Asthma Intervention Research 2 (AIR2) 5-Year Extension Study

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Wechsler ME, Laviolette M, Rubin AS, Fiterman J, Lapa e Silva JR, Shah PL, Fiss E, Olivenstein R, Thomson NC, Niven RM, Pavord ID, Simoff M, Hales JB, McEvoy C, Slebos D, Holmes M, Phillips MJ, Erzurum SC, Hanania NA, Sumino K, Kraft M, Cox G, Sterman DH, Hogarth K, Kline JN, Mansur AH, Louie BE, Leeds WM, Barbers RG, Austin JHM, Shargill NS, Quiring J, Armstrong B, Castro M, for the AIR2 Trial Study Group

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

Journal of Allergy and Clinical Immunology. 2013;132:1295-1302.

Objective

Bronchial Thermoplasty (BT) with the Alair™ System has previously been shown to improve asthma control out to 1 year in patients with severe persistent asthma. The Asthma Intervention Research 2 (AIR2) 5-Year Extension Study was designed to assess the durability of effectiveness and safety of BT out to 5 years.

The 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 room (ER) visits caused by 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).

- 79% of patients in the BT group and 64% of patients in the Sham group achieved a clinically meaningful improvement in their asthma quality of life (Asthma Quality of Life Questionnaire [AQLQ] score change from baseline of ≥0.5)—BT group superior to Sham.

This study demonstrates the long-term safety and effectiveness of BT out to 5 years after treatment in 162 of 190 BT-treated patients from the AIR2 Trial.

Methods

BT-treated patients 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. On completion of the year 1 evaluation in the AIR2 Trial, patients 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, hospitalizations for respiratory symptoms, ER visits for respiratory symptoms, and new or increased dosages of oral corticosteroids (OCS) 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 spirometry (pre- and post-bronchodilator) were performed. Severe exacerbations, ER visits, and hospitalizations for the year before BT were patient reported. One hundred patients in the BT group who had a high-resolution computed tomographic (HRCT) scan at baseline and Year 1 underwent a repeat HRCT scan at Year 3 and at Year 5.

Primary Endpoint

The primary endpoint was the percentage of patients experiencing severe exacerbations during subsequent 12-month periods out to 5 years compared with the percentage of patients who experience severe exacerbations during the first year after BT treatment. A non-inferiority margin of 20% was used to demonstrate that the percentages were not substantially worse during each of the subsequent evaluation periods (ie, the upper 95% confidence limit for the difference in percentages is less than 20%). The number of patients who completed follow-up visits for each year was used as the denominator to calculate the percentages of patients with severe exacerbations during each year. No patients withdrew from the study due to worsening of asthma.

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Bronchial Thermoplasty™

Key Effectiveness Results

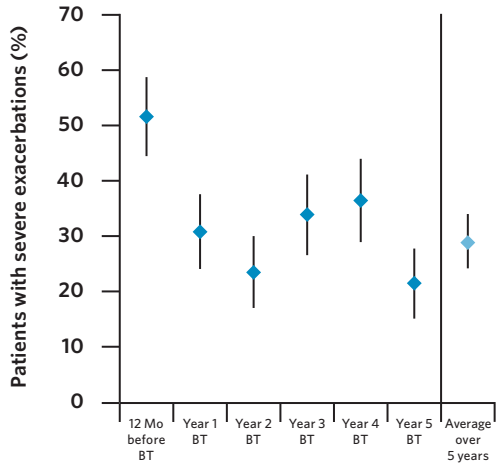
Severe Exacerbations*

The reduction in the percentage of BT-treated patients experiencing severe exacerbations (compared to sham-treated patients) seen at 1 year was maintained out to 5 years.

- There was a 44% average decrease over 5 years in the percentage of BT-treated patients having severe exacerbations compared with the 12 months prior to BT treatment. See **Figure 1**.
- There was a 48% average decrease over 5 years in severe exacerbation event rates (events per patient per year) in BT-treated patients compared with the 12 months prior to BT treatment. See **Figure 2**.

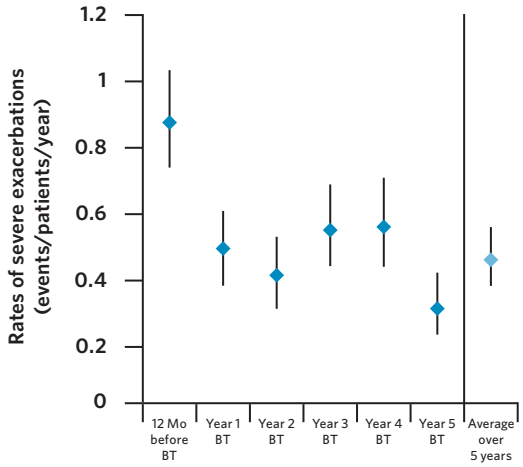
*The definition of severe exacerbations was derived from the definition originally used in the AIR2 Trial and consisted of treatment with OCSs or intravenous corticosteroids, a doubling of the baseline inhaled corticosteroid (ICS) dose for at least 3 days, or any temporary increase in the dosage of OCSs for patients taking maintenance OCSs at entry into the AIR2 Trial.

Figure 1: Percentage of patients with severe exacerbations



Values are point estimates with the upper and lower 95% confidence intervals. The upper 95% confidence limit for the difference in percentages for years 2, 3, 4, and 5 compared to year 1 (subsequent year – year 1) was 0.5, 11.3, 14.0, and -1.6, respectively. All were less than the pre-defined non-inferiority margin of 20%.

Figure 2: Severe exacerbation event rates



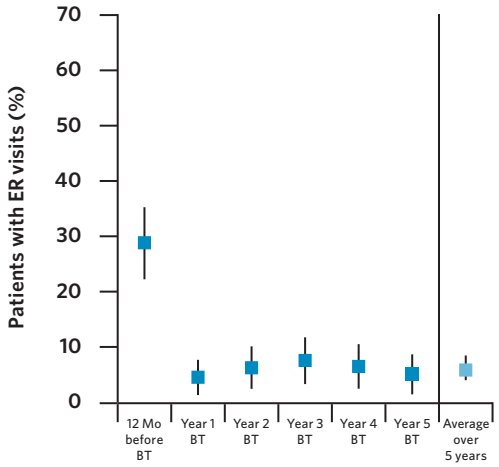
Values are point estimates with the upper and lower 95% confidence intervals.

ER Visits for Respiratory Symptoms

The reduction in the percentage of BT-treated patients having emergency room visits for respiratory symptoms (compared to sham-treated patients) seen at 1 year was maintained out to 5 years.

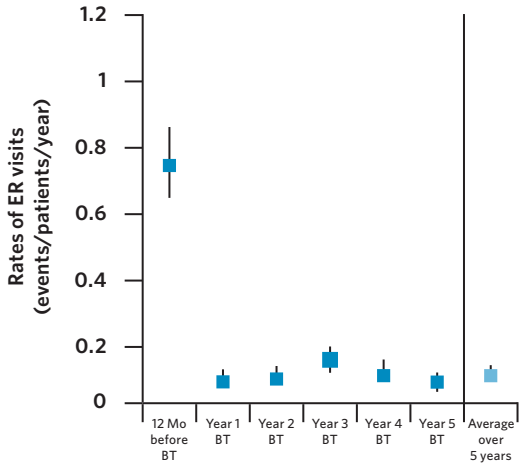
- There was a 78% average decrease over 5 years in the percentage of patients experiencing ER visits for respiratory symptoms compared with 1 year prior to BT treatment. See **Figure 3**.
- There was an 88% average decrease over 5 years in the rate of ER visits for respiratory symptoms (events per patient per year) compared with 1 year prior to BT treatment. See **Figure 4**.

Figure 3: Percentage of patients with ER visits



Values are point estimates with the upper and lower 95% confidence intervals.

Figure 4: ER visit event rates



Values are point estimates with the upper and lower 95% confidence intervals.

Maintenance Medications

- 1 in 4 BT-treated patients (25%) saw a 50% or greater reduction in their maintenance inhaled corticosteroid (ICS) dose from baseline at 5 years compared to 5% of the BT patients who had a 50% or greater increase in their maintenance ICS dose.
- There was an overall reduction of 18% in the average ICS dose at 5 years compared to baseline.

Long-Term Safety

Pulmonary Function

- The percent predicted pre-bronchodilator FEV_1 values remained unchanged over the 5 years after BT. Post-bronchodilator FEV_1 remained higher at all times; there was an increase in percent predicted FEV_1 at baseline of 8.2% and at 5 years of 5.9%.

Adverse Events

- There was no increase in either the percentage of patients or the rate of occurrence of any respiratory adverse events out to 5 years.
- There was no increase in either the percentage of patients or the rate of occurrence of asthma (multiple symptoms) adverse events out to 5 years.
- There was no increase in the baseline rate of hospitalizations for respiratory symptoms over 5 years after BT.

High Resolution Computed Tomography (HRCT)

None of the structural changes in the airways at 5 years that were of clinical significance were due to BT.

- There was no evidence of bronchial stricture, bronchiolitis obliterans, or new pulmonary emphysema in any of the HRCT pairs evaluated at year 5.
- There was no evidence of increase in bronchiectasis over the 5 years after BT; one new case was identified, representing an incidence rate of 0.2% per annum.

Conclusions

Bronchial Thermoplasty with the Alair™ System is an effective and safe therapy. The improvements in asthma control, based on reduction in severe exacerbations and ER visits in the BT group at 1 year compared with the Sham control group, are maintained for at least 5 years in patients with severe persistent asthma.

A single BT treatment comprising 3 procedures provides long-term benefit to at least 5 years.

BT has become an important addition to our treatment armamentarium for patients with severe persistent asthma who remain symptomatic despite taking ICS and LABA.

View the 5-year clinical trial results at BTat5years.com

Brief Statement of Relevant Indications for Use, Contraindications, Warnings, and Adverse Events: The Alair™ Bronchial Thermoplasty System is indicated for the treatment of severe persistent asthma in patients 18 years and older whose asthma is not well controlled with inhaled corticosteroids and long-acting beta-agonists. The Alair System is not for use in patients with an active implantable electronic device or known sensitivity to medications used in bronchoscopy. Previously treated airways of the lung should not be retreated with the Alair System. Patients should be stable and suitable to undergo bronchoscopy. The most common adverse event of BT is an expected transient increase in the frequency and worsening of respiratory-related symptoms. Rx only.

CAUTION: Law restricts this device to sale by or on the order of a physician. Indications, contraindications, precautions, and warnings can be found with product labeling.

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