Bronchial thermoplasty in patients with dynamic hyperinflation: results from the proof-of-concept HEAT trial

To the Editor:

Severe refractory asthma affects 3–5% of asthmatic patients, but represents 50–80% of asthma-related healthcare costs [1]. Although therapies targeting IgE and, more recently, IL5 and IL4/13 have recently gained approval for the treatment of severe refractory asthma in a subset of patients with type 2 phenotypes, there is still a need to cover a wider range of patients, in particular those with a non-type 2 phenotype or for whom biotherapies failed.

Bronchial thermoplasty, a bronchoscopic approach that uses radiofrequency energy to target airway smooth muscle [2], has been recently approved for the management of severe refractory asthma based on the outcomes of three randomised trials [3–5]. This procedure improves symptom control and quality of life (QoL) [3, 5], and durably [6] decreases the rate of exacerbations and emergency visits [3–5].

However, the pathophysiological mechanisms underlying bronchial thermoplasty effectiveness are poorly known and reliable markers of response are strongly needed. Of note, there is discrepancy between improvements in symptoms and QoL, and the lack of change in forced expiratory volume in 1 s (FEV_1) [3–5].

Dynamic hyperinflation during exercise is often considered to be responsible for dyspnoea in patients with severe asthma [7, 8]. We hypothesised that targeting the airway smooth muscle mass would be particularly efficient in patients harbouring dynamic hyperinflation, a phenomenon usually associated with exercise-induced bronchoconstriction [9], and this functional criteria could be used to better select patients treated with bronchial thermoplasty.

We aimed to assess change in dynamic hyperinflation, symptoms, FEV1 and QoL following treatment by bronchial thermoplasty in a selection of patients harbouring dynamic hyperinflation.

Patients with a severe refractory asthma (according to European Respiratory Society/American Thoracic Society criteria), FEV_1 >40% predicted, at least two exacerbations in the past year requiring systemic steroids, and dynamic hyperinflation were included in this proof-of-concept study (NCT02618551, HEAT trial). Patients demonstrating a decrease of more than 500 mL in inspiratory capacity (IC) at exercise (cycle ergometer) were considered to have clinically significant dynamic hyperinflation and were included.

Our study was approved by local ethical committees (Comité de Protection des Personnes, number CPP-041).

Three treatment sessions of bronchial thermoplasty (ALAIR system, Boston Scientific, Marlborough, MA, USA) were performed in patients whose asthma had been stable for the past 10 days, at approximately 3-week intervals, under general anaesthesia and through a laryngeal mask and a flexible bronchoscope (Pentax EB15-J10 and Olympus BFQ180) [10]. Patients received 5 days of oral steroids (1 $mg \cdot kg^{-1}$, starting 2 days before) and were hospitalised the day before and discharged 1 to 2 days after the procedure in the absence of complications. ACQ7 (Asthma Control Questionnaire 7) and AQLQ (Asthma Quality of Life Questionnaire), FEV_1 and dynamic hyperinflation were measured before and 3 months after bronchial thermoplasty. Dynamic hyperinflation was calculated as the difference between the IC measured during

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increased pacing and the IC at rest. Long-acting bronchodilators and inhaled corticosteroids were not discontinued, but short-acting bronchodilators were not administered in the 6 h preceding the measures, considering a recent intake could modify the phenomenon and make iterative measures more variable. The timeframe between long-acting bronchodilator intake and pulmonary function tests was 2–3 h for both pre- and post-bronchial thermoplasty evaluations. Adverse effects (asthma exacerbation, haemoptysis, lower or upper respiratory tract infections, chest pain, other) were noted.

We enrolled 10 patients for this feasibility, proof-of-concept study. The primary outcome was the percentage (with exact binomial 95% confidence intervals) of patients for whom dynamic hyperinflation decreased by 50% or more 3 months after bronchial thermoplasty. The percentage of patients with minimal clinically important changes in AQLQ (+0.5) and ACQ7 (−0.5) [11, 12], as well as the rate of patients with a 12% or more increase in FEV_1 were other secondary judgment criteria. We also analysed the changes (median and quartiles) in AQLQ and ACQ7 scores, as well as in FEV_1 and dynamic hyperinflation measures (in L).

10 patients were enrolled in the study between November 2015 and October 2019, with ages ranging from 27 to 69 years. The main patient characteristics and results are summarised in table 1. Median dynamic hyperinflation before and after treatment was −870 mL and −425 mL, respectively. 70% (95% CI 35%–93%) and 80% (95% CI 44%–97%) of patients had a decrease of at least 50% and 30% in dynamic hyperinflation, respectively, 3 months after bronchial thermoplasty. Median change in dynamic hyperinflation was 495 mL (−54%). Median change in FEV_1 was 300 mL (+13%), with 5/10 patients showing ⩾12% improvement. ACQ7 and AQLQ scores improved in all but one of the eight patients with available data, with a median increase in AQLQ of 1.57 and a median decrease in ACQ7 of 2.29. Noteworthy, of the three steroid-dependent patients, two were weaned after bronchial thermoplasty (patients 1 and 9).

No unexpected adverse effects [10] were observed after the 30 procedures (eight asthma exacerbations, all requiring one additional day of hospitalisation and two additional days of steroids, one minor haemoptysis not requiring prolonged hospitalisation, six pleuritic chest pain (likely due to the peripheral diffusion of the radiofrequency-induced heat that can cause limited and transient pleural effusions [13]), and one upper respiratory tract infection 6 days after the procedure requiring antibiotics without hospitalisation). No intensive care unit admission or non-invasive ventilation was needed.

Bronchial thermoplasty has been approved for the treatment of severe asthma, based on the positive results of three randomised controlled trials [3–5]. However, this invasive procedure is usually considered a last option after failure of all other therapies, because the overall response rate remains limited and markers of response are clearly lacking. It is obvious that a subset of patients experience dramatic improvements after bronchial thermoplasty, but the predictive factors for such outcomes have not been deciphered so far. Most of the ongoing trials are dedicated to the identification of mechanisms of action and thus phenotype(s) of response to bronchial thermoplasty.

In this proof-of-concept study involving a limited number of patients selected based upon the presence of a dynamic hyperinflation of more than 500 mL of IC at exercise, we observed some very appealing outcomes. Bronchial thermoplasty seems effective on this phenomenon known to be better correlated with dyspnoea than any static measure, such as FEV_1 [14], and to significantly impact QoL in asthma patients [7]. The significant dynamic hyperinflation improvement (median decrease of 54%) resulted in dramatic subjective improvements (ACQ7, AQLQ). The 1.57 median increase in AQLQ score and 2.29 median decrease in ACQ7 score are very encouraging, even in the absence of control group (the variations were +1.35 and +1.16 (AQLQ); and +0.82 and +0.77 (ACQ) in the bronchial thermoplasty and sham group of the AIR2 trial, respectively). Our data are in agreement with a case reported by Miki *et al*. [15], where asthma control scores improved but not resting pulmonary function, and demonstrated improved exertional breathing patterns after bronchial thermoplasty. Of note, we also observed a slight improvement in FEV_1 (median gain 300 mL, +13%), a parameter unchanged after bronchial thermoplasty in both the AIR and AIR2 randomised trials [4, 5]. One limitation of our study is the lack of follow up regarding exacerbations, precluding the evaluation of the effect on exacerbation rate in this specific population. Even if dynamic hyperinflation variations were not associated with response in all patients (one patient improved in dynamic hyperinflation but not FEV_1 and ACQ7/AQLQ, while two improved in ACQ7/AQLQ without dynamic hyperinflation decrease), our results suggest that dynamic hyperinflation should be further evaluated as a selection criterion for this treatment targeting airway smooth muscle. Bronchial thermoplasty could become cost-effective if the mechanisms by which bronchial thermoplasty improves the subjective symptoms of asthma without significantly changing resting pulmonary function are identified. In our opinion, the hypothesis that dynamic hyperinflation could enrich the responder rate should be investigated in larger controlled trials.

TABLE 1 Patient characteristics before bronchial thermoplasty (BT) and outcomes at 3 months

Patient	Sex/age years/ asthma type	Treatment	DH before	DH after	DH change in L (% of baseline)	FEV_1 before (% pred)	FEV_1 after (% pred)	FEV_1 change in L (% of baseline)	ACQ 7 change (before BT-after BT)	AQLQ change (before BT-after BT)
1	F/27/Type 2	27 OCS 10 Beclo 400 Formo 12 Tiot 36 Omali	−1.1 L	−0.5 L	−0.6 L (−55%)	3 L (91%)	4 L (120%)	+1 L (+33%)	−2.57 (4.42–1.85)	+1.65 (3.6–5.25)
2	F/27/Type 2	No OCS Fluti 2000 Salme 200 Tiot 36 Omali	−0.55 L	0	−0.55 L (−100%)	4.1 L (100%)	4.75 L (116%)	+0.65 L (+16%)	NA	NA
3	F/68/Type 2	OCS 20 Fluti 2000 Salme 200 Tiot 36 Omali	−0.72 L	−0.35 L	−0.37 L (−51%)	1.48 L (70%)	1.6 L (75%)	+0.12 L (+8%)	NA	NA
4	M/59/Type 2	No OCS Fluti 500 Formo 20 Tiot 36 Omali	−1.5 L	−0.7 L	−0.8 L (−53%)	2 L (59%)	2.2 L (67%)	+0.2 L (+10%)	−0.85 (2.7–1.85)	+1.56 (5.03–6.59)
5	M/38/Type 2	No OCS Cicle 640 Oloda 5 Tiot 36	−0.6 L	−0.8 L	+0.2 L (+33%)	2.6 L (71%)	3.3 L (90%)	+0.7 L (+27%)	−2.15 (2.86–0.71)	+1.45 (5.15–6.6)
6	F/69/Type 2	No OCS Fluti 500 Formo20 Tiot 36 Omali	−0.74 L	−0.3 L	−0.44 L (−59%)	1.5 L (64%)	1.3 L (60%)	−0.2 L (−13%)	+0.85 (3.15–4)	−1.55 (4.65–3.1)
7	F/33/Non–type 2	No OCS Fluti 2000 Salme 200 Tiot 36	−1 L	−0.3 L	−0.7 L (−70%)	3.3 L (106%)	3.5 L (116%)	+0.2 L (+6%)	−2.43 (3.43–1)	+1.57 (3.43–5)
8	M/34/Type 2	No OCS Bude 640 Formo 18 Tiot 36 Omali	−0.5 L	−0.7 L	+0.2 L (+40%)	2.4 L (70%)	2.2 L (62%)	−0.2 L (−8%)	−1.00 (2.14–1.14)	+0.73 (5.15–5.88)
9	F/36/Type 2	OCS 30 Bude 800 Formo 24 Tiot 36 Omali Mepo	−1.03 L	−0.7 L	−0.33 L (−32%)	1.8 L (54%)	2.2 L (67%)	+0.4 L (+22%)	−3.14 (5.14–2)	+4.35 (2.15–6.5)
10	M/29/Type 2	Fluti 500 Formo 20 Tiot 36 Omali Mepo	−1 L	+0.3 L	−1.3 L (−130%)	2.6 L (59%)	3.4 L (84%)	+0.8 L (+31%)	−2.86 (4.14–1.28)	+2.22 (3.34–5.56)
Median (IQR)	Median age 35		−0.87 L (−1.0; −0.6)	−0.43 L (−0.7; −0.2)	0.5 L (−54%) (+0.2 L; +0.7 L) (−78%; −16%)	2.5 L (70%) (1.7 L; 3.1 L) (59%; 93%)	2.75 L (79.5%) (2.1 L; 3.6 L) (66%; 116%)	+0.3 L (+13%) (+0.04 L; +0.73 L) (+2%; +28%)	−2.29 (−2.79; −0.89)	+1.57 (+0.91; +2.08)

DH: dynamic hyperinflation; FEV_1: forced expiratory volume in 1 s; ACQ7: Asthma Control Questionnaire 7; AQLQ: Asthma Quality of Life Questionnaire; F: female; M: male; IQR: interquartile range; OCS: oral corticosteroids; Beclo: beclomethasone; Fluti: fluticasone; Cicle: ciclesonide; Bude: budesonide; Formo: formoterol; Oloda: olodaterol, Salme: salmeterol; Tiot: tiotropium; Omali: omalizumab (IgE inhibitor); Mepo: mepolizumab (IL5 inhibitor).

In conclusion, an improvement in DH, when present, could be one of the mechanisms underlying the efficacy of bronchial thermoplasty, and this phenomenon should be further evaluated as a marker for patient selection.

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Portions of these data were presented at the ATS Annual Meeting in San Diego in 2018.

This study is registered at clinicaltrials.gov as a clinical trial (NCT02618551). Data after deidentification, statistical analysis and study protocol will be available, immediately after publication and ending 5 years after, proposals being directed to guibert.n@chu-toulouse.fr

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