
Persistence of effectiveness of bronchial thermoplasty in patients with severe asthma

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Background: Bronchial thermoplasty (BT) has been demonstrated to be safe and effective in the treatment of severe persistent asthma out to at least 1 year. Preclinical studies have demonstrated that the reduction in airway smooth muscle after bronchial thermoplasty persists out to at least 3 years.

Objectives: To examine the persistence of effectiveness of BT 2 years posttreatment in subjects with severe asthma.

Methods: Subjects participating in the long-term safety follow-up phase of the Asthma Intervention Research 2 (AIR2) Trial were evaluated by comparing the proportion of subjects who experienced exacerbations, adverse events, or healthcare utilization during the first year (year 1) after BT treatment with the proportion of subjects who experienced the same during the subsequent 12 months (year 2).

Results: Severe exacerbations, respiratory adverse events, emergency department visits for respiratory symptoms, and hospitalizations for respiratory symptoms (proportion of subjects experiencing and rates of events), and stability of pre- and post-bronchodilator forced expiratory volume in 1 second (FEV₁), were comparable between years 1 and 2. The proportion of subjects experiencing severe exacerbations in year 2 after BT was 23.0%, compared with 30.9% in year 1.

Conclusions: The reduction in the proportion of subjects experiencing severe exacerbations after BT is maintained for at least 2 years. Bronchial thermoplasty provides beneficial long-term effects on asthma outcomes in patients with severe asthma.

Trial Registration: clinicaltrials.gov, Identifier: NCT00231114.

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INTRODUCTION

Asthma is a major public health problem, affecting approximately 24.6 million people and accounting for an estimated 14.7 million lost workdays for adults annually in the United States.¹ The collective cost of the disease is estimated at more than \$19.0 billion per year.² Etiological factors involved in asthma include increased mucus, airway inflammation, and excessive and hyperresponsive airway smooth muscle.³ Because airway smooth muscle plays a key role in the broncho-

constriction causing airway obstruction, it provides a potential target for therapy. Bronchial thermoplasty (BT) delivered with the Alair System is designed to reduce the excess smooth muscle present in the airway walls of patients with severe asthma.^{4,5}

Results from a multi-center, randomized, double-blind, sham-controlled clinical trial (Asthma Intervention Research 2 [AIR2] Trial) in subjects with severe asthma demonstrated that over the 12-month period following treatment, BT-

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treated subjects experienced improved asthma control, indicated by a 32% reduction over sham in severe exacerbations, 84% reduction over sham in emergency department visits for respiratory symptoms, and 66% reduction over sham in days lost from work/school/other daily activities because of asthma, as well as an improvement in asthma-related quality of life.⁵ The long-term safety of this novel procedure has been reported over a 3- to 5-year period,^{6,7} but long-term persistence beyond 1 year in subjects with severe asthma has not been reported. We now report data on the persistence of effectiveness of BT at 2 years posttreatment based on the BT-group subjects who participated in the follow-up phase of the AIR2 Trial.

METHODS

Study Objective

The objective of this study was to evaluate the persistence of effectiveness beyond 1 year of BT in subjects with severe persistent asthma. Persistence of effectiveness was based on a non-inferiority design comparing the proportion of subjects experiencing severe exacerbations.⁸

Study Design

The AIR2 Trial was a prospective, randomized, sham-controlled study that evaluated the effectiveness and safety of BT in addition to standard of care (inhaled corticosteroid and long-acting β_2 -agonist), and compared this with sham treatment and standard of care.⁵ After evaluation of all subjects at 12 months after the last bronchoscopy procedure, subjects in the sham group exited from the study, and all BT group subjects entered an additional 4-year observation period. Follow-up evaluation of the BT subjects included quarterly phone calls to assess subject status and solicit adverse events, and annual in-office evaluations that include a physical examination, assessment of lung function, and solicitation of all adverse events, including respiratory adverse events resulting in treatment with oral corticosteroid pulses (severe exacerbation), and emergency department visits and hospitalizations for respiratory symptoms. Asthma quality-of-life information was not collected. In the absence of a control group beyond 1 year, an objective endpoint such as severe exacerbations was considered an appropriate outcome measure in the follow-up years to assess durability of the treatment.

Study Periods

For the purposes of these analyses, the 12-month evaluation period began 6 weeks after the last BT bronchoscopy to facilitate a comparison of the treatment effect over matched periods.

Study Subjects

Participants included were subjects from the BT group in the AIR2 Trial. Subjects enrolled in the AIR2 Trial were adults (18-65 years old) diagnosed with asthma, requiring regular maintenance medications of inhaled corticosteroids (ICS > 1,000 $\mu\text{g/day}$ beclomethasone dipropionate or equivalent) and a long-acting β_2 -agonist (LABA) $\geq 100 \mu\text{g/day}$ salme-

terol or equivalent). Subjects also could be taking other medications, including leukotriene modifiers, omalizumab (if used for at least 1 year prior), and oral corticosteroids (OCS) $\leq 10 \text{ mg/day}$. Key inclusion criteria included subjects on stable maintenance asthma medications for at least 4 weeks before entry, baseline asthma quality of life questionnaire score of 6.25 or less (a higher score indicates better quality of life),⁹ pre-bronchodilator FEV₁ 60% or more of predicted, airway hyperresponsiveness (methacholine provocative concentration causing a 20% drop in FEV₁ < 8 mg/mL), at least 2 days of asthma symptoms during the 4-week baseline period, and nonsmoking for at least 1 year, with less than 10 pack-years' smoking history. Key exclusion criteria were life-threatening asthma (defined as intubation for asthma in lifetime or intensive care unit admission for asthma in the prior 24 months), chronic sinus disease, respiratory diseases such as emphysema, use of immunosuppressants, β -adrenergic blocking agents or anticoagulants, and history in the previous year of 3 or more hospitalizations for exacerbations of asthma, 3 or more lower respiratory tract infections, or 4 or more pulses of OCS use for asthma.

All subjects provided informed consent. Institutional review board review and approval was obtained at each participating institution in the AIR2 Trial (see Acknowledgments). Briefly, BT was administered in 3 separate bronchoscopy procedures under moderate sedation, each separated by approximately 3 weeks. During each procedure, a different area of the lung was treated (except for the right middle lobe), with application of the radiofrequency energy with the Alair catheter to all accessible airways with diameters between 3 and 10 mm. No protocol-specified attempt was made to taper controller therapy during the course of the AIR2 Trial. Details of the enrollment, treatment procedures, and follow-up out to 12 months in the AIR2 Trial have been previously reported.⁵

Primary Endpoint

Comparison of Proportion of BT Group Subjects Experiencing Severe Exacerbations in Year 2 Compared with Year 1. Severe exacerbations were defined as severe exacerbations treated with oral or intravenous corticosteroids, or a doubling of the baseline inhaled corticosteroid dose for at least 3 days, or any temporary increase in the dosage of oral corticosteroids for a subject taking maintenance oral corticosteroids at entry into the AIR2 Trial.

Other Endpoints

Other endpoints included comparison of severe exacerbation rates (exacerbations/subject/year); respiratory adverse events (proportion of subjects with respiratory adverse events, and rates of respiratory adverse events); emergency department visits for respiratory symptoms (proportion of subjects with emergency department visits for respiratory symptoms, and rates of emergency department visits); hospitalizations for respiratory symptoms (proportion of subjects with hospitalizations for respiratory symptoms, and rates of hospitaliza-

Table 1. Proportion of Subjects Reporting Severe Exacerbations and Healthcare Resource Utilization

	Percentage of subjects	Percentage of subjects (n) [95% CI]		Upper 95% limit for difference in percent of subjects between years 1 and 2
	Year 1 sham ^a (n = 98)	Year 1 BT (n = 181)	Year 2 BT (n = 166) ^b	
Severe exacerbations	39.8	30.9 (56) [24.2, 37.7]	23.0 (38) [16.6, 29.5] ^c	−0.1*
Asthma (multiple symptoms) adverse events	42.9	28.7 (52) [22.1, 35.3]	26.5 (44) [19.8, 33.2] ^c	5.7
Emergency department visits	15.3	5.0 (9) [1.8, 8.1]	6.6 (11) [2.8, 10.4] ^c	5.8
Hospitalizations	4.1	3.3 (6) [0.7, 5.9]	4.2 (7) [1.2, 7.3] ^c	4.3

For reference in year before study entry (patient reported): Severe exacerbations: sham = 57.1%; BT = 51.6%; ED visits: sham = 31.6%; BT = 28.9%; hospitalizations: sham = 4.2%; BT = 6.1% of subjects.

^a For reference only (based on a 46-week period).

^b N = 165 for severe exacerbations only (one subject continued OCS prescription for entire year and not eligible for exacerbations in the second year).

^c Year 2 BT comparison with year 1 BT: Not significant by Fisher's exact test.

* Not statistically worse in year 2 compared with year 1 if upper 95% limit for difference in percent of subjects is >20%.

tions); stability of pre- and post-bronchodilator FEV₁, and any changes in maintenance asthma medications.

Statistical Analyses

Persistence of the treatment effect was evaluated by comparing the proportion of subjects who experienced severe exacerbations during the first year (year 1) after BT treatment with the proportion of subjects who experienced severe exacerbations during the subsequent 12 months (year 2). The respective number of subjects completing each annual follow-up visit was used to calculate the proportion of subjects with severe exacerbations in each year. If the upper 95% confidence limit of the difference in proportions (year 2 – year 1) is less than 20%, then the proportion of subjects that experienced severe exacerbations is not statistically worse during the subsequent evaluation period. Confidence limits were calculated based on large-sample confidence interval estimation methods for independent samples.

All other endpoints are reported as means with 95% confidence interval (CI) for each 12-month period starting 6 weeks after the last treatment bronchoscopy. Comparisons for the year 2 to year 1 values were made using Fisher's exact test.

RESULTS

Of one hundred ninety (190) subjects randomized to the BT group at the beginning of the AIR2 Trial, 181 subjects completed follow-up evaluations at 12 months, and 166 subjects (92% of year 1 subjects) completed the follow-up evaluations at 2 years. Fifteen subjects did not complete the year 2 evaluation: 9 were lost to follow-up, 2 were withdrawn from study by the investigator (1 had terminal colon cancer, and the other was noncompliant with scheduled visits), 2 withdrew voluntarily for nonmedical reasons, and 2 missed the year 2 visit.

The proportion of subjects experiencing severe exacerbations, asthma (multiple symptoms) adverse events, and emergency department visits and hospitalizations for respiratory symptoms in year 1 and year 2 are shown in Table 1. Data for the sham group for year 1 (46-week period from 6 weeks after the last bronchoscopy out to 12 months), and for both the BT and sham groups for the 12 months before study entry are included to provide a perspective. Event rates for each of these four measures are provided in Table 2.

Table 2. Severe Exacerbations and Healthcare Resource Utilization Rates

	Year 1 sham ^a (n = 98)	Events/subject/year [95% CI]	
		Year 1 BT (n = 181)	Year 2 BT (n = 166) ^b
Severe exacerbations	0.70	0.49 [0.38, 0.62]	0.39 [0.30, 0.52] ^c
Asthma (multiple symptoms) adverse events	0.73	0.48 [0.38, 0.61]	0.43 [0.33, 0.56] ^c
Emergency department visits	0.43	0.07 [0.05, 0.10]	0.08 [0.06, 0.12] ^c
Hospitalizations	0.11	0.04 [0.03, 0.06]	0.06 [0.04, 0.09] ^c

For reference in the year before study entry (patient reported): Severe exacerbations: sham = 1.04; BT = 0.88; ED visits: sham = 1.19; BT = 0.74; Hospitalizations: sham = 0.061; BT = 0.053 events/subject/year.

^a For reference only.

^b n = 165 for severe exacerbations only (one subject continued OCS prescription for entire year and not eligible for exacerbations in the second year).

^c Year 2 BT comparison with year 1 BT: Not significant by Fisher's exact test.

Severe Exacerbations

In the 12 months before their entry into the AIR2 Trial, 51.6% (98/190) of subjects randomized to the BT group reported having one or more severe exacerbations. In this group, a reduction in the proportion of subjects reporting 1 or more severe exacerbations in the year after BT as well as in year 2 (Table 1) was seen. The upper 95% confidence limit of the difference between the proportions for year 2 compared with year 1 was -0.1 ($<20\%$), thereby demonstrating that the proportion was not substantially worse during the subsequent evaluation period. Most severe exacerbations recorded were based on exacerbations treated with oral or intravenous corticosteroids (85 in year 1 and 64 in year 2) or doubling of the baseline inhaled corticosteroid dose for at least 3 days (3 in year 1 and 1 in year 2).

Kaplan-Meier plots for the time to first severe exacerbation for the BT and sham groups in year 1 and for the BT group in year 2 are shown in Figure 1. The slopes of the 2 curves for the BT group indicate that the times to first severe exacerbation are at least comparable, if not somewhat longer in year 2 compared with year 1 ($P = .098$, log rank test).

Other Endpoints

As with the severe exacerbations, both the proportion of subjects (Table 1), and event rates (Table 2) for asthma (multiple symptoms) adverse events, and emergency department visits and hospitalizations for asthma symptoms in year 2 were comparable to year 1.

Forced Expiratory Volume in 1 Second (FEV₁)

The pre- and post-bronchodilator FEV₁ values remained stable between year 1 and year 2 after BT. The prebronchodilator FEV₁ (% predicted) values for years 1 and 2 were $76.4 \pm 17.8\%$ ($n = 179$) and $74.5 \pm 19.3\%$ ($n = 156$), respectively. The post-bronchodilator FEV₁ (% predicted)

values for years 1 and 2 were $83.4 \pm 16.4\%$ ($n = 178$) and $80.8 \pm 18.5\%$ ($n = 155$), respectively.

Adverse Events

During the first year after BT, 369 respiratory-related adverse events were reported by 134 (71.7%) subjects, compared with 196 respiratory-related adverse events reported by 97 (58.4%) subjects in year 2.

A total of 10 hospitalizations occurred for worsening of asthma symptoms in 7 subjects during year 2 after BT. All were treated with standard therapy. The median length of hospital stays was 2.5 days.

Changes in Maintenance Asthma Medication Dose

At the 2-year assessment, 15 subjects (9.0%) had a 50% or greater decrease in their ICS dose, and 4 subjects (2.4%) had a 50% or more increase in their ICS dose. Sixteen subjects (9.6%) had 50% or greater decrease in their long-acting- β_2 -agonists (LABA) dose, and 3 subjects (1.8%) had a 50% or more increase in their LABA dose. Seven (7) subjects in the BT group entered the AIR2 trial with daily OCS as part of their maintenance asthma therapy. At the post-BT year 2 evaluation, 3 subjects had no change in their daily OCS usage, 1 subject had reduced their daily dosage, 2 subjects had stopped taking OCS altogether, and 1 subject had an increase in their dosage. Three subjects not previously on daily OCS initiated OCS usage as their maintenance asthma therapy.

DISCUSSION

Bronchial thermoplasty is a device-based procedure that involves application of controlled heat to reduce the mass of the airway smooth muscle, using a Food and Drug Administration–approved device indicated for treating severe asthma.¹⁰ It has been evaluated in a series of studies involving subjects

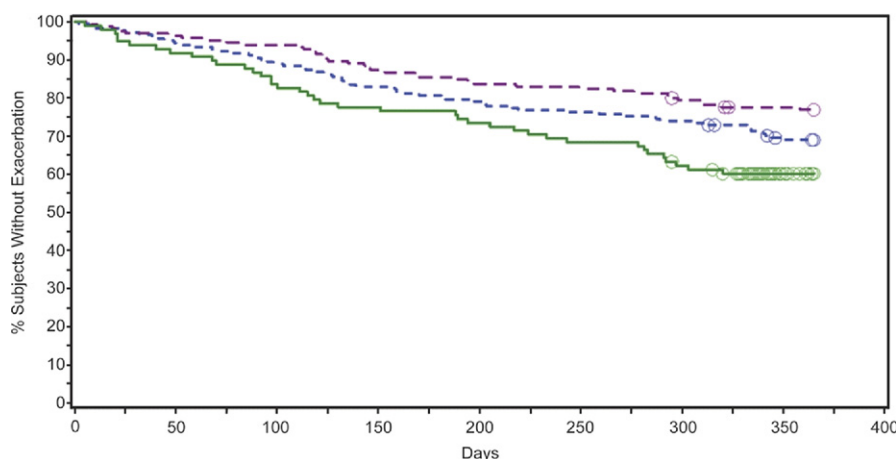


Figure 1. Time to first severe exacerbation after bronchial thermoplasty. Kaplan-Meier plots depicting time to first severe exacerbation in subjects from the AIR2 trial in year 1 (green solid line: sham group, blue dashed line: BT group) and in year 2 (purple dashed line: BT group). In the BT group, there were 8 subjects in year 1 and 2 subjects in year 2 that were experiencing an asthma exacerbation at the beginning of the period. In the sham group, there were 4 subjects in year 1 that were experiencing an asthma exacerbation at the beginning of the period. Subjects not reaching the end of the year were censored for the last date of contact (reflected by circles superimposed on the plots). Log-rank P -values: BT year 1 vs year 2 = 0.098, year 1 BT vs sham = 0.080.

with mild to severe-refractory asthma.^{5,6,11,12} The results of the AIR2 Trial demonstrated clinically significant benefits of BT compared with the sham group at 1 year posttreatment, including an improvement in asthma-related quality of life, 32% reduction in severe exacerbations, 84% reduction in emergency department visits for asthma symptoms, and a 66% reduction in time lost from work/school/ other daily activities because of asthma symptoms.⁵ Preclinical work shows that airway smooth muscle is reduced after bronchial thermoplasty out to at least 3 years after treatment.¹³ Considerable data have accumulated on the long-term safety of the procedure.^{6,7}

We now report on the persistence of effectiveness at 2 years after treatment with BT, based on data collected during follow-up of the BT-treated subjects in the AIR2 Trial. Data were collected in a “real world” attempt to collect information on exacerbations that would be generalizable. Subjects with severe asthma that were randomized to the sham-control group in the AIR2 Trial exited from the study at 1 year post-BT, because requiring these subjects to refrain from exploring alternative treatment options for their condition for an additional 4 years was deemed unethical. Therefore, our findings are limited by lack of a comparator sham-controlled group beyond year 1. However, the use of a non-inferiority model designed to show that one group is no less different at a given time than a certain amount from the same group at a different time¹⁴ allows for the comparisons of the outcomes of the BT group at year 1 with outcomes in subsequent years.

Our results have demonstrated that the benefits of BT seen at 1 year are maintained at 2 years. The proportion of subjects receiving BT experiencing severe exacerbations remained comparable at year 2 (23.0%) compared with year 1 (30.9%) and are favorably lower than the proportion reported for the 12 months before study entry (51.6% in the BT group, 57.1% in the sham group). The observed reduction in the rate of severe exacerbations (events/subject/year) in year 1 was also found and was comparable that in year 2. This rate of exacerbations occurring in patients treated with bronchial thermoplasty is comparable to that of participants with less severe asthma receiving placebo in an omalizumab study (0.23-0.34 exacerbations per patient).¹⁵ Similarly, the proportion of subjects experiencing and the rates of occurrence of multiple symptoms of asthma or emergency department visits for respiratory symptoms showed no change in year 2 compared with year 1 that might suggest any loss of the benefits observed in year 1. The rate of hospitalizations for respiratory symptoms in year 2 was also comparable to the rate of hospitalizations for respiratory symptoms in year 1. Furthermore, this rate of hospitalizations occurring in patients treated with bronchial thermoplasty is substantially less than a well-characterized group of subjects with severe asthma in the Severe Asthma Research Program, in which approximately 30% experienced hospitalization and 12% intensive care unit admission in the past year (self-report).³ Consistent with the stated goals of the National Asthma Education and Prevention Program guidelines for asthma control,¹⁶ these findings

collectively demonstrate continuing improved long-term asthma control for up to 2 years in this group of BT-treated subjects.

In agreement with findings reported from prior studies,^{6,7} the pre- and post-bronchodilator FEV₁ has remained stable out to 2 years in this group of severe asthmatics, suggesting the absence of any late-developing adverse consequences of treating asthmatic airways with BT that might affect pulmonary function in the long-term. The BT-treated airways continue to be responsive to bronchodilators, with a 7 to 10% increase in FEV₁ after bronchodilator administration. The positive benefit-to-risk profile previously established for BT⁵ is further amplified with the current data showing the persistence of effect out to at least 2 years.

Bronchial thermoplasty provides long-term asthma benefits in subjects with severe asthma. The persistence of BT's effectiveness out to 2 years compared with historically reported data suggests that BT has a disease-modifying effect, although this has not been confirmed by histology. The clinically meaningful improvements, combined with the consistent and stable long-term safety, confirm BT as an important new treatment option for patients with severe asthma whose condition is poorly controlled despite using high-dose inhaled corticosteroids and long-acting bronchodilators.

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CME ANSWERS

1. c
2. b
3. d
4. b
5. c