Bronchial thermoplasty: Long-term safety and effectiveness in patients with severe persistent asthma

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Background: Bronchial thermoplasty (BT) has previously been shown to improve asthma control out to 2 years in patients with severe persistent asthma.

Objective: We sought to assess the effectiveness and safety of BT in asthmatic patients 5 years after therapy.

Methods: BT-treated subjects from the Asthma Intervention Research 2 trial (ClinicalTrials.gov NCT01350414) were evaluated annually for 5 years to assess the long-term safety of BT and the durability of its treatment effect. Outcomes assessed after BT included severe exacerbations, adverse events, health care use, spirometric data, and high-resolution computed tomographic scans.

Results: One hundred sixty-two (85.3%) of 190 BT-treated subjects from the Asthma Intervention Research 2 trial completed 5 years of follow-up. The proportion of subjects experiencing severe exacerbations and emergency department (ED) visits and the rates of events in each of years 1 to 5 remained low and were less than those observed in the 12 months before BT treatment (average 5-year reduction in proportions: 44% for exacerbations and 78% for ED visits). Respiratory adverse events and respiratory-related hospitalizations remained unchanged in years 2 through 5 compared with the first year after BT. Prebronchodilator FEV_1 values remained stable between years 1 and 5 after BT, despite a 18% reduction in average daily inhaled corticosteroid dose. High-resolution computed tomographic scans from baseline to 5 years after BT showed no structural abnormalities that could be attributed to BT.

Conclusions: These data demonstrate the 5-year durability of the benefits of BT with regard to both asthma control (based on maintained reduction in severe exacerbations and ED visits for respiratory symptoms) and safety. BT has become an important addition to our treatment armamentarium and should be considered for patients with severe persistent asthma who remain symptomatic despite taking inhaled corticosteroids and long-acting β_2-agonists. (J Allergy Clin Immunol 2013;■■■:■■■-■■■.)

Key words: *Bronchial thermoplasty, asthma, bronchoscopic procedure, Alair System, asthma exacerbation*

Abbreviations used

AE:	Adverse event
AIR2:	Asthma Intervention Research 2
AQLQ:	Asthma Quality of Life Questionnaire
BT:	Bronchial thermoplasty
ED:	Emergency department
HRCT:	High-resolution computed tomography
ICS:	Inhaled corticosteroid
LABA:	Long-acting β_2-agonist
NAEPP:	National Asthma Education and Prevention Program
OCS:	Oral corticosteroid

More than 25 million persons in the United States have asthma.[1,2] Approximately 5% of patients have severe persistent asthma and continue to experience asthma symptoms, despite treatment with current state-of-the-art medications.[3] Poorly controlled and not well controlled asthma remain a significant social and economic burden[2,4] and lead to increased health care use, with negative effects on the patient's quality of life.

Bronchial thermoplasty (BT) is a nonpharmacologic treatment for asthma that has been shown to result in significant improvements in a number of asthma control measures in 3 randomized clinical trials in patients with moderate-to-severe persistent asthma.[5-7] The Asthma Intervention Research 2 (AIR2) trial, a double-blind, sham-controlled, randomized clinical trial of BT in patients with severe asthma, showed a 32% reduction in severe exacerbations, an 84% reduction in emergency department (ED) visits caused by respiratory symptoms, a 73% reduction in hospitalizations for respiratory symptoms, and a 66% reduction in time lost from work/school/other daily activities because of asthma symptoms compared with a sham-treated group in the year after the BT treatment period (day of first BT procedure until 6 weeks after the last bronchoscopy, approximately 12 weeks).[7] We previously reported safety out to 5 years in patients with moderate-to-severe persistent asthma through extended follow-up of 45 (86.5%) of 52 BT-treated subjects in the AIR trial.[8] The safety and durability of the treatment effect (reduced severe exacerbations and ED visits for respiratory symptoms) were previously

reported out to 2 years after BT in subjects with severe persistent asthma in the AIR2 trial.[9] We now describe the long-term safety and durability of BT out to 5 years after treatment in 162 of 190 subjects from the AIR2 trial.

METHODS

Study procedures

Subjects undergoing BT in the AIR2 trial were followed to 5 years. The study population and design of the AIR2 trial have been published.[7] Data collected during the 5-year follow-up and episodes of severe exacerbations were analyzed by using a noninferiority approach to demonstrate that the benefit of BT in the year after the procedure was maintained in each of the subsequent years out to 5 years (ClinicalTrials.gov no. NCT01350414).

On completion of the year 1 evaluation in the AIR2 trial, subjects in the BT group were instructed to maintain their use of controller medications (unless changes were medically indicated as determined by the investigator) and were contacted by telephone every 3 months. Information on adverse events (AEs; defined as any sign, symptom, illness, clinically significant abnormal laboratory value, or other adverse medical event that appeared or worsened in a patient during the clinical study regardless of whether it was considered related to the procedure used as part of the protocol), hospitalizations, ED visits for

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respiratory symptoms, and new or increased dosages of oral corticosteroids (OCSs) for worsening of asthma symptoms were collected by using a specific set of questions. An in-office evaluation was performed annually at years 2, 3, 4, and 5, at which time the same questions as above were posed and a physical examination and prebronchodilator and postbronchodilator spirometry were performed. Severe exacerbations, ED visits, and hospitalizations for the year before BT were subject reported. One hundred subjects in the BT group who had a high-resolution computed tomographic (HRCT) scan at baseline and year 1 underwent a repeat HRCT scan at years 3 and 5.

Evaluation periods

The posttreatment evaluation period for the purposes of these analyses consisted of 52-week windows beginning at 6 weeks after the last BT bronchoscopy to facilitate a comparison of the durability of the treatment effect over matched periods of time. An additional analysis of the annualized rate of exacerbations and emergency department visits beginning at the time of randomization, including the 3 bronchoscopies, was also performed.

Evaluation of HRCT

Baseline and year 5 follow-up HRCT images for 93 evaluable pairs were read by an independent pulmonary radiologist who was blinded to time point (baseline or year 5; J.H.M.A., with >33 years of thoracic CT experience). On completing this assessment, the radiologist was unblinded and assessed whether findings in follow-up images were new observations, improvements from baseline, or deteriorations from baseline. The radiologist's findings were reviewed by an independent pulmonologist (Dr Nizar Jarjour, with 24 years of pulmonology experience) who attributed a clinical significance to each finding based on the subject's information, including lung function and AE profiles, as well as occurrence and timing of respiratory events and severe exacerbations.

Statistical analyses

All statistical processing was performed with SAS software Version 9.1 (SAS Institute, Cary, NC).

Severe exacerbations. Point estimates and 95% CIs for the proportion of subjects (number of subjects with events over the total number of subjects evaluated in the period) experiencing severe exacerbations during each of the 12-month evaluation periods were calculated. The definition of severe exacerbations was derived from the definition originally used in the parent trial[7] and consisted of treatment with OCSs or intravenous corticosteroids, a doubling of the baseline inhaled corticosteroid (ICS) dose for at least 3 days, or any temporary increase in the dosage of OCSs for subjects taking maintenance OCSs at entry into the AIR2 trial. Additionally, the upper 95% confidence limit for the difference in proportions between 12-month follow-up periods and the first year was calculated. A noninferiority margin of 20% was used to demonstrate that the proportions were not substantially worse during each of the subsequent evaluation periods (ie, the upper 95% confidence limit for the difference in proportions is less than 20%). The number of subjects who completed follow-up visits for each year was used as the denominator to calculate the proportions of subjects with severe exacerbations during each year. No imputations were made for missing data. A subject who terminated during the follow-up was still counted in those years that the subject provided data.

Hospitalizations and ED visits for respiratory symptoms. Descriptive statistics with 95% CIs were tabulated for the event rates (events/subject/year) and the proportions of subjects experiencing respiratory AEs, ED visits for respiratory symptoms, and hospitalizations for respiratory symptoms for each 12-month period starting 6 weeks after the last treatment bronchoscopy.

Maintenance medications. Changes in ICS dose from baseline to year 5 were analyzed with the sign test. Medication change was defined as an increase or decrease of 50% or more in daily dose.

Subgroup analyses. Responder analysis based on improvements in the Asthma Quality of Life Questionnaire (AQLQ) scores at year 1 after BT in this group showed that 79% of the subjects achieved a minimally important difference of 0.5 or more. In the absence of a control group during long-term follow-up, key parameters were evaluated for the responders (subjects achieving an AQLQ score change of ≥0.5) and nonresponders (subjects not achieving an AQLQ score change of ≥0.5).

Ethics

Written informed consent was obtained from all participating subjects after the AIR2 trial was approved by the institutional review boards/ethics committees at each participating institution. The study was conducted in accordance with the principles of the Declaration of Helsinki (2004[10] and 2008[11]).

RESULTS

Of the 190 subjects who underwent BT treatment in the AIR2 trial, 162 (85.3%) completed the 5-year follow-up. The number of subjects undergoing BT and completing annual follow-up at years 1, 2, 3, 4, and 5 was 181, 165, 162, 159, and 162, respectively. Twenty-eight (14.7%) subjects undergoing BT did not complete the year 5 evaluation (18 were lost to follow-up, 4 were withdrawn by the investigators [terminal illness: 1; noncompliance with physician's instructions: 3], 5 were withdrawn for nonmedical reasons, and 1 died in a motor vehicle accident). Four subjects missed the year 4 visit but remained in the study.

Demographics and clinical characteristics

The baseline demographics and clinical characteristics of the 190 subjects enrolled in the BT group in the AIR2 trial, the 162 subjects completing follow-up at 5 years, and the 28 subjects who did not complete follow-up at 5 years are summarized in Table I. There was no difference in baseline characteristics between the subjects completing the 5-year follow-up compared with the subjects not completing follow-up at 5 years or the original cohort of 190 subjects at enrollment, except for age, with the cohort not completing follow-up at year 5 being younger ($P = .019$). At baseline, 32% of the subjects had symptoms that were not well controlled, and 68% had symptoms that were poorly controlled according to the National Asthma Education and Prevention Program (NAEPP) Expert Panel Report 3 (2007) guidelines, despite their maintenance asthma medication.

Treatment parameters

The average (± SEM) numbers of activations for the 3 treatment procedures were 44 ± 1.2 (procedure 1, right lower lobe), 47 ± 1.2 (procedure 2, left lower lobe), and 60 ± 1.6 (procedure 3, both right and left upper lobes), with coverage of all accessible airways between 3 and 10 mm in diameter. For the 162 patients who completed follow-up at 5 years, the total number of activations for the 3 procedures was 151.

Severe exacerbations

The proportion of subjects experiencing severe exacerbations (>97% of which were based on systemic corticosteroid administration) in each of years 1 to 5 are shown in Fig 1, *A*, with the period constituting year 1 beginning at 6 weeks after the last BT bronchoscopy. The proportion of subjects having severe exacerbations in each subsequent year (years 2, 3, 4, and 5) compared with the first year after BT were not significantly different. In addition, the reduction in the proportion of subjects experiencing severe exacerbations in the year after BT (30.9%) compared with

TABLE I. Demographics and clinical characteristics

	All subjects undergoing BT at baseline (n = 190)	Subjects undergoing BT completing 5-y follow-up (n = 162)	Subjects undergoing BT not completing 5-y follow-up (n = 28)
Age (y)	40.7 ± 11.9	41.5 ± 11.8	35.8 ± 11.3§
Sex	Male: 81 (42.6%)	Male: 68 (42.0%)	Male: 13 (46.4%)
	Female: 109 (57.4%)	Female: 94 (58.0%)	Female: 15 (63.6%)
Race			
White	151 (79.5%)	134 (82.7%)	17 (60.7%)
African American/black	19 (10.0%)	13 (8.0%)	6 (21.4%)
Hispanic	6 (3.2%)	4 (2.5%)	2 (7.1%)
Asian	4 (2.1%)	3 (1.9%)	1 (3.6%)
Other	10 (5.3%)	8 (4.9%)	2 (7.1%)
Weight (kg)	81.7 ± 18.4	81.4 ± 17.1	83.4 ± 24.6
ICS dose (μg)*	1960.7 ± 745.2	1958.9 ± 757.9	1900 ± 551.6
LABA dose (μg)†	116.8 ± 34.4	120.8 ± 47.7	108.9 ± 23.8
Symptom-free days (%)	16.4 ± 24.0	16.1 ± 24.1	18.4 ± 24.1
Asthma Control Questionnaire score	2.1 ± 0.87	2.1 ± 0.84	2.3 ± 1.02
AQLQ score	4.30 ± 1.17	4.32 ± 1.17	4.23 ± 1.16
ED visits for respiratory symptoms in prior 12 mo,‡ no. of events (no. of subjects)	141 (55)	115 (47)	26 (8)
Hospitalizations for respiratory symptoms in prior 12 mo,‡ no. of events (no. of subjects)	10 (8)	10 (8)	0 (0)
Seasonal allergies, no. (%)‡			
Yes	103 (54.5%)	85 (52.8%)	18 (64.3%)
No	86 (45.5%)	76 (47.2%)	10 (35.7%)
Lung function measures			
Prebronchodilator FEV_1	77.8 ± 15.65	77.8 ± 15.84	78.0 ± 14.75
Postbronchodilator FEV_1	86.1 ± 15.76	85.9 ± 15.83	87.1 ± 15.57
Morning PEF (L/min)	383.8 ± 104.3	380.9 ± 106.0	400.7 ± 93.8
Methacholine PC_{20} (mg/mL), geometric mean (range)	0.27 (0.22-0.34)	0.27 (0.21-0.35)	0.29 (0.15-0.54)

Values are means ± SDs, except when indicated otherwise.
PEF, Peak expiratory flow.
*Beclomethasone or equivalent.
†Salmeterol or equivalent.
‡Patient reported.
§P = .019 comparing subjects completing 5-year follow-up versus subjects not completing 5-year follow-up (t test).

the 12 months before BT (51.6%) was maintained for the entire 5-year follow-up period, with an average decrease of 44% over this period. Matched-pairs analysis comparing the 162 subjects completing the year 5 evaluations with the same group in previous years showed a similar proportion of subjects having a severe exacerbation in years 1 to 5 (30.9%, 23.5%, 34.0%, 36.4%, and 21.6%, respectively), representing a persistent reduction compared with the 12 months before BT, when 53.1% of subjects experienced 1 or more exacerbations. The decrease in severe exacerbation rates that was achieved in the posttreatment period after BT in year 1 was maintained out to 5 years (Fig 1, *B*). Compared with the 12 months before BT treatment, the average reduction over 5 years in the rate of severe exacerbations was 48%. The upper 95% confidence limit for the difference in percentages for years 2, 3, 4, and 5 compared with year 1 (subsequent year − year 1) was 0.5, 11.3, 14.0, and −1.6, respectively. All were less than the predefined noninferiority margin of 20%. The rates of severe exacerbation during years 2 through 5 were also low when compared with the annualized exacerbation rate during the approximately 64-week "year 1" period that included both the treatment period (the approximately 12-week period from the first bronchoscopy until 6 weeks after the third bronchoscopy) and posttreatment period (the 52-week period beginning 6 weeks after the last bronchoscopy, see Fig E1 in this article's Online Repository at www.jacionline.org).

There was no difference in the average proportion of subjects experiencing severe exacerbations over 5 years between those reporting seasonal allergy (29.3%) and those with no allergies (29.5%). On average, both patients with FEV_1 values of 60% to 70% of predicted value and those with FEV_1 values of greater than 70% of predicted value had sustained improvements in exacerbations over the 5-year period (data not shown).

Safety

The proportions of subjects having ED visits for respiratory symptoms and the yearly rates of ED visits over the 5 years after BT are shown in Fig 1, *C* and *D*, respectively. The decrease in the proportion of subjects experiencing ED visits for respiratory symptoms that was achieved after BT in year 1 was maintained out to 5 years. Compared with the 12 months before BT, the average reduction over the 5 years in the proportion of subjects having ED visits for respiratory symptoms was 78%. The decrease in rates of ED visits that was achieved after BT in year 1 was maintained out to 5 years (Fig 1, *D*). Compared with the 12 months before BT treatment, the average reduction over 5 years in the rate of ED visits was 88%. The rates of ED visits during years 2 through 5 were lower when compared with the annualized rate of the approximately 64-week year 1 period that included both the treatment period (the approximately 12-week period from the first

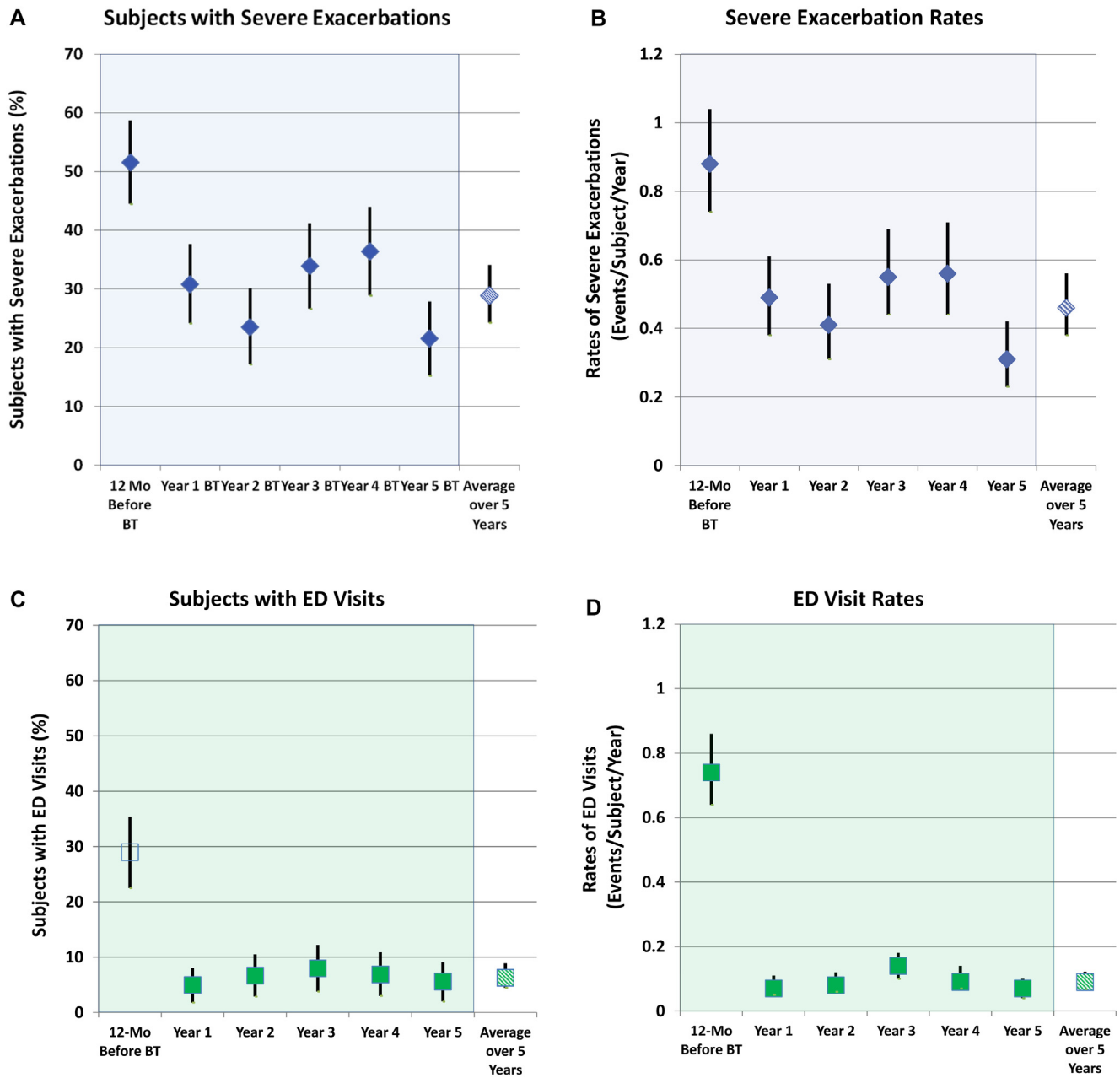

FIG 1. Severe exacerbations and ED visits in the 5 years after BT. **A,** Proportion of subjects with severe exacerbations. **B,** Severe exacerbation rates. **C,** Proportion of subjects with ED visits for respiratory symptoms. **D,** ED visit rates. Values are point estimates with 95% upper and lower CIs. The 365-day period constituting year 1 began at 6 weeks after the last BT bronchoscopy.

bronchoscopy until 6 weeks after the third bronchoscopy) and posttreatment period (the 52-week period beginning 6 weeks after the last bronchoscopy, see Fig E1).

The proportion of subjects experiencing any respiratory AEs, asthma (multiple symptoms) AEs, and hospitalizations for respiratory symptoms did not increase over 5 years (see Table E1 in this article's Online Repository at www.jacionline.org). The reduction in respiratory AEs and asthma (multiple symptoms) AEs that was observed at 1 year persisted through the 5 years of follow-up, with no increase in rates from years 1 through 5 (see Table E1). Respiratory AEs that occurred at an incidence rate of 3.0% or greater of subjects in any of years 1 through 5 included sinusitis, asthma (multiple symptoms), bronchitis, cough, lower respiratory tract infections, influenza, nasopharyngitis, pneumonia, rhinitis, upper respiratory tract infections, and wheezing. There was no incidence of pneumothorax, intubation/mechanical ventilation, cardiac arrhythmias, or death as a result of BT treatment over the 5 years of follow-up. The proportion of subjects experiencing hospitalization and the rate of hospitalization for respiratory symptoms was low at baseline and remained unchanged over the 5 years after BT.

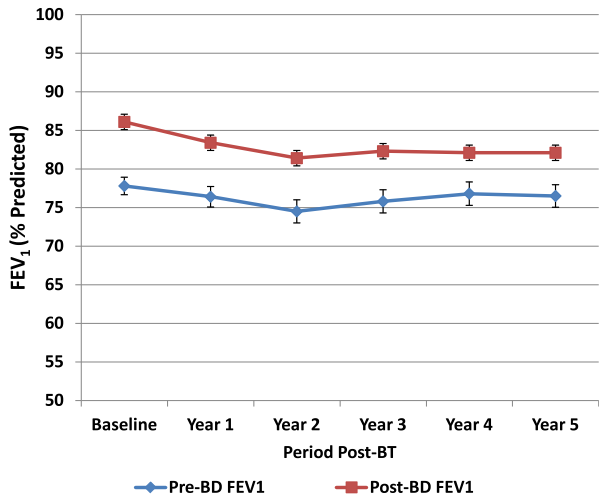

FIG 2. Prebronchodilator and postbronchodilator FEV_1 over 5 years (percent predicted). Percent predicted prebronchodilator and postbronchodilator FEV_1 values (means ± SEMs) for subjects completing follow-up during each year. The percent predicted prebronchodilator FEV_1 values remained unchanged over the 5 years after BT. Postbronchodilator FEV_1 remained higher at all times; increase in percent predicted FEV_1 at baseline of 8.2% and at 5 years of 5.9%. *BD*, Bronchodilator.

Lung function

Percent predicted prebronchodilator FEV_1 values remained unchanged over the 5 years after BT. Postbronchodilator FEV_1 remained higher at all times; increase in percent predicted FEV_1 at baseline of 8.2% and at 5 years of 5.9% (Fig 2).

Maintenance medication changes

At baseline, 116 (72%) of the 162 subjects who completed evaluations at 5 years were prescribed 2 maintenance asthma medications (ie, high-dose ICS [>1000 μg beclomethasone equivalent] + long-acting β_2-agonist [LABA]), and 45 (28%) of the 162 subjects were prescribed 3 or more maintenance asthma medications. At 5 years after BT, 28% (45/162) of subjects had decreases of 50% or more of their ICS maintenance medications, with half of this group (21/162) having reduced their daily ICS dose to equal to or less than 500 μg/d beclomethasone equivalent. Eight (5%) of the 162 subjects had an increase of 50% or greater in their ICS maintenance medications. Of those with changes in ICS doses of 50% or greater, significantly more subjects had a decrease compared with those with an increase ($P <$ .001). There was an overall reduction of 18% in the average ICS dose at 5 years. Twenty (12%) of the 162 subjects were completely weaned off LABAs, 9% (15/162) were weaned off ICS and LABA maintenance medications, and 7% (12/162) were no longer taking any maintenance asthma medications.

HRCT

Of the 93 evaluable HRCT pairs at year 5, 82% showed either no radiologic changes or improvement from baseline. At 5 years after BT compared with baseline, 71% of the HRCT pairs showed no radiologic changes of clinical significance. A similar proportion of subjects had improvements or deteriorations of clinical significance (improvements in 14% and deteriorations in 15%), which represented predominantly changes in gas trapping, bronchial wall thickening, or consolidation. Over the 5-year period, 3 (3%) subjects were noted to have increased or new bronchiectasis: 1 involved worsening of pre-existing bronchiectasis; 1 involved mild bronchiectasis in 2 lobes, including the right middle lobe, that had not been treated with BT; and 1 involved bronchiectasis newly identified by means of HRCT at 3 years. Unfortunately, no 5-year HRCT for this subject was obtained, but the subject was clinically stable. There was no evidence of bronchial stricture, bronchiolitis obliterans, or new pulmonary emphysema in any of the HRCT pairs evaluated at year 5.

Subgroup analyses

The event rates (events/subject/year) averaged over years 2 through 5 were higher in the nonresponders than in the responders: severe exacerbations, 0.720 versus 0.389; respiratory AEs, 1.487 versus 1.012; asthma (multiple symptoms) AEs, 0.745 versus 0.376; ED visits for respiratory symptoms, 0.214 versus 0.068; and hospitalizations for respiratory symptoms, 0.079 versus 0.051, respectively (see Table E2 in this article's Online Repository at www.jacionline.org).

DISCUSSION

In this study we examined the long-term follow-up of patients who underwent BT in the AIR2 trial[7] through an open-label observation of posttherapy events. Previously published data have demonstrated the persistent benefits of BT out to 2 years in patients with severe persistent asthma.[9] This study demonstrates an improvement in asthma control as measured by a maintained reduction in the proportion of subjects experiencing severe exacerbations that persists out to at least 5 years after BT. There was minimal loss to follow-up, with 85.3% of subjects completing the evaluations at year 5. A 44% average reduction in the proportion of subjects experiencing severe exacerbations over a 5-year period might be associated with a substantial reduction in the use of systemic corticosteroids in these patients and provide a meaningful improvement in quality of life.

Consistent with the persistent reduction in severe exacerbations, the data also demonstrate a persistent reduction in ED visits for respiratory symptoms, with an average decrease in the proportion of subjects with ED visits over 5 years of 78% compared with the 12 months before BT. The absence of an increase in respiratory AEs and asthma (multiple symptoms) AEs over a 5-year period provides further support for the long-term effectiveness of BT. These improvements with BT were noted in the presence of reduced use of maintenance medications. Collectively, these data raise the possibility that BT might be a disease-modifying therapy. Further work will be needed to test this intriguing hypothesis.

The safety of BT over the long-term is supported by the absence of any decrease in lung function (no deterioration of FEV_1), the lack of increase from the low baseline rate of hospitalizations, and the absence of any significant structural changes in the airways (from HRCT review) over the course of 5 years of follow-up. These data confirm the previously established safety profile.[6-9,12-14]

The potential for a transient increase in AEs (including severe exacerbations) around the time of BT procedures compared with those seen in sham control subjects[7] should be considered in seeking to achieve a sustained improvement in asthma control defined by maintained reduction in severe exacerbations and ED visits out to at least 5 years after BT. The long-term benefits of BT,

including the reduction in severe exacerbations and ED visits reported here, are consistent with the stated goals of asthma control, as defined by the NAEPP.[15] Unlike other currently available therapies for asthma, BT appears to provide long-term (years) asthma control for many patients after a 1-time treatment comprising 3 procedures. Physicians must consider these short-term risks of the procedure along with the long-term safety and efficacy described here to assess the appropriateness of this therapy for the individual patient.

Follow-up out to 5 years in this large cohort of patients with severe asthma treated with BT addresses many concerns previously expressed regarding the long-term safety of this novel therapy. Furthermore, the stable lung function, as assessed based on FEV_1 values over 5 years and the absence of any unexpected structural alterations in HRCT scans in 93 matched HRCT pairs from patients with severe asthma evaluated at 5 years, is reassuring and consistent with findings previously reported in subjects with mild-to-moderate asthma after BT.[12] The observed radiologic improvements or deteriorations of gas trapping, bronchial wall thickening, or consolidation at 5 years after BT represent findings that are commonly associated with severe asthma and are often temporary and transient in nature[16,17] and have been shown in cross-sectional surveys to correlate with indicators of airway obstruction by means of spirometric and lung volume measurements.[18] The 3 cases of bronchiectasis are of particular interest. One involved existing bronchiectasis that would currently be considered a contraindication to BT treatment. The second case involved bronchiectasis in the lingula and the untreated right middle lobe, making a cause-and-effect relationship with BT treatment unlikely. The third case represents the only case of bronchiectasis that is theoretically possibly related to BT treatment within the study population. Gupta et al[19] have previously reported a baseline prevalence of bronchiectasis in asthmatic patients of approximately 31% when compared with healthy control subjects (approximately 12.5%), and therefore it is not clear in the present cases whether the development of bronchiectasis is due to the underlying severe asthma or BT. The approximate incidence of less than 0.2% per annum in the present study is reassuring and suggests that BT does not cause bronchiectasis. Although the main purpose of this study was to assess long-term (5-year) durability and safety follow-up in a cohort of patients who underwent BT, as in other long-term studies of therapies for severe asthma, a limitation of this study is the lack of a sham control group beyond 1 year, including the lack of HRCT scans for the sham group beyond 1 year. Collecting meaningful 5-year study data without confounding would have required maintaining the study blind for the entire 5-year period in both the treatment and sham groups, which was believed to be unethical in this study population. On the other hand, maintaining sham-treated patients in the follow-up study after breaking the blind and requiring them to continue the same treatment regimen despite poor control was deemed neither ethical nor practical and likely to result in poor patient retention, thus leading to further difficulty in study result interpretation because of missing data and confounding. Because of these concerns, the sham group exited the study at the end of the first year and was not followed in the long-term extension study.

Although comparison with historical control subjects has not been possible because of the lack of studies with long-term (>1 year) follow-up of patients with severe asthma receiving current standard-of-care therapy, one potential approach to address this in the present study was to compare the outcomes of those subjects whose symptoms improved after BT and those whose symptoms did not improve. The analysis of the data for responders and nonresponders after BT treatment (based on an AQLQ score improvement of ≥0.5 [responders] and <0.5 [nonresponders]) provided insight into the subsequent course of these 2 groups and is consistent with previously published literature suggesting the AQLQ score is linked with health care use[20]; over the 5 years of follow-up, severe exacerbation rates, respiratory AE rates, asthma (multiple symptoms) AE rates, and rates of ED visits and hospitalizations for respiratory symptoms remained higher in the nonresponders compared with the responders.

Despite the absence of the sham control group comparison at 5 years, the present data are meaningful because the benefits in the BT group demonstrated in the first year after BT were maintained at 5 years. The effects of BT that were reported for the first year after the treatment were based on a mean of 151 activations for the full treatment[7] and the mean number of activations were not different for the 162 subjects who completed follow-up at 5 years. It has not been possible to demonstrate a dose response that defines the minimal number of activations that might be necessary for producing an effect at 1 year. The intent of BT remains to treat all accessible airways reachable with the bronchoscope, and therefore activations will vary based on the patient's airway anatomy.

The question of phenotyping to define responders cannot be addressed from the present data because assessments of the fraction of exhaled nitric oxide, sputum eosinophil counts, or other biomarkers were not performed at baseline as part of the AIR2 trial. However, there was no difference in outcome based on the subjects' self-reported allergy status (allergic vs nonallergic). Describing the phenotypes that benefit most from this therapy remains an area of considerable interest. BT might benefit a heterogeneous group of patients with severe asthma who remain symptomatic despite standard care. These patients are identified at steps 5 or 6 of the NAEPP guidelines[15] by the need for high-dose ICSs and LABAs with continued breakthrough asthma symptoms. Although patients in this study were reasonably stable (ie, FEV_1 >60%, no more than 3 hospitalizations in the prior year, and ≤8 puffs of rescue medications per day on average) and able to undergo bronchoscopy, the experience of the patients with severe refractory asthma in the Research in Severe Asthma Trial[5] (ie, no limit on previous hospitalizations or rescue medication use) provides assurance that patients with more severe disease might also benefit from BT.

These data demonstrate that BT is an effective and safe therapy. The improvements in asthma control in the posttreatment period at 1 year based on reduction in severe exacerbations and ED visits compared with the sham control group[7] are maintained for at least 5 years in the BT group of patients with severe persistent asthma. A single BT treatment comprising 3 procedures provides long-term benefit to at least 5 years. Whether BT is a disease-modifying therapy will depend on the results of future appropriately designed clinical studies. BT has become an important addition to our treatment armamentarium for patients with severe persistent asthma who remain symptomatic despite taking ICSs and LABAs.

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Data and Safety Monitoring Board: William Busse, MD; Robert Schellenberg, MD; Scott Berry, PhD; and Arthur S. Slutsky, MD (Chair).

Clinical implications: With 5 years of data demonstrating safety and durability of effect, BT should be considered for patients with severe persistent asthma who remain symptomatic despite taking ICSs and LABAs.

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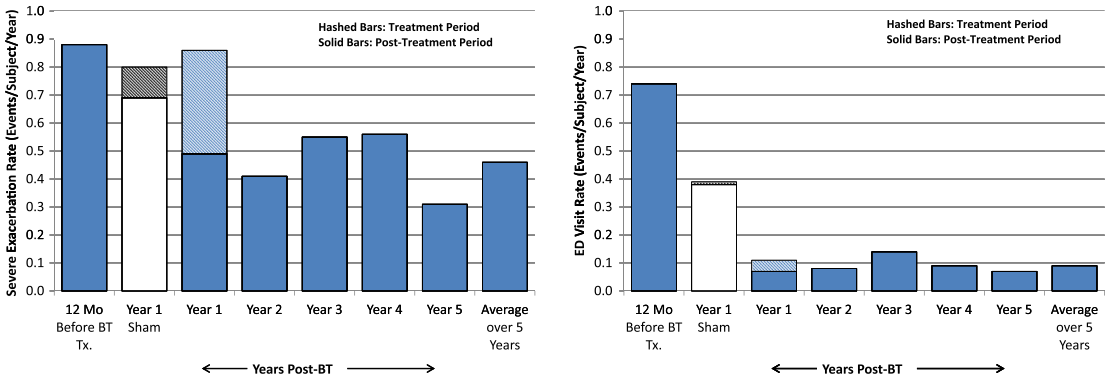

FIG E1. Annualized severe exacerbation rates *(left panel)* and ED visit rates *(right panel)* in the AIR2 trial over the 5-year evaluation period. The data for year 1 in these figures for both the sham *(white bars)* and BT *(blue bars)* groups are standardized to 52 weeks. The *solid bars* in both graphs represent the posttreatment period, and the *hashed bars* represent the treatment period.

TABLE E1. Respiratory AEs, asthma (multiple symptoms) AEs, and hospitalizations in the 5 years after BT

	Proportion of subjects undergoing BT experiencing ≥1 events (%)			Event rates (events/subject/year)		
	Respiratory AEs*	Asthma (multiple symptoms) AEs†	Hospitalizations for respiratory symptoms	Respiratory AEs*	Asthma (multiple symptoms) AEs†	Hospitalizations for respiratory symptoms
12 mo Before BT (n = 190)	NA‡	NA‡	4.2 (1.4-7.1)	NA‡	NA‡	0.053 (0.04-0.08)
Year 1 (n = 181)	72.9 (66.5-79.4)	28.7 (22.1-35.3)	3.3 (0.7-5.9)	2.02 (1.764-2.318)	0.481 (0.379-0.609)	0.04 (0.025-0.060)
Year 2 (n = 165)	58.8 (51.3-66.3)	27.9 (21.0-34.7)	4.2 (1.2-7.3)	1.22 (1.013-1.465)	0.461 (0.357-0.594)	0.061 (0.042-0.087)
Year 3 (n = 162)	58.0 (50.4-65.6)	29.6 (22.6-36.7)	6.2 (2.5-9.9)	1.25 (1.037-1.499)	0.506 (0.396-0.646)	0.068 (0.048-0.096)
Year 4 (n = 159)	54.7 (47.0-62.5)	31.4 (24.2-38.7)	5.7 (2.1-9.3)	1.18 (0.971-1.424)	0.503 (0.393-0.644)	0.076 (0.054-0.105)
Year 5 (n = 162)	47.5 (39.8-55.2)	24.7 (18.1-31.3)	1.9 (0.0-3.9)	0.78 (0.616-0.982)	0.321 (0.236-0.436)	0.025 (0.014-0.044)
Average over 5 y	58.7 (53.4-63.8)	28.4 (23.7-33.6)	3.9 (2.3-6.6)	1.30 (1.149-1.481)	0.45 (0.374-0.554)	0.053 (0.038-0.073)

Values are point estimates (95% CIs). Year 1 is 365 days after the treatment period (365 days after 6 weeks after the last bronchoscopy). There were a total of 44 respiratory hospitalizations over 5 years in 23 subjects (7 hospitalizations in 6 subjects in year 1, 10 hospitalizations in 7 subjects in year 2, 11 hospitalizations in 10 subjects in year 3, 12 hospitalizations in 9 subjects in year 4, and 4 hospitalizations in 3 subjects in year 5). Three subjects accounted for 20 (45.5%) of the 44 total hospitalizations spread out over 5 years.

*Respiratory AEs are any events related to the respiratory system.

†Asthma (multiple symptoms) AEs represent 2 or more asthma symptoms, such as wheeze, cough, dyspnea, or mucus production, occurring at the same time.

‡AEs were not collected for the 12-month period before BT.

TABLE E2. Event rates: Responders versus nonresponders (events/subject/year)

	Event rates (events/subject/year)					
	Year 1	Year 2	Year 3	Year 4	Year 5	Mean, year 2 to year 5
Severe exacerbations						
Responders	0.425	0.288	0.458	0.504	0.313	0.389
Nonresponders	0.743	0.879	0.936	0.800	0.290	0.720
Respiratory AEs*						
Responders	1.849	1.061	1.176	1.001	0.718	1.012
Nonresponders	2.743	1.849	1.548	1.500	1.032	1.487
Asthma (multiple symptoms) AEs†						
Responders	0.397	0.364	0.420	0.434	0.282	0.376
Nonresponders	0.829	0.849	0.871	0.800	0.484	0.745
ED visits for respiratory symptoms						
Responders	0.062	0.038	0.107	0.070	0.061	0.068
Nonresponders	0.114	0.273	0.258	0.200	0.097	0.214
Hospitalizations for respiratory symptoms						
Responders	0.021	0.046	0.061	0.085	0.015	0.051
Nonresponders	0.114	0.121	0.097	0.033	0.065	0.079

Responders are defined as subjects with AQLQ score changes from baseline to year 1 of 0.5 or greater (year 1, n = 146; year 2, n = 132; year 3, n = 131; year 4, n = 129; year 5, n = 131).

Nonresponders are defined as subjects with AQLQ score changes from baseline to year 1 of less than 0.5 (year 1, n = 35; year 2, n = 33; year 3, n = 31; year 4, n = 30; year 5, n = 31).

*Respiratory AEs are any events related to the respiratory system.

†Asthma (multiple symptoms) AEs represent 2 or more asthma symptoms, such as wheeze, cough, dyspnea, or mucus production, occurring at the same time.