Editorial: European Respiratory Journal

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

[1] Neil C Thomson

[2] Pascal Chanez

[1] Institute of Infection, Immunity & Inflammation, University of Glasgow, Glasgow, United Kingdom

[2] Inserm U1067 and CNRS UMR7733, Department of Respiratory Diseases, APHM Aix-Marseille University, Marseille, France.

Corresponding author:

Professor Neil C Thomson, Institute of Infection, Immunity & Inflammation, University of Glasgow, Glasgow, G12 OYN, United Kingdom E- mail: neil.thomson@glasgow.ac.uk

Word count: 1587 words

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 randomized 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 to one year [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 two to five following the AIR trial [6], RISA trial [7] and AIR2 trial [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 & Drug Administration (FDA) gave premarket approval (PMA) for the Alair® bronchial thermoplasty system as a treatment of severe persistent asthma in patients 18 years and older whose asthma is not well controlled with inhaled corticosteroids and a long-acting beta-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 [5] (Table 1). Published information on the effectiveness of bronchial thermoplasty in clinical practice is limited to a few small case series from Australia, Canada, France, UK and the US [11-17] (Table 2) and from a UK national registry [18]. In this issue of the *European Respiratory Journal*, Chupp *et al* [19], 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, multi-center 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 United States (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 of the PAS2 study is that it provides observation 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 suggests 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 years vs 40.7 years), had a higher body mass

index, had a higher proportion taking maintenance oral corticosteroids (18.9% vs 4.2%), had more subjects who experienced severe exacerbations (74% vs 52%) and hospitalizations (15.3% vs 4.2%) in the 12 months prior to bronchial thermoplasty, had more subjects with chronic sinus disease (30.4% vs 18.4%) and had a larger number assessed to have severe asthma (94.7% vs 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 [11-17] (Table 2). The British Thoracic Society (BTS) Difficult Asthma Registry and Hospital Episodes Statistics database of 59 patient with severe refractory asthma undergoing bronchial thermoplasty in clinical practice between 2011 and 2015 reported that bronchial thermoplasty patients were, on average, older, had worse baseline FEV_1 and lower AQLQ scores compared with published clinical trials [18].

Of interest, improvements in efficacy outcomes in the PAS2 populations and AIR2 participants were reported to be similar. Three years after treatment with bronchial thermoplasty, the proportion of people with severe exacerbations emergency department visits and hospitalizations 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% to 75% of patients undergoing the procedure [12, 15-17] (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% vs. 40.5%) and emergency room visits (15.8% vs. 5.3%). Emergency respiratory hospital readmission rates (within 30 days) of bronchial thermoplasty were similar in the PAS2 study (13.2%) to AIR2 (8.4%) [5] and to those reported from the UK BTS Difficult Asthma Registry (11.8%) [18].

Although important, the study by Chupp *et al* [19] has some limitations. The criteria used to define a severe exacerbation in PAS2 and AIR2 was 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 a criterion, 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 the 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-one year follow-up of AIR2 do 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. Of importance, the results are an interim analysis of a subgroup of PAS2 participants who had completed 3 years of follow-up and require to be confirmed when the total cohort reach five 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 FEV_1 <60%, more than 3 hospitalizations, 4 or more courses of systemic corticosteroids in the last 12 months and oral corticosteroids maintenance dose >10 mg/day (Table 1).

What are the clinical implications of the PAS2 study by Chupp *et al* [19] 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-year 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 reach 5-years of follow-up in 2020. Uncertainties remains about the use of bronchial thermoplasty in the management of severe asthma including how to identify patients who will response to this intervention, particularly alongside new biologic 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 (ClinicalTrials.gov Identifiers: NCT01777360, NCT01185275, 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.

References

1. Thomson NC, Bicknell S, Chaudhuri R. Bronchial thermoplasty for severe asthma. *Curr Opin Allergy Clin Immunol* 2012: 12(3): 241-248
2. Dombret M-C, Alagha K, Philippe Boulet L, Yves Brillet P, Joos G, Laviolette M, Louis R, Rochat T, Soccal P, Aubier M, Chanez P. Bronchial thermoplasty: a new therapeutic option for the treatment of severe, uncontrolled asthma in adults. *Eur Respir Rev* 2014: 23(134): 510-518.
3. Cox G, Thomson NC, Rubin AS, Niven RM, Corris PA, Siersted HC, Olivenstein R, Pavord ID, McCormack D, Chaudhuri R, Miller JD, Laviolette M, the AIRTSG. Asthma Control during the Year after Bronchial Thermoplasty. *N Eng J Med* 2007: 356(13): 1327-1337.

4. Pavord ID, Cox G, Thomson NC, Rubin AS, Corris PA, Niven RM, Chung KF, Laviolette M, the RTSG. Safety and Efficacy of Bronchial Thermoplasty in Symptomatic, Severe Asthma. *Am J Respir Crit Care Med* 2007: 176(12): 1185-1191.
5. 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, for the AIRTSG. Effectiveness and Safety of Bronchial Thermoplasty in the Treatment of Severe Asthma: A Multicenter, Randomized, Double-Blind, Sham-Controlled Clinical Trial. *Am J Respir Crit Care Med* 2010: 181(2): 116-124.
6. Thomson NC, Rubin A, Niven R, Corris P, Siersted H, Olivenstein R, Pavord I, McCormick D, Laviolette M, Shargill N, Cox G, Study Group tAIRT. Long term (5 Year) safety of bronchial thermoplasty: Asthma Intervention Research (AIR) trial. *BMC Pulm Med* 2011: 11(1): 8.
7. Pavord ID, Laviolette M, Thomson NC, Niven RM, Cox G, Corris PA, Chung KF. 5-year safety of bronchial thermoplasty demonstrated in patients with severe refractory asthma: Research in Severe Asthma (RISA) Trial. *Am J Respir Crit Care Med* 2011: 183: A6362.
8. 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-J, 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. Bronchial thermoplasty: Long-term safety and effectiveness in patients with severe persistent asthma. *J Allergy Clinical Immunol* 2013: 132: 1295-1302.
9. Torrego A, Solà I, Munoz A, Roqué I, Figuls M, Yepes-Nuñez J, Alonso-Coello P, Plaza V. Bronchial thermoplasty for moderate or severe persistent asthma in adults. *Cochrane Database Syst Rev* 2014: Issue 3. Art. No.: CD009910. DOI: 10.1002/14651858.CD009910.pub2.

10. U.S. Food and Drug Administration. Bronchial thermoplasty for severe asthma. http://www.fda.gov/medicaldevices/productsandmedicalprocedures/deviceapprovalsandclearances/recently-approveddevices/ucm212594.htm, 2010.
11. Doeing DC, Mahajan AK, White SR, Naureckas ET, Krishnan JA, Hogarth DK. Safety and feasibility of bronchial thermoplasty in asthma patients with very severe fixed airflow obstruction: A case series. *J Asthma* 2013: 50: 215-218.
12. Chakir J, Haj-Salem I, Gras D, Joubert P, Beaudoin È-L, Biardel S, Lampron N, Martel S, Chanez P, Boulet L-P, Laviolette M. Effects of Bronchial Thermoplasty on Airway Smooth Muscle and Collagen Deposition in Asthma. *Annals ATS* 2015: 12(11): 1612-1618.
13. Salem IH, Boulet L-P, Biardel S, Lampron N, Martel S, Laviolette M, Chakir J. Long-Term Effects of Bronchial Thermoplasty on Airway Smooth Muscle and Reticular Basement Membrane Thickness in Severe Asthma. *Annals ATS* 2016: 13(8): 1426-1428.
14. Denner DR, Doeing DC, Hogarth DK, Dugan K, Naureckas ET, White SR. Airway Inflammation after Bronchial Thermoplasty for Severe Asthma. *Annals Am Thor Soc* 2015 12(9): 1302-1309.
15. Bicknell S, Chaudhuri R, Lee N, Shepherd M, Spears M, Pitman N, Cameron E, Cowan D, Nixon J, Thompson J, McSharry C, Thomson NC. Effectiveness of bronchial thermoplasty in severe asthma in 'real life' patients compared with those recruited to clinical trials in the same centre. *Therap Adv Respir Dis* 2015: 9(6): 267-271.
16. Langton D, Sha J, Ing A, Fielding D, Wood E. Bronchial thermoplasty in severe asthma in Australia. *Intern Med J* 2017: 47(5): 536-541.
17. Pretolani M, Bergqvist A, Thabut G, Dombret M-C, Knapp D, Hamidi F, Alavoine L, Taillé C, Chanez P, Erjefält JS, Aubier M. Effectiveness of bronchial thermoplasty in patients with severe refractory asthma: clinical and histopathological correlations. *J Allergy Clin Immunol* 2016: 139(4): 1176-1185.
18. Burn J, Sims AJ, Keltie K, Patrick H, Welham SA, Heaney LG, Niven R. Procedural and short-term safety of bronchial thermoplasty in clinical practice: evidence from a national registry and Hospital Episode Statistics. *J Asthma* 2016: Dec 1:0. [Epub ahead of print].

19. Chupp G, Laviolette M, Cohn L, McEvoy C, Bansal S, Shifren A, Khatri S, Grubb G, McMullen E, Strauven R, Kline J. Long term Outcomes of Bronchial Thermoplasty in Subjects with Severe Asthma: A Comparison of Three-Year Follow-Up Results from Two Prospective Multi-Center Studies. *Eur Respir J* 2017 in press.
20. Global Initiative for Asthma (GINA) 2016 [cited; Available from: http://www.ginasthma.org/
21. Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, Adcock IM, Bateman ED, Bel EH, Bleecker ER, Boulet L-P, Brightling C, Chanez P, Dahlen S-E, Djukanovic R, Frey U, Gaga M, Gibson P, Hamid Q, Jajour NN, Mauad T, Sorkness RL, Teague WG. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J* 2014: 43(2): 343-373.

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

- Aged >65 years
- Chronic sinus disease
- Prebronchodilator FEV_1 <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 more than 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 (AIR2 trial)

* Note: Similar key exclusion criteria used in the PAS2 study [19], except for chronic sinus disease.

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

	UK [15]	Canada [12, 13]	France [17]	Australia [16]
Number	10	16	15	20
Age				
Maintenance oral corticosteroids (%)	40%	30%	66%	50%
FEV_1 percent predicted (range or SD)	72% (45-96%)	67% (42-103%)	71% (17)	63% (33-95%)
Number of months post bronchial thermoplasty treatment when clinical outcomes assessed	12	12 (n=9, ≥27)	12	6
Asthma control score(s)[#]	Improved (40%)*	Improved	Improved	Improved (85%)*
Asthma quality of life score	Improved (50%)*		Improved	
Severe exacerbations	Decreased (30%)*	Decreased	Decreased	Decreased
ED visits/hospital admissions			Decreased	
Daily oral corticosteroid dose	Decreased (n=1)	Decreased (n=4)	Decreased	Decreased
FEV_1	No change	No change	No change	No change overall (Increase if FEV_1 <60%)
Assessment of overall benifcial response to bronchial thermoplasty	50%		73%	65-85%

Abbreviations: FEV_1, forced expiratory volume in one second; ED, emergency department

[#] Assess using different asthma symptom questionnaire: asthma control questionnaire[15, 16]; asthma control test [17]; asthma control scoring system [12, 13]

* Percent of patients with $\geq$ minimal clinical important difference (MCID) in clinical outcome