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Bronchial Thermoplasty
Reappraising the Evidence (or Lack Thereof)

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Bronchial thermoplasty (BT) involves the application of radiofrequency energy to visible proximal airways to selectively ablate airway smooth muscle. BT is the first nonpharmacologic interventional therapy approved by the US Food and Drug Administration (FDA) for severe asthma. This approval was based on the results of the pivotal Asthma Intervention Research (AIR)-2 trial, which is the only randomized, double-blind, sham-controlled trial of BT. The primary end point of the AIR-2 trial was improvement in the Asthma Quality of Life Questionnaire (AQLQ). The results of the AIR-2 trial have generated enormous interest, controversy, and confusion regarding the true efficacy of BT for severe asthma. Current marketing of BT highlights its use for patients with "severe" asthma, which is interpreted by most practicing clinicians as meaning oral corticosteroid dependence, frequent exacerbations, or a significantly reduced FEV_1 with a poor quality of life. Did the AIR-2 trial include patients with a low FEV_1, oral steroid dependence, or frequent exacerbations? Did the trial show efficacy for any of the primary or secondary end points? The FDA approved the device based on the reduction in severe asthma exacerbations. However, were the rates of asthma exacerbations, ED visits, or hospitalizations truly different between the two groups, and was this type of analysis even justified given the original study design? This commentary is designed to specifically answer these questions and help the practicing clinician navigate the thermoplasty literature with confidence and clarity. We carefully dissect the design, conduct, and results of the AIR-2 trial and raise serious questions about the efficacy of bronchial thermoplasty.

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ABBREVIATIONS: AIR = Asthma Intervention Research; AQLQ = Asthma Quality of Life Questionnaire; ASM = airway smooth muscle; FDA = US Food and Drug Administration; ICS = inhaled corticosteroid; PPS = posterior probability of success; QOL = quality of life

Bronchial thermoplasty was approved by the US Food and Drug Administration (FDA) for asthma in April 2010 for patients aged 18 years and older "whose severe and persistent asthma is not well-controlled with inhaled corticosteroids and long-acting beta agonist medications."[1] The FDA approved the device based on the reduction in severe asthma exacerbations as reported in the Asthma Intervention Research (AIR)-2 trial.[2]

Given the availability and ongoing marketing of thermoplasty to the general public and health-care professionals, it is imperative

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that we reappraise the evidence from the AIR-2 trial in an unbiased fashion. This commentary is designed to help the clinician navigate and understand the thermoplasty literature and, we hope, make an informed decision about the usefulness of this procedure for patients with severe asthma. We begin with the AIR-2 trial design, critically reappraise the trial results (from a statistical and clinical standpoint), and also discuss shortcomings of the AIR-2 postapproval follow-up studies. We discuss issues with the reporting methodology of the AIR-2 trial and the accompanying editorial controversy. Finally, the critical importance of sham control in asthma clinical trials will be discussed along with a brief review of the FDA device approval process as it pertains to thermoplasty.

A Brief Overview of Airway Smooth Muscles and Thermoplasty

Thermoplasty involves applying radiofrequency energy to selectively ablate airway smooth muscle (ASM) in visible proximal airways (typically up to the subsegmental level). Early animal studies documented selective loss of ASM without significant fibrosis, epithelial injury, or structuring.[3] The distal airways (< 2-3 mm in diameter) account for about 10% of the total airway resistance in a normal person. However, in asthma, there exists a continuum of inflammation all the way from the proximal to the most distal airways, which results in a significant increase in distal airways resistance.[4] In fact, the distal airways may be the major site for airways obstruction in asthma and with a significant impact on airway hyperresponsiveness.[5-7] Thus, it is important to note that thermoplasty only treats the ASM in the proximal airways, with no impact on either the distal airways or airway inflammation in general.

AIR-2 Trial Design

The AIR-2 trial was a high-quality multicenter (multinational) double-blind sham-controlled study that randomized patients with severe asthma on a 2:1 basis to bronchial thermoplasty vs sham thermoplasty. A total of 288 patients were analyzed, of which 190 subjects underwent bronchial thermoplasty and 98 subjects underwent sham thermoplasty (2:1 randomization). It is important to note that the sham procedure was elaborate and mimicked the actual thermoplasty procedure in every way except for the actual delivery of thermal energy to the airways. Eligible patients were aged 18 to 65 years and needed to be on stable doses of inhaled corticosteroids (≥ 1,000 μg/d of beclomethasone or equivalent and ≥ 100 μg/d of salmeterol or equivalent) for at least 4 weeks. Severe asthma in this study was defined by the use of a high dose of inhaled corticosteroids (ICSs) and a second controller for maintenance therapy. The 2014 European Respiratory Society/American Thoracic Society consensus statement defines severe asthma as a requirement for high-dose ICSs (equivalent to ≥ 1,000 μg beclomethasone) plus a second controller medication (and/or systemic corticosteroids) to "prevent asthma from becoming uncontrolled" or for asthma that remains "uncontrolled despite a lower level of therapy."[8] However, overtreatment with ICSs is common, with prospective studies reporting up to 50% of subjects being able to reduce ICS dose by one-half while maintaining good control.[9] The requirement for high-dose ICSs to maintain control is central to the definition of severe asthma in the AIR-2 trial. The lack of a run-in period or verification process puts their definition of severe asthma in question. Other studies have switched recruited subjects over to beclomethasone to standardize ICS dosage and objectively confirmed the high ICS dose requirement to maintain control.[10]

The AIR-2 trial excluded patients with a need for ≥ 10 mg of prednisone per day. As a result, only 2.7% of subjects were on daily low-dose (5-6 mg) oral corticosteroids at baseline. The study also excluded subjects with three or more hospitalizations/lower respiratory tract infections or four or more oral corticosteroids pulses within the previous year. This would exclude subjects with severe asthma characterized primarily by frequent exacerbation, a defining feature that has consistently emerged from the majority of studies of severe asthma phenotypes.[11] Thus, it is unclear as to how many patients in the AIR-2 trial would qualify for the American Thoracic Society definition of refractory asthma.[12] This point was also made in the accompanying editorial to the AIR-2 trial.[13] Blinding in the trial was also of concern, with more patients in the thermoplasty arm being able to correctly guess their treatment after the first bronchoscopy procedure.[2]

AIR-2 Trial Results: Primary and Secondary End Points

The primary end point of the AIR-2 trial was the change in the Asthma Quality of Life Questionnaire (AQLQ) from baseline to 12 months. The AQLQ has 32 items in four domains: activities (12 items), asthma symptoms (11 items), emotional function (five items), and environmental exposure (four items). The minimal