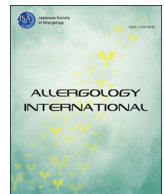




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Letter to the Editor

Bronchial thermoplasty for severe uncontrolled asthma in Japan

Dear Editor,

Bronchial thermoplasty (BT) is an effective non-pharmacological therapy for patients with severe uncontrolled asthma.¹ BT has been known to inhibit bronchoconstriction by reducing airway smooth muscles,^{2,3} improving asthma-related quality of life (QOL) and reducing the frequency of severe exacerbation for at least 5 years.^{1,4,5} BT treatment has been available in Japan since 2015.⁶ The present study investigated the effectiveness and safety of BT treatment in Japanese patients.

Methods, including patient characteristics, are shown in Table 1 and the Supplementary Methods.

Outcomes are shown in Table 2. Asthma-related Quality of Life Questionnaire (AQLQ) and Asthma Control Questionnaire (ACQ)-5 scores were improved at both 1 and 12 months after BT. Mean FEV1 was increased at 1 and 12 months. The typical improvement in symptoms was a resolution or decrease in the frequency of night awakening, wheezing, exertional dyspnea, work discontinuation, cough, sputum production, and chest tightness. This improvement was observed from 1 month after BT and was sustained for at least 12 months. The mean annual number of severe exacerbations requiring systemic corticosteroids decreased from 5.8 to 2.0 at 12 months after BT. Reduction of maintenance asthma drug use was observed in 2 patients. In 1 patient, injection of triamcinolone was reduced by 75% at 12 months. In another patient, ICS use was reduced by 25% and theophylline had been discontinued at 12 months.

In the series of 36 procedures, no deaths, need for invasive ventilation, or cardiac arrhythmia were encountered. Focal peribronchitis/bronchitis at the site of BT treatment, accompanied by cough, local wheezing, chest discomfort, and chest pain, were observed in 97.2% of patients. Among the extended cases, 16.7% developed progression to atelectasis. The extent of atelectasis is usually segmental or subsegmental. These adverse events started within several hours after BT, progressed after 1 day, and resolved within 7 days without any additional treatment. Other adverse events were asthma attacks requiring systemic steroids (8.3%), bacterial pneumonia (8.3%), endobronchial fungal infection including candidiasis and aspergillosis (5.6%), and hemoptysis (5.6%). Bacterial pneumonia is easily diagnosed based on findings of sudden onset of fever, purulent sputum and pulmonary infiltration. However, identification of endobronchial fungal infection is difficult because of a lack of characteristic symptoms. Endobronchial fungal infection is usually only identified on second-look bronchoscopy at

the next performance of BT. Administration of anti-fungal drug was required in these cases.

In this study, Japanese patients with severe uncontrolled asthma were treated with BT in a real-world clinical practice. Despite the use of five kinds of asthma controllers, including systemic steroids or omalizumab, patients remained symptomatic, showed impaired QOL and experienced frequent exacerbations. Based on our results, BT treatment improved asthma-related QOL, control, and airflow obstruction, and reduced the frequency of severe exacerbations in these patients.

Our results should be interpreted in comparison with results from previous studies. The largest sham-controlled Asthma Intervention Research (AIR)2 trial on severe asthmatic patients treated with BT demonstrated improvements in asthma-related QOL with a reduction in the frequency of severe exacerbations.¹ Compared

Table 1
Patient characteristics (n = 12).

Age (years)	56.1 ± 14.5
Sex, n (%)	
Men	6 (50.0)
Women	6 (50.0)
Height (cm)	159.9 ± 10.2
Body weight (kg)	56.7 ± 14.3
BMI	21.9 ± 3.9
Smoking status, n (%)	
Never-smoker	9 (75.0)
Ex-smoker	3 (25.0)
Nasal comorbidities, n (%)	9 (75.0)
Peripheral eosinophils (/μl)	199.3 ± 248.8
IgE (IU/ml)	410.3 ± 630.0
Disease duration (years)	31.8 ± 14.1
GINA treatment step, n (%)	
4	3 (25.0)
5	9 (75.0)
Exacerbations in previous year	5.8 ± 5.3 (range, 1–20)
Baseline ACQ-5 score	1.5 ± 0.9 (range, 0.0–3.2)
Baseline ACT score	19.0 ± 4.2 (range, 11–25)
Baseline AQLQ score	4.9 ± 1.1 (range, 3.2–7.0)
FEV1 (% predicted)	70.5 ± 21.7
FEV1 <60% predicted, n (%)	5 (41.7)
FeNO (ppb)	50.2 ± 70.8 (range, 10–259)
Systemic steroid use, n (%)	5 (41.7)
Omalizumab use, n (%)	6 (50.0)
ICS dose (μg/day)	1675.0 ± 402.5
LABA use, n (%)	12 (100)
LAMA use, n (%)	9 (75.0)
LTRA use, n (%)	11 (91.7)
Theophylline use, n (%)	10 (83.3)

Unless otherwise indicated, values are presented as mean ± SD. ICS dose was calculated as a beclomethasone-equivalent dose.

ACQ, Asthma Control Questionnaire; ACT, Asthma Control Test; AQLQ, Asthma Quality of Life Questionnaire; LAMA, long-acting muscarinic receptor antagonist; LTRA, leukotriene receptor antagonist.

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Table 2
Effectiveness outcomes of BT.

	Baseline	1 Month after BT	12 Months after BT
AQLQ	4.9 ± 1.1	5.7 ± 1.4*	5.8 ± 1.3*
Change from baseline		0.8	0.9
Subjects with AQLQ change ≥0.5, n (%)		7 (58.3%)	8 (66.7%)
ACQ-5	1.5 ± 0.9	0.9 ± 1.0*	0.9 ± 0.9*
Subjects with ACQ-5 change ≥0.5, n (%)		7 (58.3%)	6 (50.0%)
ACT	19.0 ± 4.2		20.5 ± 4.4
Subjects with ACT >19, n (%)	5 (41.7%)		7 (58.3%)
FEV1 (% predicted)	70.5 ± 21.7	82.2 ± 20.6*	82.3 ± 21.8**
Subjects with increased FEV1, n (%)		9 (75.0%)	10 (83.3%)
FeNO (ppb)	50.2 ± 70.8	51.3 ± 61.0	68.8 ± 80.4*
Subjects with decreased FeNO, n (%)		6 (50.0%)	1 (9.1%)
Exacerbations per year	5.8 ± 5.3		2.0 ± 2.8*
Subjects with reduced exacerbation, n (%)			10 (83.3%)
Asthma-induced hospitalization, n (%)	2 (16.7%)		0 (0.0%)
Reduction in drugs used, n (%)			2 (16.7%)

Unless otherwise indicated, values are presented as mean ± SD.

Statistical significance: **p* < 0.05; ***p* < 0.01.

ACQ, Asthma Control Questionnaire; ACT, Asthma Control Test; AQLQ, Asthma-related Quality of Life Questionnaire.

with the AIR2 trial, our study demonstrated somewhat better AQLQ scores at baseline, but almost the same rate of improvement in AQLQ at 12 months. The better AQLQ score at baseline in our study might be explained by the strict asthma control recommendations in the Japanese asthma guidelines⁷ and the administration of more maintenance asthma drugs in clinical practice. Because the proportion of patients with AQLQ improvement in our study was almost the same as that in the sham-control group of the AIR2 trial,¹ the possibility of a placebo effect for BT in clinical practice is difficult to exclude. The results of asthma control resembled those of QOL in our study. Compared with findings from previous studies, including the AIR2 trial, our study included patients with better asthma control at baseline and similar changes in ACQ-5 from baseline.^{1,4}

The most reliable and important effect of BT treatment was a reduction in the frequency of exacerbations.^{1,5} Compared with the AIR2 trial, our patients experienced severe exacerbations more frequently at baseline, probably because more severe asthma patients were included in our study. Based on our results, the efficacy of BT treatment in clinical practice was about 80% in Japanese patients with severe asthma. Although patients with higher exacerbation risk was anticipated in our clinical practice compared to the AIR2 trial, the reduction rate for severe exacerbation after BT treatment was almost the same as that in the AIR2 trial.

In our study, significant improvements in FEV1 were observed. This result differed from that of the AIR2 trial, which reported that FEV1 remained unchanged for 5 years after BT.^{1,5} One of the reasons could be patient selection for BT treatment. Patients with FEV1 <60% of the predicted value were excluded from the AIR2 trial,¹ whereas patients with more severe obstructive lung function were included in our study. Although significant improvement of % FEV1 was not observed in FEV1 subgroups because of the small sample size, greater improvement of FEV1 was observed in patients with <60% of predicted FEV1 compared to those with ≥60% of predicted FEV1 (Supplementary Table 1). Improvement of FEV1 was observed in the Research in Severe Asthma trial⁸ and in an

Australian study,⁹ both of which included patients with more obstructive lung function. Another reason for the discrepancy in results might be the higher number of BT activations in our study. The total number of BT activations in our study was 1.28 times that in the AIR2 trial,⁵ implying that more peripheral bronchial subsegments were treated in our study. Although no relationship was seen between total number of BT activations and effectiveness of BT, including improvements of ACQ5, AQLQ, FEV1 and exacerbations in our small study (data not shown), further studies are required to elucidate the relation between effectiveness of BT and number of BT activations.

The major mechanism of BT treatment is reduction of airway smooth muscle mass.^{2,3,10} Chronic eosinophilic airway inflammation is one of the specific features of asthma and is associated with a high concentration of exhaled nitric oxide. In our study, FeNO level was not decreased after BT treatment, indicating that eosinophilic airway inflammation was unaffected by BT. This result is consistent with that of a previous study.¹⁰

Worsening of asthma-like symptoms was reported in previous studies as an early adverse event associated with BT.^{1,4} The bronchial/peribronchial damage induced by heat energy during BT probably induced these asthma-like symptoms. This adverse event resolved within 7 days and was unaffected by the administration of steroids or antibiotics. Among other adverse events, attention should be paid to respiratory tract infection. The bronchial mucosal damage induced by heat energy and the inevitable bronchial stenosis after BT will predispose patients to bacterial or fungal infection. This risk of opportunistic infection seems likely to be aggravated by the administration of high-dose systemic steroids during BT treatment.

This study had some limitations. The single-center design and small number of subjects might cast doubt on the applicability of our results to all Japanese patients with severe asthma.

In conclusion, BT was a relatively safe procedure that improved asthma-related QOL, control, and airflow obstruction, and reduced the frequency of severe exacerbation in Japanese patients with severe uncontrolled asthma.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.alit.2017.07.006>.

Conflict of interest

MI received lecture fees from Boston Scientific Japan. The rest of the authors have no conflict of interest.

Motoyasu Iikura*, Masayuki Hojo, Naoko Nagano, Keita Sakamoto, Konomi Kobayashi, Shota Yamamoto, Masao Hashimoto, Satoru Ishii, Shinyu Izumi, Haruhito Sugiyama

Department of Respiratory Medicine, National Center for Global Health and Medicine, Tokyo, Japan

* Corresponding author. Department of Respiratory Medicine, National Center for Global Health and Medicine, 1-21-1, Toyama, Shinjuku-ku, Tokyo 162-8655, Japan. E-mail address: iikura-ky@umin.ac.jp (M. Iikura).

References

1. Castro M, Rubin AS, Laviolette M, Fiterman J, Lima MDA, Shah PL, et al. Effectiveness and safety of bronchial thermoplasty in the treatment of severe asthma. *Am J Respir Crit Care Med* 2010;**181**:116–24.
2. Pretolani M, Dombret MC, Thabut G, Knap D, Hamidi F, Debray MP, et al. Reduction of airway smooth muscle mass by bronchial thermoplasty in patients with severe asthma. *Am J Respir Crit Care Med* 2014;**190**:1452–4.
3. Chakir J, Haj-Salem I, Gras D, Joubert P, Beaudoin ÈL, Biardel S, et al. Effects of bronchial thermoplasty on airway smooth muscle and collagen deposition in asthma. *Ann Am Thorac Soc* 2015;**12**:1612–8.
4. Cox G, Thomson NC, Rubin AS, Niven RM, Corris PA, Siersted HC, et al., AIR Trial Study Group. Asthma control during the year after bronchial thermoplasty. *N Engl J Med* 2007;**356**:1327–37.
5. Wechsler ME, Laviolette M, Rubin AS, Fiterman J, Silva JRL, Shah PL, et al., AIR2 Trial Study Group. Bronchial thermoplasty: long-term safety and effectiveness in patients with severe persistent asthma. *J Allergy Clin Immunol* 2013;**132**:1295–302.
6. Iikura M, Hojo M, Ro S, Shiozawa A, Takazawa I, Kobayashi K, et al. Technical description of bronchial thermoplasty in two Japanese severe persistent asthma patients. *JJSRE* 2015;**37**:450–7.
7. Ichinose M, Sugiura H, Nagase H, Yamaguchi M, Inoue H, Sagara H, et al., Japanese Society of Allergology. Japanese guidelines for adult asthma 2017. *Allergol Int* 2017;**66**:163–89.
8. Pavord ID, Cox G, Thomson NC, Rubin AS, Corris PA, Niven RM, et al. Safety and efficacy of bronchial thermoplasty in symptomatic, severe asthma. *Am J Respir Crit Care Med* 2007;**176**:1185–91.
9. Langton D, Sha J, Ing A, Fielding D, Wood E. Bronchial thermoplasty in severe asthma in Australia. *Intern Med J* 2017;**47**:536–41.
10. Pretolani M, Bergqvist A, Thabut G, Dombret MC, Knapp D, Hamidi F, et al. Effectiveness of bronchial thermoplasty in patients with severe refractory asthma: clinical and histopathologic correlations. *J Allergy Clin Immunol* 2017;**139**:1176–85.

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Supplementary Methods

This study was approved by the institutional review board of the National Center for Global Health and Medicine. Written informed consent was obtained from each participant. This study was conducted according to the principles expressed in the Declaration of Helsinki.

Eligible subjects were adult patients (>18 years old) who underwent BT treatment between February 2015 and April 2016 at our hospital for severe uncontrolled asthma. All subjects met the European Respiratory Society (ERS)/American Thoracic Society (ATS) definition of severe asthma and required regular maintenance medications using high-dose ICS and LABA, according to the Global Initiative for Asthma (GINA) treatment step 4 or 5.^{1,2} Twelve patients were included in the study. We collated the baseline characteristics of patients (Table 1). Eight patients (66.7%) used systemic steroids or omalizumab. The mean number of maintenance asthma drugs used was 5.4 ± 1.2 . Despite this treatment, symptom control was poor. Mean Asthma Control Questionnaire (ACQ-5) score was 1.5 ± 0.9 ; 6 cases (50.0%) showed ACQ-5 score >1.5; mean Asthma Control Test (ACT) score was 19.0 ± 4.2 . Mean Asthma-related Quality of Life Questionnaire (AQLQ) score was 4.9 ± 1.1 . Seven cases (58.3%) demonstrated a baseline FEV1 <80% of the predicted value and a mean FeNO level of 50.2 ± 70.8 ppb. Within the 12 months prior to treatment, the mean number of

exacerbations requiring prednisolone per patient was 5.8 ± 5.3 . Eleven cases (91.7%) had received ≥ 2 prednisolone courses in the previous year and 2 cases (16.7%) had been hospitalized for asthma attacks at least once in the previous year.

BT was performed by experienced bronchoscopists using the Alair Bronchial Thermoplasty System (Boston Scientific Japan, Tokyo, Japan) through the Olympus BF P240 or 260 bronchoscope (Olympus, Tokyo, Japan).³ All bronchoscopy procedures were performed under local anesthesia with midazolam or propofol. Prednisolone (40-50 mg) was prescribed for 3 days prior to the procedure and was continued for 1 day post-procedure. In cases of prolonged airflow obstruction after BT, systemic steroid administration was continued for several days. Mean ($\pm$ SD) number of activations for each of the three treatment procedures was 53.9 ± 15.8 for the right lower lobe, 50.8 ± 11.5 for the left lower lobe, and 88.9 ± 20.0 for both right and left upper lobes. The total number of activations for all three procedures was 193.7 ± 40.3 . Mean ($\pm$ SD) duration for each of the three treatment procedures was 76.6 ± 20.3 min for the first procedure, 69.6 ± 16.1 min for the second procedure, and 85.8 ± 24.5 min for the third procedure. Patients were discharged after improvement of airflow obstruction (to $>80\%$ of FEV₁ before procedure). Subjects were evaluated 4 weeks after the last BT procedure. Assessments of BT effectiveness and safety were completed at 1 and 12 months.

Statistical analyses were undertaken using SPSS Statistics version 17.0.0 software (IBM Japan, Tokyo, Japan). Differences between two groups were assessed using Pearson's χ^2 test, Student's t-test, or the Mann-Whitney U test, as appropriate.

References

1. Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J* 2014; 43:343-373.
2. FitzGerald M, Bateman ED, Boulet LP, Cruz AA, Inoue H, Haahtela T, et al. Global strategy for asthma management and prevention 2016 (update). (online) Available: <http://www.ginasthma.org>
3. Iikura M, Hojo M, Ro S, Shiozawa A, Takazawa I, Kobayashi K, et al. Technical description of bronchial thermoplasty in two Japanese severe persistent asthma patients. *JJSRE* 2015; 37:450-457.

Supplementary Table 1.

Comparison of effectiveness outcomes of BT between FEV1 subgroups.

	%FEV1 < 60% (n = 5)		%FEV1 ≥ 60% (n = 7)	
	Baseline	12 months	Baseline	12 months
%FEV1	50.4 ± 7.9	67.3 ± 22.9	84.8 ± 15.6	93.0 ± 14.1
AQLQ	4.4 ± 0.9	5.8 ± 1.4	5.2 ± 1.2	5.8 ± 1.3
ACQ-5	1.6 ± 1.2	0.7 ± 0.6	1.4 ± 0.8	1.0 ± 1.0
Exacerbations per year	6.0 ± 3.9	2.2 ± 3.3*	5.7 ± 6.4	1.9 ± 2.7

Unless otherwise indicated, values are presented as mean ± SD.

Statistical significance: * $p < 0.05$ compared to baseline.

AQLQ, Asthma-related Quality of Life Questionnaire.

ACQ, Asthma Control Questionnaire.