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Bronchial thermoplasty for severe asthmatics: a 'real-world' clinical study from Malaysia

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INTRODUCTION

Over the past century, the emergence of different phenotypes, and endotypes of asthma has resulted in the development of new specific pathway targeted therapies such as anti-IL-5, anti-IgE and anti-IL-4/IL-13.

The hallmark of asthma involves airway hyperreactivity, chronic airway inflammation, and reversible airflow obstuction.[1] Interest in the remodelling process and increased airway smooth muscle (ASM) mass in asthmatic patients shifted the treatment paradigm towards bronchial thermoplasty (BT). BT is an endoscopic procedure that utilises controlled thermal energy which is delivered in 3 separate sessions via a basket catheter to achieve a reduction in ASM mass, thus antagonising airway remodelling and reducing the amount of bronchoconstriction.[2,3] An activation is recorded when the basket catheter delivers a 10-s radiofrequency heat charges of approximately 65°C[4,5] It is listed in GINA step 5 treatment options.[6]

METHODS

We retrospectively reviewed medical records of patients with severe asthma as defined by ERS/ATS[7] who underwent BT between the year 2012 till 2018. Patient demographics, baseline post-bronchodilator forced expiratory volume in 1 sec (FEV_1)(ERS/ATS standards),[8] medications, exacerbation frequency and severity, Asthma Control Questionnaire (ACQ) and Asthma Quality of Life Questionnaire (AQLQ) scores,[9-11] and total activations were recorded pre and post BT and at 12 months (at respective centres).

BT was performed according to published protocols by a trained interventional pulmonologist using Alair™ Bronchial Thermoplasty System (Boston Scientific) and Olympus BF Q190 flexible bronchoscopy (Olympus Medical, Tokyo, Japan) under general anaesthesia.

IBM SPSS Statistics for Macintosh (Version 23.0, Armonk, NY: IBM Corp) was used for all statistical analysis. Mean ± standard deviation and median (interquartile (IQR) range) were used for normally distributed and non-normally distributed data respectively. The results were compared using the Wilcoxon signed-rank test and pair-T test. *P* values were two-sided with a statistical significance value if < 0.05.

RESULTS

Twenty patients with severe asthma underwent BT. Three patients had to be excluded from the analysis due to lost follow-up. A retrospective analysis was done on the remaining 17 patients. (Table I) shows the demographics of the patients.

14 (82%) patients were female. Median age was 48 years old (IQR 33-55). All patients were on high dose of inhaled corticosteroids (ICS) (budesonide equivalent mean 1106 mcg (± 571) and long-acting β2-agonist. Twelve patients (71%) were on long-acting anti-muscarinic, and three (18%) were on bronchodilator with ultra-fine properties. Other maintenance medications included Montelukast sodium (100%), Theophylline (76%) and OCS (13 patients: 76%) with a median daily OCS (prednisolone) dosage of 10mg (IQR 0-13.75). Three patients (18%) had undergone treatment with Omalizumab. Mean total BT activation was 126 (± 27.6).

ACQ improved from 3.7 (±0.5) to 2.6 (±0.8) at 12 months; 1.1 (95% CI, 0.8 – 1.5) P < 0.001 (Fig. 1a). 15 out of 17 patients (88%) demonstrated a minimal clinically significant difference of 0.5 unit. The baseline AQLQ score of 3.4 (IQR 2.5-3.6) showed a significant improvement of 0.9 to 4.3 (IQR 3.9 - 4.6) (P<0.001) post BT (Fig. 1b).

Reduction in mild to moderate exacerbations (per patient) from 4 (IQR 2.50-8.50) pre-BT to 1 (IQR 0-2.00) post-BT. A reduction rate of 3 exacerbations (p<0.005). Severe exacerbation (per patient) was 2(IQR 1-2) and 0(IQR 0-1) for pre and post-procedure respectively. An improvement of 2 exacerbation (P = 0.02) (see Fig. 1c).

The mean pre-procedure FEV_1 was 59.2% (±15.7). At twelve months, the mean FEV_1 was 62.8% (±14.7). Improvement in mean FEV_1 was 3.6% (P = 0.23). Thirteen patients (76%) were dependent on OCS with a median dosage of 10mg (IQR 0-13.75). Post-BT, 10 (59%) patients were oral corticosteroids free. Median dose of OCS reduction was 10mg (P < 0.005). One patient (6%) remained on the baseline dosage. No correlation established between number of activations and changes in ACQ, AQLQ score, or exacerbation rates. A summary of the results is shown in (Table II).

Exacerbation was defined according to the AST/ERS statement.[12] Overall, 12 (71%) patients recorded mild to moderate exacerbation; two (12%) had isolated incidence of severe exacerbation requiring intubation (one patient developed severe anaphylactic reaction with bronchospasm secondary to naloxone). There were no deaths. Fifteen out of a total of fifty bronchoscopies (30%) had exacerbation requiring an extended duration of OCS (7 days). Other isolated complications included one incident of hospital-acquired pneumonia and transient middle lobe atelectasis secondary to mucus plugging.

DISCUSSION

Precision medicine in the management of severe persistent asthma coincides with improvement in phenotyping of the condition.[7,13] Targeted therapies are explored specifically for T2-high subtype of patients. Macrolides antibiotics can be considered in T2-low non-eosinophilic patients. BT may have a role when unsatisfactory response to the targeted therapies mentioned. Our patients had debilitated symptoms despite on third-line treatment and were evaluated for targeted therapies. The exorbitant cost of targeted therapies has resulted BT as a reasonable alternative.

Our patient's demographics were somewhat similar to the previous randomised controlled trials.[14,15] However, the degree of asthma (baseline FEV_1, AQLQ scores and

exacerbation rates) was more severe compare to the cohorts seen in AIR2 and PAS2.[15,16] AIR2 trial recruited patients with prebronchodilator $FEV_1 \geq 60\%$ predicted and excluded patients who had more than three hospitalizations for asthma in the previous year. This was echoed in the data from post-market arm in PAS2. Both demonstrated mean AQLQ scores of > 4. Our patients had a mean post-bronchodilator of FEV_1 value of 59.2%, median baseline AQLQ of 3.4 and experienced a median of four exacerbations requiring hospital admission in the previous year. Our practice (to apply BT) still adhered to the strict recommendations to exclude patients with life-threatening exacerbations requiring intubation or ICU admissions two years prior procedure.

BT was carried out by a single trained bronchoscopist. This reduces potential proceduralist-influenced bias results. Generally, 40 to 70 and between 50 to 100 activations are required for both lower and upper lobes, respectively.[4] Data from Asia demonstrated 1.28 times higher in the number of activations compared to 151 activations reported in AIR2.[17] Another study reported a minimum of 140 activations is required for significant improvement in ACQ, and the overall response to treatment can be determined by the number of activations provided.[5] Interestingly, the mean total number of activations in our patients was only 126 (± 27.6). We are unable to establish a correlation between the number of activations and improvement in AQLQ scores or exacerbation rates.

The main reason for a low total number of activations is attributed to low total mean activations recorded for both upper lobes (47 ± 12.8). The subsegments of the upper lobes were "short" and were able to accommodate either one or at most two activations only. This was most evident involving the sub-apical segments. Although evidence in ethnicity differences in human lung segments are lacking, we postulated the length and size of these subsegments could be influenced by smaller body habitus and height of the Asian population. A further study to

analyse activation numbers corresponding to bronchial length measured on chest CT would reinforce this hypothesis.

Despite lower total mean activation, our patients demonstrated significant improvement in ACQ, AQLQ scores and reduction in exacerbation rates at 12-month. BT also helped to liberate patients from prolong OCS usage. Usage of other maintenance medications remained similar.

One patient declined the third BT session due to an increased in exacerbation rates despite reasonable explanation and potential reduction in treatment efficacy informed. She was a non-responder to BT at 12 months review. Despite a 30% exacerbation rate in the first week post-procedure (15 incidents out of total 50 bronchoscopies), incidence of intubation was isolated. More severe patients in our cohort could have resulted in the higher incidence of exacerbation post BT compared to the AIR2 trial.[15] Long-term follow-up studies demonstrated no side-effects and a sustained treatment response of up to 5 years duration.[18-20] In addition, it is believed that BT may be cost-effective once a lower cost of procedure is established.[21]

Some limitations of this study include small number of subjects and the involvement of single-centre design. Missing data from the three patients could have an impact on measured outcomes. The use of monoclonal antibody for severe allergic asthma also could have contributed to a small cohort in our study.

In conclusion, BT is effective in preventing exacerbation in problematic asthma patients of Asian population. It is well tolerated and has proven safety profile. Future large-scale prospective cohort studies are invaluable in providing more robust data to improve our understanding of BT in the Asian population.

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Table I Characteristics of patients with severe persistent asthma who underwent BT and completed 12 months follow-up (n=17).

Characteristics	
Age in years, median (IQR)	48(33-55)
Sex (male), n (%)	3(18%)
Sex (female), n (%)	14(82%)
Height (cm), mean (SD)	157 (±5.4)
Body mass index (BMI), median (IQR)	24.8(19.7-34.0)
Race, n (%):	
Malay	6(35%)
Chinese	6(35%)
Indian	4(24%)
Others	1(6%)
Medications, n (%)	
ICS & LABA	4(24%)
ICS, LABA & LAMA	10(59%)
ICS & LABA (UF particles)	1(6%)
ICS, LABA (UF particles) & LAMA	2(11%)
Montelukast sodium	17(100%)
Oral theophylline	13(76%)
Oral prednisolone (OCS)	13(76%)
Omalizumab	3(18%)
Nebulization:	
Less than weekly	5(25%)
Daily	6 30%)
2-3 weekly	6(30%)
Weekly	3(15%)
History of intubation (2 years and above prior BT), n (%)	9 (45%)

Mean ± standard deviation (SD), median (interquartile range: IQR)
ICS: inhaled corticosteroids, LABA: Long-acting β-agonists, LAMA: Long-acting muscarinic antagonists, UF: ultrafine

Table II Evaluation for asthma control, quality of life, lung function, exacerbation rates and usage of corticosteroid before BT and at 12 months post BT.

Outcome	**Baseline**	**12 months**	***P* value**
ACQ	3.7(±0.5)	2.6 (±0.8)	< 0.001
AQLQ	3.4 (1.1)	4.3 (0.7)	< 0.001
FEV_1 % predicted	59.2% (±15.7)	62.8% (±14.7)	0.23
Mild to moderate exacerbation	4 (6)	1 (2)	<0.005
Severe exacerbation	2(1)	0(1)	0.02
OCS dose (mg) /day	10(15)	0 (0)	< 0.005

Mean ± standard deviation (SD), median (interquartile range: IQR); Asthma Control Questionnaire (ACQ), Asthma Quality of Life Questionnaire (AQLQ), forced expiratory volume in 1 sec (FEV_1) pre-bronchodilator, oral corticosteroid (OCS)

Fig. 1a: Boxplot showing the comparison of ACQ score pre-BT and post-BT at 12 months
Fig. 1b: Boxplot showing the comparison of AQLQ score pre-BT and post-BT at 12 months
Fig. 1c: Boxplot showing the comparison of exacerbation rates pre and post-BT at 12 months

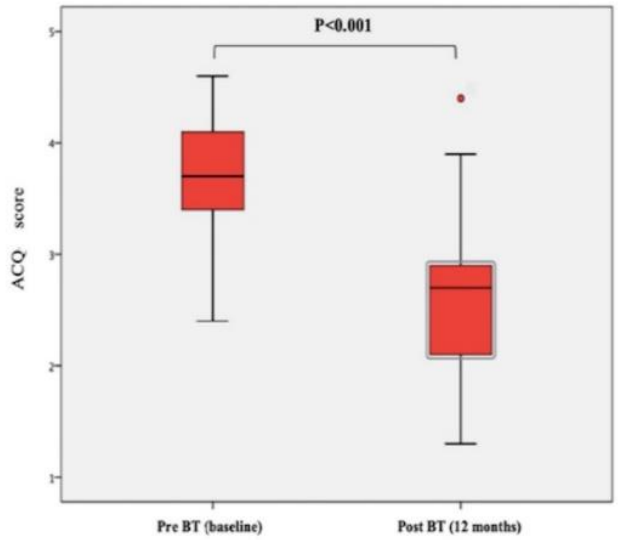

Figure.1a

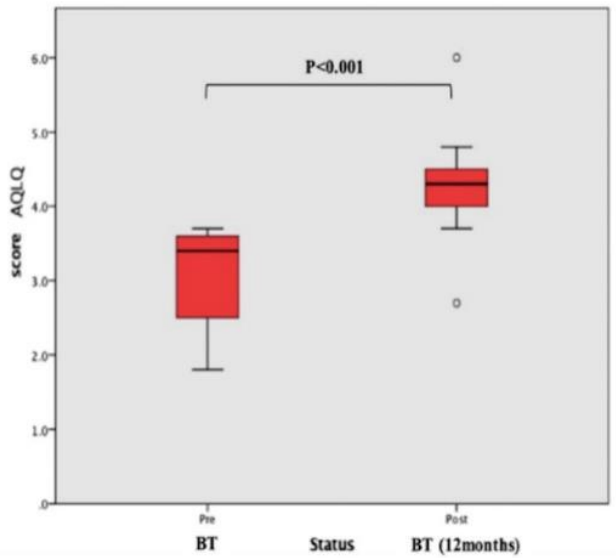

Figure.1b

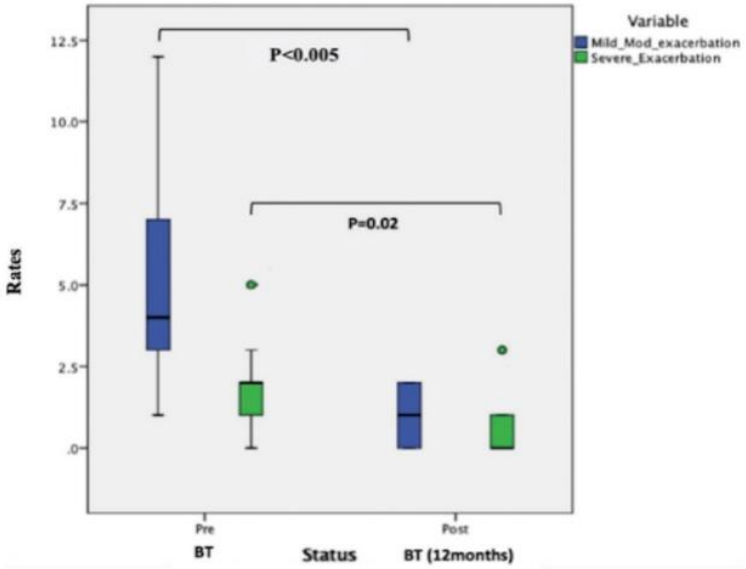

Figure.1c