

Asthma Intervention Research 2 (AIR2) Trial

Castro M, Rubin AS, Laviolette M, Fiterman J, de Andrade Lima M, Shah PL, Fiss E, Olivenstein R, Thomson NC, Niven RM, Pavord ID, Simoff M, Duhamel DR, McEvoy C, Barbers R, ten Hacken NHT, Wechsler ME, Holmes M, Phillips MJ, Erzurum S, Lunn W, Israel E, Jarjour N, Kraft M, Shargill NS, Quiring J, Berry SM, Cox G; AIR2 Trial Study Group.

Effectiveness and safety of bronchial thermoplasty in the treatment of severe asthma: A multicenter, randomized, double-blind, sham-controlled clinical trial.

American Journal of Respiratory and Critical Care Medicine. 2010;181:116-124.

The Asthma Intervention Research Trial 2 (AIR2) Trial was a multi-center, randomized, double-blind, sham-controlled trial designed to evaluate effectiveness and safety of Bronchial Thermoplasty (BT), delivered by the Alair™ System, in a population of patients with severe asthma who were still symptomatic despite being managed on conventional therapy of inhaled corticosteroids (ICS—doses greater than 1000 µg per day beclomethasone or equivalent) and long-acting β₂-agonists (LABA—doses of at least 100 µg per day salmeterol or equivalent).

Methods

This study randomized patients on the highest level of care (eg, Advair™ 500 equivalent) to undergo three bronchoscopy procedures; each procedure separated by 3 weeks. Two-thirds of patients received BT and one-third received a sham procedure. The treatment was administered by an un-blinded Bronchoscopy team. All follow-up and assessment visits were conducted by a blinded Assessment team. Thus, neither the patient nor the Assessment team member was aware of the individual treatment assignment. Sham procedures were performed using a radio-frequency (RF) controller that provided audio and visual cues that mimicked the active controller, but did not deliver RF energy through the catheter.

The clinical trial was conducted at 30 Investigational Sites in 6 countries (United States, Canada, United Kingdom, the Netherlands, Brazil, and Australia), with a total of 297 randomized patients (196 BT group, and 101 Sham group, 288 patients formed the Intent-to-Treat group, as 9 patients withdrew from the study prior to any treatment/sham procedure).

Key Effectiveness Results

Key findings for BT-treated patients versus Sham during the Post-Treatment Period:

- 79% of patients in the BT group and 64% 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
- 32% reduction in severe exacerbations
- 84% reduction in emergency room visits for respiratory symptoms
- 66% reduction in time lost from work/school/other daily activities due to asthma

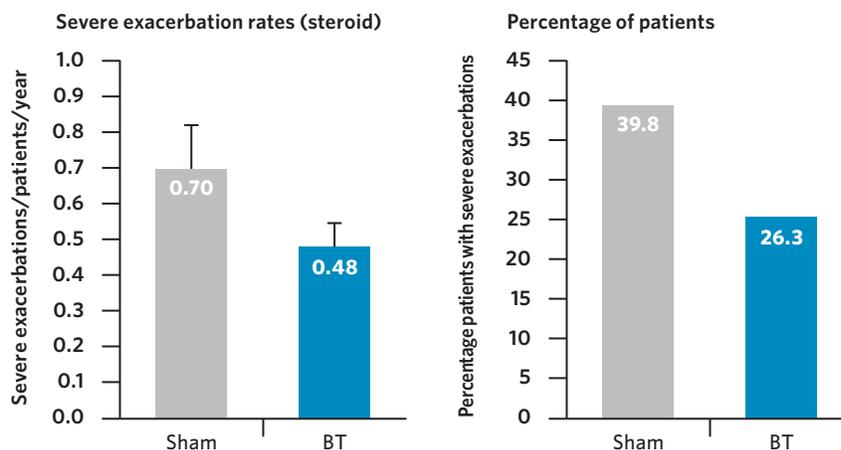
Although the clinical study was powered only for the primary effectiveness endpoint (see next page), several other effectiveness and safety endpoints that can be considered effectiveness endpoints demonstrated clinically meaningful differences with the BT group being superior to the Sham group. The effectiveness endpoints were rates of severe asthma exacerbations, percentages of patients with severe asthma exacerbations, and days lost from work, school, or other daily activities due to asthma symptoms. The safety endpoints considered for effectiveness were rates of asthma (multiple symptoms) adverse events, emergency room visits for respiratory symptoms, and hospitalization rates for respiratory symptoms.

NOW AVAILABLE from Boston Scientific
for the treatment of severe asthma in adults



There was a 32% reduction in rate of Severe Exacerbations requiring systemic corticosteroids (Steroid Exacerbations) in the BT group compared to the Sham group (0.48 versus 0.70 severe exacerbations per patient per year in the BT and Sham groups, respectively [Posterior Probability of Superiority of 95.5% (95% CI [Sham - BT]: -0.031, 0.520)]). During the post-treatment period, the percentage of patients experiencing Steroid Exacerbations was 26.3% in the BT group and 39.8% in the Sham group, Posterior Probability of Superiority of 99.0% [95% CI (Sham - BT): 2.1%, 25.1%]. See **Figure 1**.

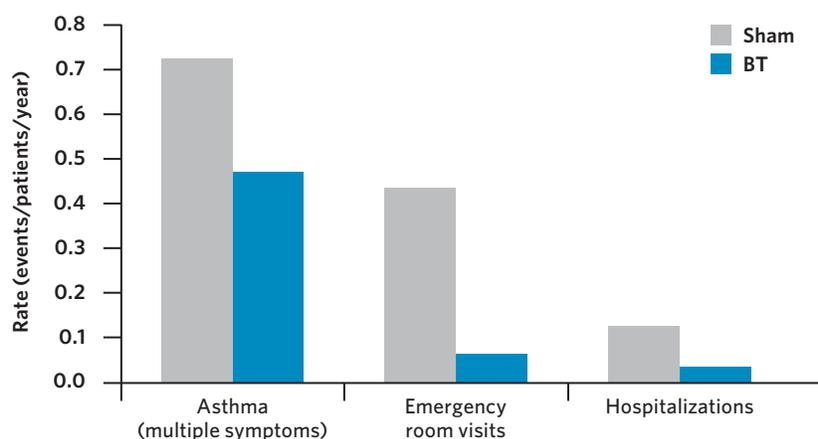
Figure 1: Severe exacerbations during the Post-Treatment Period



Measures such as Emergency Room Visits and Hospitalizations for respiratory symptoms are generally considered to be important measures of safety, especially if an intervention results in an increase in the rate of one or more of these events. However, these measures can also be considered important measures of effectiveness if an intervention results in a measurable decrease in the rate of one or more of these events. During longer-term follow-up (> 6 weeks after the last BT treatment), there was a reduction in asthma (multiple symptoms) adverse events (Posterior Probability of Superiority of 96.0%), emergency visits for respiratory symptoms (Posterior Probability of Superiority of 99.9%), and hospitalizations for respiratory symptoms. See **Figure 2**.

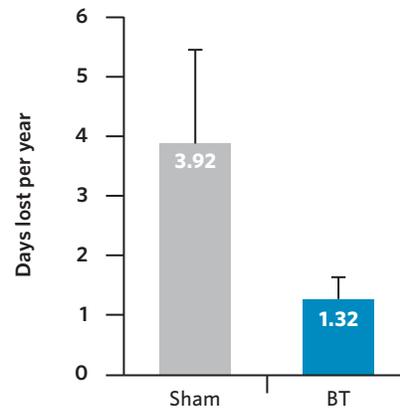
There was also a significant reduction in the percentage of patients having asthma (multiple symptoms) adverse events (Posterior Probability of Superiority of 99.6%: [95% CI (Sham - BT): 4.0%, 27.3%]), and in the percentage of patients having Emergency Room Visits for respiratory symptoms in the BT group (3.7% in the BT group compared to 15.3% in the Sham group), Posterior Probability of Superiority of >99.9% (95% CI [Sham - BT]: 4.6%, 19.7%). See **Figure 2**.

Figure 2: Safety endpoints demonstrating effectiveness (ITT population)



During the post-treatment period, patients in the BT group lost an average of 1.3 days/year/patient from work, school, or other activities due to asthma symptoms, compared to the Sham group that lost 3.9 days/year/patient (annualized rates per patient are extrapolated from the 46-week post-treatment period from 6 weeks after the last bronchoscopy procedure to the 12-month follow-up visit); Posterior Probability of Superiority 99.3% (95% CI [Sham - BT]: 0.425, 6.397). See **Figure 3**.

Figure 3: Days lost from work, school, or other daily activities due to asthma symptoms (ITT population)



Primary Effectiveness Endpoint - Integrated AQLQ Score

AQLQ score is a numeric score on a 7-point scale. A higher AQLQ score represents better Asthma Quality of Life. The average of the 6-, 9-, and 12-month AQLQ scores is referred to as the "Integrated AQLQ score." The BT group had improved Asthma Quality of Life compared to the Sham group as demonstrated by the observed difference between the BT and Sham groups in the average change in AQLQ score from Baseline at the 6-, 9-, and 12-month follow-up visits. For the ITT population, the difference between the groups had a Posterior Probability of Superiority of 96.0%, and for the PP population, the difference between the groups had a Posterior Probability of Superiority of 97.9%, demonstrating an improvement in the Asthma Quality of Life in the BT group compared to Sham.

- 79% of BT-treated patients achieved ≥ 0.5 increase, versus 64% of sham-treated patients (PPS 99.6%).

Key Safety Results

A total of 850 bronchoscopy procedures were performed in 288 patients in the AIR2 Trial. Of these 558 were BT treatment bronchoscopy procedures performed in 190 patients and 292 Sham bronchoscopy procedures performed in 98 patients. In addition to the safety endpoints described above that indicated effectiveness (severe exacerbations, ER visits for respiratory symptoms and days lost from work/school/other daily activities due to asthma symptoms), the key safety findings from the AIR2 Trial include:

- Transient Increase in Respiratory Adverse Events Peri-Procedure: During the treatment period (from first treatment through 6 weeks after the third treatment), there was a significant transient increase in respiratory adverse events, including asthma (multiple symptoms), upper respiratory tract infection, atelectasis, lower respiratory tract infection, wheezing, hemoptysis, and anxiety in the BT group compared to the Sham group. There was a significantly lower incidence of throat irritation in the BT group compared to the Sham group. 84.7% of patients in the BT group had respiratory adverse events compared to 75.5% of patients in the Sham groups.
- During the treatment period, 16 patients (8.4%) in the BT group required 19 hospitalizations for respiratory symptoms (worsening of asthma [12 hospitalizations in 10 patients]; segmental atelectasis [3 hospitalizations in 2 patients], lower respiratory tract infection [1 patient], low FEV₁ [1 patient], hemoptysis [1 patient; treated with bronchial artery embolization], and an aspirated prosthetic tooth [1 patient]) compared to 2 patients (2.0%) in the Sham group requiring two hospitalizations (both worsening of asthma). Ten of the 19 hospitalizations in the BT group occurred on the day of the procedure.

All adverse events were resolved with standard therapy.

- Median time to onset of respiratory adverse events after bronchoscopy was 1 day. Median time to resolution was 7 days.
- High Resolution CT Scans (HRCT): Blinded comparison of HRCT scans at Baseline and 12-Month Follow-up from 100 BT group and 50 Sham group patients revealed no structural changes in the lung that are of safety concern. In addition, there was:
 - No evidence of bronchial dilation, bronchiectasis, bronchiolitis obliterans, or pulmonary emphysema in any of the BT-treated patients at 1-year post-treatment
 - No single radiological change seen exclusively in the BT group
- Adverse events never observed: There were no incidences of pneumothorax, intubation, mechanical ventilation, airway stenosis or focal narrowing (observed during bronchoscopy), cardiac arrhythmias, or death as a result of BT treatment or Sham bronchoscopy.

Conclusions

Bronchial Thermoplasty, delivered by the Alair™ System, is a safe and effective procedure 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 β_2 -agonists.

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.



Alair and  are registered trademarks of Boston Scientific Corporation or its affiliates. All other trademarks are the property of their respective owners.
© 2014 Boston Scientific Corporation or its affiliates. All rights reserved. ENDO-147801-AB January 2014

