



How effective is bronchial thermoplasty for severe asthma in clinical practice?

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Bronchial thermoplasty can be effective in patients who often have features of more severe asthma than in AIR2 <http://ow.ly/Qv5730cTIuB>

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Bronchial thermoplasty is an intervention developed for the treatment of asthma through the delivery of radio frequency energy to the airways [1, 2]. Evidence for the efficacy and safety of bronchial thermoplasty in severe asthma is based on the results of three randomised controlled trials [3–5]. Two trials compared bronchial thermoplasty with usual care, the Asthma Intervention Research (AIR) trial [3] and the Research in Severe Asthma (RISA) trial [4], whereas the third trial (AIR2) compared bronchial thermoplasty with a sham procedure [5]. The AIR2 trial reported improved asthma quality of life questionnaire (AQLQ) scores, reduced severe exacerbations and decreased emergency department visits in the post-bronchial thermoplasty treatment period [5]. Bronchial thermoplasty was associated with a short-term increase in asthma-related symptoms and hospital admissions for asthma during the treatment phase [3–5]. Follow-up observational studies to date support the long-term safety of the procedure, based on unchanged rates of respiratory adverse events, lung function, serial computed tomography scans and rates of hospital admissions or emergency department visits in years 2–5 following the AIR [6], RISA [7] and AIR2 trials [8]. A Cochrane systematic review of the trials concluded that there was a modest clinical benefit in asthma quality of life and a reduction in exacerbation rates 12 months after bronchial thermoplasty [9]. In 2010, the Food and Drug Administration (FDA) gave premarket approval for the Alair bronchial thermoplasty system (Boston Scientific, Marlborough, MA, USA) as a treatment for severe persistent asthma in patients 18 years and older whose asthma is not well controlled with inhaled corticosteroids and a long-acting β -agonist [10]. Bronchial thermoplasty is also approved for the treatment of asthma in the European Union and in many countries worldwide.

The introduction of bronchial thermoplasty to clinical practice may involve the treatment of patients with severe asthma who do not satisfy the inclusion and exclusion criteria used in the pivotal AIR2 trial (table 1) [5]. Published information on the effectiveness of bronchial thermoplasty in clinical practice is limited to a few small case series from Australia, Canada, France, the UK and the USA (table 2) [12–18], and from a UK national registry [19]. In this issue of the *European Respiratory Journal*, CHUPP *et al.* [11], describe the interim 3-year results of the Post-FDA Approval Clinical Trial Evaluating Bronchial Thermoplasty in Severe Persistent Asthma (PAS2) study, which is a prospective, open-label, multicentre, observational post-market study mandated by the FDA to evaluate the durability of the treatment effect, and the short and long-term efficacy and safety of the procedure. 284 participants were enrolled from 2011 at 27 centres in the USA (n=23) and Canada (n=4), of whom 279 subjects received at least one bronchial thermoplasty treatment. The last subject is expected to complete 5 years of follow-up in January 2020. A major strength

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TABLE 1 Key exclusion criteria used in AIR2 trial of bronchial thermoplasty in asthma [5]

Aged >65 years
 Chronic sinus disease
 Prebronchodilator FEV₁ <60% predicted
 Four or more oral corticosteroid courses for asthma exacerbation within the past 12 months
 Three or more hospitalisations for asthma within the past 12 months
 Former smoker, if >10 pack-years total smoking history
 A history of intubation for asthma or ICU admission for asthma within the prior 24 months
 Taking maintenance oral corticosteroids >10 mg daily

Similar key exclusion criteria were used in the PAS2 study [11], except for chronic sinus disease. FEV₁: forced expiratory volume in 1 s; ICU: intensive care unit.

of the PAS2 study is that it provides observational data on baseline characteristics and clinical effectiveness of bronchial thermoplasty from a relatively large group of patients with severe asthma enrolled in clinical practice, and allows this data to be compared with the AIR2 results and with the findings from previous small observational studies (table 2).

An important finding of the study was that baseline demographic and clinical features of the PAS2 study participants suggest that they had more severe disease than those recruited to the AIR2 trial. For example, participants in the PAS2 study, compared with those recruited to the AIR2 clinical trial, were slightly older (age 45.9 *versus* 40.7 years), had a higher body mass index, had a higher proportion taking maintenance oral corticosteroids (18.9% *versus* 4.2%), had more subjects who experienced severe exacerbations (74%

TABLE 2 Previous observational studies on baseline characteristics and efficacy outcomes in real-life patients with severe asthma treated with bronchial thermoplasty

	UK [12]	Canada [13, 14]	France [15]	Australia [16]
Patients	10	16	15	20
Maintenance oral corticosteroids	40%	30%	66%	50%
FEV₁ % predicted	72 (45–96)	67 (42–103)	71±17	63 (33–95)
Time post-bronchial thermoplasty treatment when clinical outcomes assessed months	12	12 [13] (n=9, ≥27) [14]	12	6
Asthma control score[#] (patients with ≥MCID change)	Improved (40%)	Improved	Improved	Improved (85%)
Asthma quality of life score (patients with ≥MCID change)	Improved (50%)		Improved	
Severe exacerbations (patients with ≥MCID change)	Decreased (30%)	Decreased	Decreased	Decreased
ED visits/hospital admissions			Decreased	
Daily oral corticosteroid dose	Decreased (n=1)	Decreased (n=4)	Decreased	Decreased
FEV₁	No change	No change	No change	No change overall (increase if FEV ₁ <60%)
Assessment of overall beneficial response to bronchial thermoplasty	50%		73%	65–85%

Data are presented as median (range) or mean±SD, unless otherwise stated. FEV₁: forced expiratory volume in 1 s; MCID: minimal clinically important difference; ED: emergency department. #: assessed using different asthma symptom questionnaires (Asthma Control Questionnaire [12, 16], Asthma Control Test [15] and Asthma Control Scoring System [13, 14]).

versus 52%) and hospitalisations (15.3% *versus* 4.2%) in the 12 months prior to bronchial thermoplasty, had more subjects with chronic sinus disease (30.4% *versus* 18.4%) and had a larger number assessed as having severe asthma (94.7% *versus* 82.1%). Previous observation studies have also noted that patients treated with bronchial thermoplasty in clinical practice have more severe disease than those recruited to AIR and AIR2 trials [12–18] (table 2). The British Thoracic Society (BTS) Difficult Asthma Registry and Hospital Episodes Statistics database of 59 patients with severe refractory asthma undergoing bronchial thermoplasty in clinical practice between 2011 and 2015 reported that bronchial thermoplasty patients were, on average, older, and had worse baseline forced expiratory volume in 1 s (FEV₁) and lower AQLQ scores compared with published clinical trials [19].

Of interest, improvements in efficacy outcomes in the PAS2 populations and AIR2 participants were reported to be similar. 3 years after treatment with bronchial thermoplasty, the proportion of people with severe exacerbations, emergency department visits and hospitalisations was reduced by 45%, 55% and 40%, respectively, when compared to the 12 months prior to treatment, which were comparable to reductions of 37%, 72% and 25%, respectively, reported in AIR2. Nevertheless, during the third year of follow-up after the last bronchial thermoplasty procedure, 40% of PAS2 subjects experienced at least one severe exacerbation, demonstrating the difficulty in achieving complete asthma control in this patient group. Pre- and post-bronchodilator spirometry was unchanged over the 3 years of follow-up after bronchial thermoplasty in PAS2, a finding in keeping with clinical trial data and with previous observations studies. There was some evidence of a reduction in the proportion of patients taking maintenance oral corticosteroids in the PAS2 group at 3 years (19% *versus* 10%), although it is difficult to assess the clinical significance of this change in treatment in the absence of a control group. Previous published information from observational studies on the effectiveness of bronchial thermoplasty for severe asthma in real-life patients have reported improvement in AQLQ scores, reductions in exacerbations and/or a step-down in treatment in 50–75% of patients undergoing the procedure [12, 13, 15, 16] (table 2).

Respiratory-related serious adverse effects during the treatment phase with bronchial thermoplasty (first bronchial thermoplasty treatment to 6 weeks after last procedure) were greater in the PAS2 study compared to the AIR2 for severe exacerbations (55.8% *versus* 40.5%) and emergency department visits (15.8% *versus* 5.3%). Emergency respiratory hospital readmission rates (within 30 days) of bronchial thermoplasty were similar in the PAS2 study (13.2%) and AIR2 (8.4%) [5], and to those reported from the UK BTS Difficult Asthma Registry (11.8%) [19].

Although important, the study by CHUPP *et al.* [11] has some limitations. The criteria used to define a severe exacerbation in PAS2 and AIR2 were not identical. Although both studies included worsening asthma symptoms requiring use of systemic corticosteroids or an increased in the daily dose of systemic corticosteroids in subjects already taking oral corticosteroid as criteria, the AIR2 trial also included a doubling of inhaled corticosteroid dose [5]. The authors report that a *post hoc* evaluation of the different criteria of severe exacerbation used in PAS2 and AIR2 resulted in a difference of only one severe exacerbation. The PAS2 study did not collect post-bronchial thermoplasty treatment AQLQ score data, which is unfortunate, as this measure was the primary outcome of the AIR2 trial. PAS2 did not include computed tomography imaging that would have provided additional data on potential changes to airway structure after bronchial thermoplasty. The results of PAS2 and the post-1 year follow-up of AIR2 did not include a control group that was not treated with bronchial thermoplasty, and it is unclear whether clinical outcomes differ from usual care. The study population in PAS2 were enrolled from North America centres whereas AIR2 also included participants from other part of the world, which might influence the findings. Importantly, the results are an interim analysis of a subgroup of PAS2 participants who had completed 3 years of follow-up and need to be confirmed when the total cohort reaches 5 years post-bronchial thermoplasty. Additionally, it is not clear whether an interim analysis was pre-specified. Although the PAS2 study population is described as “real world”, the most severe patients seen in clinical practice were excluded, such as subjects with a baseline FEV₁ <60% predicted, more than three hospitalisations, four or more courses of systemic corticosteroids in the last 12 months and oral corticosteroid maintenance dose >10 mg daily (table 1).

What are the clinical implications of the PAS2 study by CHUPP *et al.* [11] and other observational studies for the use of bronchial thermoplasty in the management of patients with severe asthma in clinical practice [20, 21]? Real-life patients treated with bronchial thermoplasty are more likely to have features of more severe disease than those treated in the AIR2 trial. Despite the limitations of observational study designs, the interim analysis of PAS2 suggests that reductions in exacerbations rates and emergency department visits at 3 years post-bronchial thermoplasty in patients with severe asthma are comparable to those reported in the AIR2 trial, although adverse respiratory clinical outcomes occur more frequently during the treatment period. The PAS2 study also provides reassurance on the long-term safety of bronchial thermoplasty in clinical practice, although the interim results await confirmation when the total

PAS2 cohort reaches 5 years of follow-up in 2020. Uncertainty remains about the use of bronchial thermoplasty in the management of severe asthma, including how to identify patients who will respond to this intervention, particularly alongside new biological therapies. Future analysis of the total PAS2 population of severe asthma may identify potential clinical predictors of response. Separate studies are underway that may help inform decisions about the place of bronchial thermoplasty in severe asthma, including whether bronchial airway smooth muscle mass or other biomarkers can identify responders (www.ClinicalTrials.gov identifiers NCT01777360, NCT01185275 and NCT02975284). The increasing use of biologics to treat patients with severe asthma associated with type-2 inflammation may position bronchial thermoplasty mainly for patients with type-2-low severe asthma.

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