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Early View

Research letter

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

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Take Home Message: Bronchial thermoplasty improves severe asthma with dynamic hyperinflation. The presence of dynamic hyperinflation is a potential marker for bronchial thermoplasty efficacy in severe refractory asthma.

Key words: Bronchial thermoplasty, severe asthma, dynamic hyperinflation, quality of life, ACQ, AQLQ

Introduction

Severe refractory asthma affects 3-5% of asthmatic patients but represent 50 to 80% of asthma-related healthcare costs (1). Though 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 patient with type 2 phenotypes, there is still a need to cover a wider range of patients, in particular those with a non-T2 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 randomized 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 BT effectiveness are poorly known and reliable markers of response are strongly needed. Of note, there is discrepancy between improvements in symptom and QoL and the lack of change in one-second forced expiratory volume (FEV1) (3–5).

Dynamic hyperinflation (DH) during exercise is often considered to be responsible for dyspnea in patients with severe asthma (7,8). We hypothesized that targeting the airway smooth muscle mass would be particularly efficient in patients harboring DH, a phenomenon usually associated with exercise-induced bronchoconstriction (9), and this functional criteria could be used to better select patients treated with BT.

We aimed to assess change in DH, symptoms, FEV1 and QoL following the treatment by BT in a selection of patients harboring DH.

Methods

Patients

Patients with a severe refractory asthma (ERS/ATS criteria), FEV1 > 40% predicted, at least two exacerbations in the past year requiring systemic steroids, and DH were included in this proof-of-concept study (NCT02618551, HEAT trial). Patients demonstrating a decrease of more than 500 ml of inspiratory capacity (IC) at exercise (cycle ergometer) were considered to have clinically significant DH and were included.

Ethical considerations

Our study was approved by local ethical instances (Comité de Protection des Personnes (CPP), n° CPP-041).

Procedure and follow up

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 three-week intervals, under general anesthesia and through a laryngeal mask and a flexible bronchoscope (PENTAX™ EB15-J10 and OLYMPUS™ BFQ180) (10). Patients received five days of oral steroids (1 mg/kg, starting two days before) and were hospitalized the day before and discharged two days after the procedure in the absence of complications. ACQ7 (Asthma Control Questionnaire 7) and AQLQ (Asthma Quality of Life Questionnaire), FEV1 and DH were measured before and three months after BT. DH was calculated as the difference between the IC measured during 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 six hours preceding the measures, considering a recent intake could modify the phenomenon and

make iterative measures more variable. The timeframe between long acting bronchodilators intake and pulmonary function tests was two to three hours for both pre and post BT evaluations. Adverse effects (asthma exacerbation, hemoptysis, lower or upper respiratory tract infections, chest pain, other) were noted.

Statistics

We enrolled 10 patients for this feasibility, proof-of-concept study. The primary outcome was the percentage (with exact binomial 95% confidence intervals [95%CI]) of patients for whom DH decreased by 50% or more three months after BT. The percentage of patients with minimal clinically important changes in AQLQ (+0.5) and ACQ (-0.5) (11,12), as well as the rate of patients with a 12% or more increase in FEV1 were other secondary judgment criteria. We also analyzed the changes (median and quartiles) in AQLQ and ACQ scores, as well as in FEV1 and DH measures (L).

Results

Ten patients were enrolled in the study between November 2015 and October 2019, with ages ranging from 27 to 69 year old. The main patients characteristics and results are summarized in **Table 1**. Median DH before and after treatment was -870 ml and -425 ml, respectively. Seventy percent (95%CI=[35%-93%]) and eighty percent (95%CI=[44%-97%]) of patients had a decrease of at least 50% and 30% in DH, respectively; three months after BT. Median change in DH was 495 ml (-54%). Median change in FEV1 was 300 ml (+13%), with 5/10 patients showing ≥12% improvement. ACQ 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 ACQ of 2.29. Noteworthy, of the three steroid dependent patients, two were weaned after BT (pt #1 and #9).

No unexpected adverse effects (10) were observed after the 30 procedures (eight asthma exacerbations, all requiring one additional day of hospitalization and two additional days of

steroids, one minor hemoptysis not requiring prolonged hospitalization, six pleuritic chest pain (likely due to the peripheral diffusion of the radiofrequency-induced heat that can cause limited and transient pleural effusions (13)), one upper respiratory tract infection six days after the procedure requiring antibiotics without hospitalization). No intensive care unit admission or non-invasive ventilation was needed.

Discussion

BT has been approved for the treatment of severe asthma, based on the positive results of three randomized 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 BT 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 BT.

In this proof-of-concept study involving a limited number of patients selected based upon the presence of a DH of more than 500 ml of IC at exercise, we observed some very appealing outcomes. BT seems efficient on this phenomenon known to be better correlated with dyspnea than any static measure such as FEV1 (14) and to significantly impact QoL in asthma patients (7). The significant DH improvement (median decrease of 54%) resulted in dramatic subjective improvements (ACQ, AQLQ). The 1.57 median increase in AQLQ score and 2.29 median decrease in ACQ 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 BT and sham group of the AIR2 trial, respectively). Our data are in agreement with a case reported by Miki et al. where asthma control scores improved but not resting pulmonary function, and demonstrated improved exertional breathing patterns after BT (15). Of note, we also observed a slight improvement in FEV1 (median gain 300 ml, +13%), a parameter unchanged after BT in both the AIR and AIR2 randomized 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 DH variations were not associated with response in all patients (1 patient improved in DH but not FEV1 and ACQ/AQLQ while two improved in ACQ/AQLQ without DH decrease), our results suggest that DH should be further evaluated as a selection criterion for this treatment targeting airway smooth muscle. BT could become cost-effective if the mechanisms by which BT improves the subjective symptoms of asthma without significantly changing the resting pulmonary function are identified. In our opinion, the hypothesis that DH could enrich the responder rate should be investigated in larger controlled trials.

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

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Table legend:

Table 1: Patients' characteristics before BT and outcomes at 3 months.

F: Female; M: Male; NA: Not applicable; BT: Bronchial thermoplasty; DH: Dynamic hyperinflation; FEV1: one-second forced expiratory volume; ACQ: Asthma Control Questionnaire; AQLQ: Asthma Quality of Life Questionnaire. Pt: Patient; Pred: Predicted.

OCS: Oral Corticosteroids; ICS (Inhaled Corticosteroids): Beclo: beclomethasone; Fluti: Fluticasone; Cicle: Ciclesonide; Bude: Budesonide.

LABA (long-acting beta2-agonists): Formo: Formoterol; Oloda: olodaterol, Salme: Salmeterol.

LAMA (long-acting muscarinic antagonists): Tiot: Tiotropium.

Biotherapies: Omali: Omalizumab (IgE inhibitor); Mepolizumab (IL5 inhibitor).

Pt, Gender, Age, Asthma Type	Treatment Bioth	DH before	DH after	DH change in L (% of baseline)	FEV1 before (% pred)	FEV1 after (% pred)	FEV1 change in L (% of baseline)	ACQ 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 Formo 20 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 [Q1; Q3] 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]