respir Med* 2005;99:553–558.
22. Juniper EF, Guyatt GH, Willan A, Griffith LE. Determining a minimal important change in a disease-specific quality of life questionnaire. *J Clin Epidemiol* 1994;47:81–87.