

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 FEV₁ with a poor quality of life. Did the AIR-2 trial include patients with a low FEV₁, 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 ($\geq 1,000$ $\mu\text{g}/\text{d}$ of beclomethasone or

equivalent and ≥ 100 $\mu\text{g}/\text{d}$ 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 $\geq 1,000$ 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 corticosteroid 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

clinically important difference for the AQLQ is determined to be 0.5 (range, 0.42-0.58), with higher scores (a greater positive change) indicating improved asthma-related quality of life (QOL). For example, an AQLQ increase of 1 (range, 0.77-1.51) indicates moderate improvement, whereas an improvement ≥ 1.5 indicates a large improvement in asthma-related QOL.¹⁴

In the AIR-2 trial, the AQLQ improved by 1.16 ± 1.23 in the sham group and by 1.35 ± 1.10 in the thermoplasty group, with a difference in AQLQ between the two groups of only 0.19 (Fig 1).¹⁴ Thus, there was a large placebo effect in the sham procedure arm, with the AQLQ improving by 1.16 points, or “moderate improvement.” It is, therefore, not surprising that of the four domains composing the AQLQ, only the emotional domain showed an improvement in the thermoplasty group. Thus, it would seem that the sham thermoplasty procedure was just as effective as the actual thermoplasty in improving asthma-related QOL.

Regarding the secondary end points of the study (ΔFEV_1 , Δ peak expiratory flow, decrease in symptom-free days, reduction in severe exacerbations, rescue medication use, days lost from work, and so forth), there was no real difference between the two groups.²

AIR-2 Trial Results: Unplanned Analysis of Health-care Use

The AIR-2 trial also reported on some other end points that had not been prospectively included in their planned analysis. These included unscheduled physician office visits, ED visits, and hospitalizations (Table 1). A quick look at Table 1 would make one realize that these three outcomes are interlinked. For example, a patient

who was hospitalized was also likely to have visited the ED and also to be simultaneously classified as having had a severe asthma episode. This is a very important point, because there appears to be an outlier in the sham group (with nine hospitalizations) who likely had multiple ED visits and multiple severe asthma episodes. It is not inconceivable that this patient with nine hospitalizations also had a large number of ED visits and severe asthma exacerbations (thus influencing all three end points simultaneously). Thus, one or two outliers in the control group could have driven the entire statistical difference between the groups for these unplanned analyses.

Clinical vs Statistical Significance

How are we to interpret the AIR-2 results? As noted above, if one were to use routine frequentist statistical methods (eg, a *t* test), the AQLQ difference of 0.19 between the two groups would not reach statistical significance ($P = .2$).¹⁵ In fact, even in the AIR-2 trial, this primary end point did not reach statistical significance. The AIR-2 trial used Bayesian statistics to analyze the primary and secondary end points. The concept of posterior probability of success (PPS) was used in their analysis. In the “statistical analysis” section of that paper, the authors declare that for the AQLQ, a PPS of $\geq 96.4\%$ would be used to declare success. However, the PPS value obtained for the AQLQ was only 96%. Thus, it is unclear whether statistical significance was ever achieved, even for the primary end point using Bayesian statistics.²

The second important question is regarding clinical vs statistical significance. As mentioned earlier, an AQLQ improvement of 0.5 is considered to be the minimal clinically important difference for the AQLQ instrument.¹⁴ Thus, the AQLQ difference of 0.19 (one-third of 0.5) in the AIR-2 trial would not reflect any meaningful improvement in asthma QOL for patients or clinicians.

The use of other (non-prespecified) end points, such as asthma exacerbations, hospitalizations, and ED visits, is also very problematic because of the presence of outliers (as discussed previously). Thus, it is quite unclear from the AIR-2 data whether there thermoplasty is any better than a sham procedure in improving asthma outcomes.

Editorial Controversy

The original AIR-2 trial had an accompanying editorial that did point out flaws in the trial design (lack of run-in period) and results (statistical but lack of clinical significance regarding the AQLQ difference between groups).¹³ Very surprisingly, exactly 1 year after the original editorial, the same authors wrote an unsolicited

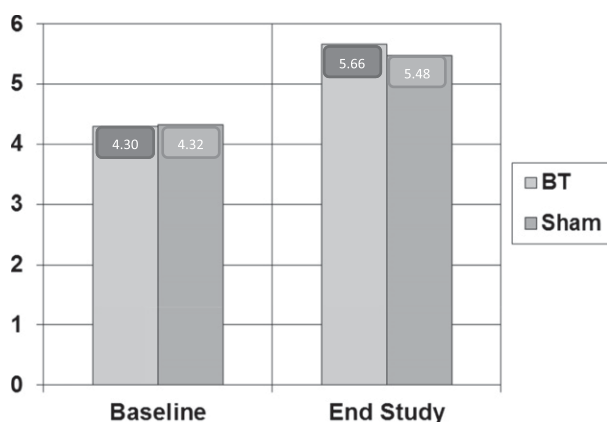


Figure 1 – Asthma Quality of Life Questionnaire values at baseline at end of follow-up (12 mo). BT = bronchial thermoplasty.

TABLE 1] Health-care Use (Posttreatment Period)

Health-care Use	BT	Sham
Hospitalizations	5 patients (6 admits); 1 patient had 2 admits	4 patients (12 admits), including 1 patient with 9 admits
ED, visits/subject/y	0.07 (13 visits)	0.43 (42 visits)
Severe asthma episodes, %	27	43

BT = bronchial thermoplasty.

letter to the editor sharply criticizing the AIR-2 trial design and reporting methodology.¹⁵ They rightfully pointed out that the outcomes based on which the FDA approved thermoplasty (hospitalizations, ED visits, severe exacerbations, and time lost from work) were never part of original planned statistical analysis.¹⁵ These outcomes were also not part of the prespecified primary or secondary end points. In fact, frequent exacerbations and hospitalizations (three or more per year) were an explicit exclusion criterion in the AIR-2 trial. They again noted that the AQLQ difference between the two groups (0.19) was significantly lower than the minimal clinically important difference of 0.5 and would not have been statistically significant ($P = .2$) with the use of a routine t test. Potential outcome reporting bias and inappropriate statistical use of multiple tests without adjustments are also serious flaws.¹⁵ Similar criticisms have been made elsewhere.^{15,16}

Problems With the AIR-2 Postapproval Follow-up Studies

A number of post-approval safety and efficacy studies have been published, and we now have 5-year postthermoplasty safety and efficacy data.^{17,18} The biggest criticism regarding these studies is the absence of any information regarding outcomes in the sham group. One must again recall the large improvement in AQLQ of 1.16 in the sham group. This beneficial effect was likely a result of the more diligent and protocol-driven asthma care they received as part of the AIR-2 trial. These benefits would likely have been sustained over time had follow-up been continued. Thus, to ignore the sham group and to report only on the patients who underwent thermoplasty does not really inform us regarding the true benefit of thermoplasty (if any). An analogy to this situation would be a sham-controlled trial of a new radiofrequency ablation device to convert atrial fibrillation into sinus rhythm. If the authors were to report only on outcomes in patients undergoing the radiofrequency procedure and not on patients undergoing the sham procedure, how would one know whether the real ablation was any better than the sham

procedure in maintaining sinus rhythm? Given the strong placebo effects at play in asthma symptom perception, reporting a benefit in only the thermoplasty group is really without meaning without comparison with outcomes in the sham group. In addition, a recent case report noted the lack of any ASM reduction in the airways of a patient who failed to improve after thermoplasty.¹⁹ Thus, ASM reduction/elimination in airways treated with thermoplasty cannot be taken for granted.

Critical Importance of Having a Sham-Controlled Arm in Asthma Trials

Asthma is a poorly defined entity with vast intersubject variability in disease perception, disease severity, and quality of life. The power of the placebo has been long recognized (and skillfully exploited) in medicine.²⁰ Several sham-controlled trials of arthroscopy, vertebroplasty, and so forth have all upended decades of conventional wisdom regarding the usefulness of those procedures.^{21,22} The placebo effect is particularly well recognized in asthma, and this aspect was elegantly highlighted in a trial.²³ In that trial, subjects experienced similar symptomatic benefits (symptoms being subjective measures of disease) whether they used an albuterol or a placebo inhaler. This was despite a marked improvement in the FEV₁ (an objective measure) in the albuterol group vs no change in FEV₁ in the placebo (dummy) inhaler group. This (and other trials) have emphasized that subjective and objective improvements in asthma do not always correlate and that just the act of using an inhaler (even a placebo one) is quite efficacious in improving subjective perception of asthma control. This concept is extremely important when one assesses the body of evidence regarding thermoplasty. To our knowledge, the AIR-2 trial is the only sham-controlled thermoplasty trial ever performed. The AIR-2 trial was preceded by the AIR trial²⁴ and the RISA (Research in Severe Asthma) trial,²⁵ both of which had no sham-control arms. Thus, the results of these two previous trials need to be interpreted with a great deal of caution, given the strong potential for a placebo effect. One must not conflate the AIR-2 trial data with any

previous thermoplasty data because of lack of sham-control groups in those trials.

FDA Device Approval Process

Bronchial thermoplasty was approved by the FDA in 2010 based on a single pivotal trial. This process is based on the 1997 FDA modernization act (aka FDAMA), which allowed for “one or more clinical investigations” to be the new standard for device approval, replacing the previous standard, which required that clinical investigations be required prior to a new device approval. This innocuous-sounding change in the approval process allowed for medical device approval based on just one positive pivotal trial. The previous rules had implied a minimum of more than one positive trial as being necessary for device approval. The approval of bronchial thermoplasty for human use based on a single pivotal study with negative results on both the primary and secondary end points is very surprising and raises skepticism about the approval process and patient protection. Although the 5-year post-approval data do not show any major adverse effects from thermoplasty, the long-term adverse effects of thermoplasty (if any) are truly unknown at this time. The typical patient with asthma treated with thermoplasty is likely to be alive for several decades after the procedure, and just 5 years of safety data are likely not sufficient.

Conclusions

Current marketing of thermoplasty highlights its use for patients with severe asthma, which is interpreted by most clinicians as meaning oral corticosteroid dependence, frequent exacerbations, or a significantly reduced FEV₁ with a poor QOL. These types of patients were specifically excluded from the AIR-2 trial. We all care for patients with severe asthma for whom existing treatment options appear ineffective. We owe it to these patients to accept only the highest standards for efficacy, safety, and transparency from any clinical trial before making changes to our clinical practice.

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