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Original Article

Clinical Characteristics of Severe Refractory Asthma Associated with the Effectiveness of Bronchial Thermoplasty

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We investigated the clinical characteristics of refractory asthma associated with the effectiveness of bronchial thermoplasty (BT). We retrospectively evaluated data from 10 patients who underwent BT between June 2016 and December 2017 at Okayama Medical Center. The following were measured before and 6 months post-BT: forced expiratory volume in 1.0 s (FEV_1), fractional exhaled nitric oxide (FeNO), immunoglobulin E (IgE) level, blood eosinophil counts (Eosi), Asthma Quality of Life Questionnaire (AQLQ) score, and preventive medication use. At baseline, the mean post-bronchodilator FEV_1 was 80.9% of the predicted value (range 45.6-115.7%). All patients were being treated with moderate- or high-dose inhaled corticosteroids and long-acting β2 agonists. The AQLQ improved from 4.26 ± 1.67 at baseline to 5.59 ± 0.94 at 6 months post-BT ($p < 0.05$). The $\%FEV_1$, FeNO, IgE, and Eosi did not change significantly between baseline and 6 months post-BT. No severe complications were reported. BT was effective for non-allergic and non-eosinophilic in 3 patients, and allergic or eosinophilic in 4 patients. Their AQLQ improved by > 0.5 points post-BT. For both allergic and eosinophilic asthmatics following mepolizumab, BT was not useful. BT was effective for non-allergic and non-eosinophilic or allergic asthmatics, but insufficient for both allergic and eosinophilic following mepolizumab.

Key words: bronchial thermoplasty, non-allergic asthma, non-eosinophilic asthma, airway hyper-responsiveness, patient selection

Three major trials have supported the efficiency of bronchial thermoplasty (BT) as a safe modality that improves the quality of life of patients with severe refractory asthma [1-3]. The U.S. Food and Drug Administration approved BT for the treatment of refractory asthma in 2010, and BT has been available in Japan since 2015 [4]. The BT procedure reduces the smooth muscle mass of peripheral sub-segmental airways by applying radiofrequency energy to large airways. As an add-on therapy, BT is an alternative to biologic therapies (such as omalizumab and mepolizumab) which can involve more costly pharmacotherapy [5]. There are still many unanswered questions about the selection and management of patients and the mechanism of action of BT, although reductions in airway smooth muscle and inflammation have been documented [6,7]. Here, we explored the clinical characteristics of patients with uncontrolled severe asthma that are associated with the effectiveness of BT.

Patients and Methods

Patients. We retrospectively evaluated the patients who underwent BT at the National Hospital Organization of Okayama Medical Center between June

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2016 and December 2017. The BT was performed in 10 consecutive patients with severe refractory asthma. Severe refractory asthma was defined according to the Global Initiative for Asthma (GINA) guideline [8]. The following outcomes were measured before and 6 months after the BT: forced expiratory volume in 1.0 s (FEV_1), fractional exhaled nitric oxide (FeNO), immunoglobulin E (IgE) level, blood eosinophil counts (Eosi), Asthma Quality of Life Questionnaire (AQLQ) score, and preventative medication use. The study protocol was approved by the Institutional Ethics Committee of the National Hospital Organization, Okayama Medical Center (approval no. H29-RINKEN-ZINSOKU-009).

Procedures. The BT procedure was performed using a flexible bronchoscope (BF-260; Olympus, Tokyo). All proceduralists had been trained in using the Alair bronchial thermoplasty system (Boston Scientific, Tokyo). The BT was performed under local and/or general anesthesia. Immediately before the procedure, an inhaled bronchodilator (0.5% salbutamol sulfate 0.3 ml or procaterol hydrochloride hydrate 20 μg) and an antisialagogue (atropine 0.25 mg intramuscularly) were administered. For local anesthesia, 2% (w/v) lidocaine with sedation drugs (midazolam plus fentanyl) was used. Patients were given prednisone 50mg/day for 3 days: the day before, the day of, and the day after the BT procedure. All patients were electively observed in-hospital for 24-48 h after the procedure.

The airways were treated on three separate sessions, each 3 weeks apart: the right lower lobe was treated in the first session, the left lower lobe in the second session, and both upper lobes in the final session. The number of radiofrequency activations, operating times, and adverse events were recorded for each treatment session.

Statistical analyses. Statistical analyses were performed using Microsoft Office Excel 2010 (Redmond, WA, USA). Between-group comparisons were made using the paired Student's *t*-test. A p-value < 0.05 was considered significant.

Results

Table 1 summarizes the baseline characteristics of the 10 patients with refractory asthma. The median age was 59 (range 27-74) years. The mean body mass index was 23.5 (range 19.8-26.8) kg/m^2. Eight patients were never-smokers, and two were ex-smokers. All patients were being treated with moderate- or high-dose inhaled corticosteroids and long-acting β2 agonists. Three patients (30%) were taking maintenance oral prednisolone at < 10 mg/day. Most of the patients also required at least one of the following: montelukast (100%), omalizumab (40%), and mepolizumab (20%). The mean baseline post-bronchodilator FEV_1 was 80.9% of the predicted value (range 45.6-115.7%); two patients (20%) had an FEV_1 of < 60% of the predicted value.

All 10 of the patients, 7 women and 3 men, completed the BT treatment and the 6-month follow-up (Table 2). Their AQLQ scores improved from 4.26 ± 1.67 at baseline to 5.59 ± 0.94 at 6 months post-BT ($p < 0.05$). Asthma exacerbations were also reduced significantly (baseline 6 months before BT 1.80 ± 1.81 vs. 6 months post-BT 0.4 ± 0.51; $p < 0.05$; values are the mean ± standard deviation [SD]), although the follow-up term was only 6 months. The $\%FEV_1$, FeNO, IgE, and Eosi values did not change significantly between baseline and 6 months post-BT.

Table 3 summarizes the $\%FEV_1$, BT technique, and adverse events following BT. The BT was performed under local anesthesia in 4 of the 10 patients, because the patients' baseline post-bronchodilator FEV_1 was > 60% of the predicted value. In 6 of the 10 patients, the BT was performed under local and/or general anesthesia because of deteriorating lung function and patient anxiety. For Patients 2, 7, and 9, due to a severe cough under local anesthesia in the first session, BT was performed under general anesthesia in the other sessions, uneventfully. No severe complication was seen following the BT.

Patient 1 was treated with systemic corticosteroids (125 mg of methylprednisolone sodium succinate) for wheezing, and Patient 3 was treated with antibiotics (2 g of ceftriaxone per day in the first session and 100 mg of sitafloxacin hydrate per day in the other sessions for 4 days) for bacterial pneumonia, but the adverse effects disappeared within 1 week. Table 4 summarizes the clinical characteristics of the 10 patients. Allergic predominant asthma is defined as positivity for at least one of the following: atopy factor and specific IgE antigen. Eosinophilic predominant asthma is defined as positivity for at least one of the following: blood eosinophils > 300 count/μL and mepolizumab therapy before BT [8].

BT was effective for non-allergic and non-eosino-

Table 1 Patient characteristics (n = 10)

Characteristic	Value (range)
Male/female, *n*	3/7
Median age (range), years	59 (27–74)
Mean height (range), cm	156.7 (145–169)
Mean weight (range), *n*	58.2 (44–75)
Mean body mass index (range)	23.5 (19.8–26.8)
Smoking status (never-smoker/ex-smoker), *n*	8/2
Nasal comorbidities, *n* (%)	2 (20)
Median peripheral eosinophils (range), count/μL	119 (0–660)
Median immunoglobulin E (range), IU/mL	94 (45–506)
GINA treatment step (4/5), *n*	2/8
Median exacerbations in previous 6 months (range), *n*	1 (0–5)
Median baseline AQLQ score	4.40 (1.93–5.96)
Mean FEV_1 (range), mL	1,995 (910–3,130)
Mean %FEV_1 (range), %	80.9 (45.6–115.7)
FEV_1 < 60% predicted, *n* (%)	2 (20)
Median FeNO (range), ppb	35 (8–125)
Systemic steroid use, *n* (%)	3 (30)
Omalizumab use, *n* (%)	4 (40)
Mepolizumab use, *n* (%)	2 (20)
Inhaled corticosteroids dose (moderate/high), *n*	2/8
LABA/LAMA/LTRA/theophylline use, *n*	10/5/10/6

GINA, Global Initiative for Asthma; AQLQ, Asthma Quality of Life Questionnaire; FEV_1, post-bronchodilator forced expiratory volume in 1.0 s; FeNO, fractional exhaled nitric oxide; LABA, long-acting beta agonists; LAMA, long-acting muscarinic receptor antagonist; LTRA, leukotriene receptor antagonist.

Table 2 Outcomes 6 months after bronchial thermoplasty (BT)

	Baseline	6 months after BT	*P*-value
Reduction in drugs used, *n* (%)	–	4 (40)	–
AQLQ	4.26 ± 1.67	5.59 ± 0.94	0.027*
Proportion with AQLQ change ≧ 0.5, *n* (%)	–	7 (70)	–
%FEV_1, %	80.9 ± 24.5	77.1 ± 25.5	0.39
FeNO, ppb	58.6 ± 39.1	59.1 ± 33.6	0.96
Immunoglobulin E, IU/mL	191.1 ± 174.2	146.7 ± 130.2	0.32
Peripheral eosinophils, count/μL	213.4 ± 244.1	407.7 ± 308.5	0.062

BT, bronchial thermoplasty; AQLQ, Asthma Quality of Life Questionnaire; FEV_1, post-bronchodilator forced expiratory volume in 1.0 s; FeNO, fractional exhaled nitric oxide.
*$P < 0.05$ was considered to reflect statistical significance. Between-group comparisons were made using the paired Student's *t*-test. Values are presented as the mean ± standard deviation (SD).

philic asthma in Patients 1, 5, and 6, but it was not sufficiently effective for both the allergic and eosinophilic asthma following mepolizumab in Patients 3 and 8. The cases of two representative patients for whom BT was beneficial are described below.

Patient 1. A 70-year-old woman presented with a 5-year history of refractory asthma. She had been characterized as a non-allergic, non-eosinophilic asthmatic (negative results for perennial inhalant allergen sensitivity, and her IgE and Eosi values before BT were 155 IU/mL and 110 count/μL, respectively. BT was performed before biological therapy selection. The patient's FEV_1 showed a tendency to improve, from 910 mL (%FEV_1 49.4%) to 1,450 mL (%FEV_1 82.4%) at 24 months post-T (Fig. 1).

Patient 2. Patient 2 was a 26-year-old woman who had a history of refractory asthma with a severe cough for 6 years. She had been treated with omali-

Table 3 The $\%FEV_1$ values, BT technique, and adverse events following BT

Patient	$\%FEV_1$, %	Anesthesia	Operating time (1/2/3), minutes	Activation times (1/2/3), *n*	Adverse events
1	$\%FEV_1 < 60\%$	General	27/32/34	42/40/59	Asthma attack
2	$\%FEV_1 \geqq 60\%$	Local and general	25/20/25	30/38/43	None
3	$\%FEV_1 < 60\%$	General	25/19/28	30/43/52	Atelectasis, pneumonia
4	$\%FEV_1 \geqq 60\%$	Local	16/21/15	17/33/27	None
5	$\%FEV_1 \geqq 60\%$	Local	20/30/30	30/38/43	None
6	$\%FEV_1 \geqq 60\%$	Local	25/18/35	25/24/40	None
7	$\%FEV_1 \geqq 60\%$	Local and general	46/55/48	58/38/85	None
8	$\%FEV_1 \geqq 60\%$	Local	20/20/30	20/30/56	None
9	$\%FEV_1 \geqq 60\%$	Local and general	20/20/32	30/30/52	None
10	$\%FEV_1 \geqq 60\%$	General	35/16/25	31/31/51	None

FEV_1, post-bronchodilator forced expiratory volume in 1.0 s.
The right lower lobe was treated in the first session, the left lower lobe in the second, and both upper lobes in the final session. No adverse events that required additional treatment occurred, although there was focal bronchitis, cough, local wheezing, and chest discomfort.

Table 4 Clinical characteristics of the patients who underwent BT

Patient	Clinical characteristics	Atopy factor, *n*	IgE, IU/mL	Specific IgE antigen, *n*	Blood eosinophils, count/μL	FeNO, ppb	Biological therapy before BT	AQLQ before BT after BT*
1	Non-allergic Non-eosinophilic	None	50	None	11	25	None	3.04 5.70
2	Allergic	1	45	2	119	8	Omalizumab	5.84 6.78
3	Allergic Eosinophilic	2	506	7	0	35	Mepolizumab	5.06 5.00
4	Eosinophilic	None	86	0	1,050	133	None	2.12 5.12
5	Non-allergic Non-eosinophilic	None	89	0	250	35	None	5.81 6.49
6	Non-allergic Non-eosinophilic	None	236	0	133	11	None	1.93 3.61
7	Allergic	2	94	1	0	25	Omalizumab	5.96 6.47
8	Allergic Eosinophilic	1	501	1	0	151	Mepolizumab	4.4 4.53
9	Allergic	None	171	4	280	88	Omalizumab	5.87 6.25
10	Allergic	1	133	3	291	75	Omalizumab	2.65 6.61

Allergic predominant asthma defines at least one positive followings: Atopy factor and specific IgE antigen. Eosinophilic predominant asthma defines at least one positive followings: Blood eosinophils > 300 count/μL and mepolizumab therapy before BT.
FEV_1, post-bronchodilator forced expiratory volume in 1.0 s; IgE, Immunoglobulin E; FeNO, fractional exhaled nitric oxide; BT, bronchial thermoplasty; AQLQ, Asthma Quality of Life Questionnaire.
*6 months after bronchial thermoplasty.

zumab for 2 years, and she had been characterized as an allergic asthmatic (positive results for perennial inhalant allergen sensitivity; her IgE value before BT was 45 IU/mL). The omalizumab became unnecessary at 6 months post-BT (Fig. 2).

Discussion

In randomized clinical trials, bronchial thermoplasty was shown to be a safe, effective additional modality for the management of patients with poorly controlled asthma despite standard therapy [1-3]. In our present study, the results of asthma control resembled those of the above-cited trials (Table 2). A notable improvement in FEV_1 was observed in Patient 1. Her FEV_1 improved from 910 mL (%FEV_1 49.4%) to 1,450 mL (%FEV_1 82.4%) at 24 months after the procedure (Fig. 1). In her case, BT was performed before biological therapy selection because the patient was a non-allergic, non-eosinophilic asthmatic (negative results for perennial inhalant allergen sensitivity; pre-BT IgE and Eosi were 155 IU/mL and 110 count/μL, respectively). Other research groups have reported post-BT improvements in FEV_1 [2,9]. Langton *et al.* showed that some asthmatic patients with a predicted baseline FEV_1 <60% showed a significantly improved FEV_1 after BT [10]. In the present study, BT was useful for non-allergic and non-eosinophilic asthma in Patients 1, 5, and 6, although in Patients 5 and 6 the %FEV_1 values did not tend to change between baseline and 6 months post-BT. A further prospective study would be of interest.

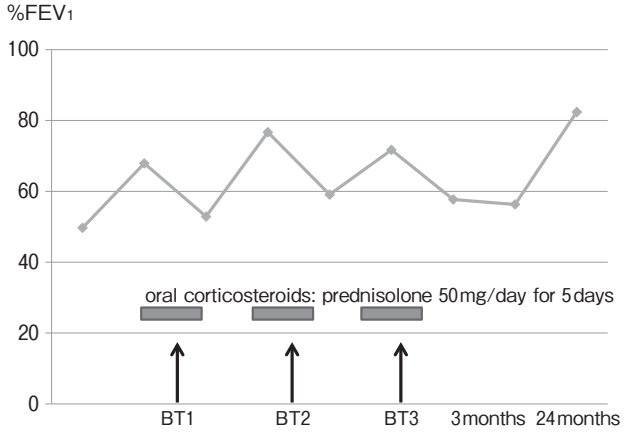

Fig. 1 Time course of %FEV_1 values in Patient 1. The pulmonary function showed a tendency to improve at 24 months after BT. The patient was given prednisone 50 mg/day for 3 days: the day before, the day of, and the day after the procedure. %FEV_1, % post-bronchodilator forced expiratory volume in 1.0 s; BT, Bronchial thermoplasty.

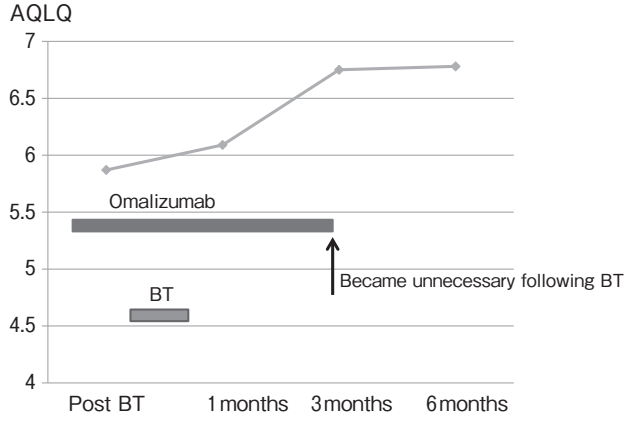

Fig. 2 Time course of the AQLQ scores in Patient 2. Omalizumab became unnecessary at 6 months post-BT. AQLQ, Asthma Quality of Life Questionnaire; BT, Bronchial thermoplasty.

Moreover, an allergic asthma patient with refractory cough (Patient 2) improved following BT, and omalizumab became unnecessary following the procedure (Fig. 2). BT is an alternative to biologic therapies that may involve more costly pharmacotherapy [5]. Another clinical trial suggested that BT is indicated when severe airway hyper-responsiveness and frequent exacerbations persist despite absent or controlled airway inflammation [11]. Kanemitsu *et al.* recently reported a marked improvement of severe refractory cough by BT [12]. Patients whose symptoms might be driven largely by airway hyper-responsiveness might benefit from smooth muscle-directed therapies, such as bronchial thermoplasty. In this report, we did not evaluate the cough response to capsaicin. Moreover, BT was not effective for both allergic and eosinophilic asthma following mepolizumab in Patients 3 and 8 (Table 4). A large-scale trial is required to test the hypothesis that BT is not effective for both allergic and eosinophilic asthma.

Bronchial thermoplasty has been available in Japan since 2015 [4]. The mechanism of action is uncertain, but it is known that BT reduces airway smooth muscle mass via the delivery of localized thermal energy [2]. Additional mechanisms of action may contribute to symptom reduction, including structural effects on neuroendocrine epithelial cells and bronchial nerve

endings [13]. Future studies will help to define these mechanisms [14]. The anesthetic management strategies for BT are also poorly described, although BT is often performed under local anesthesia in Japan. Aizawa showed the feasibility and safety of general anesthesia for bronchial thermoplasty in Japanese patients [15]. In our patients, BT was performed under general anesthesia in the second and third sessions uneventfully for Patients 2, 7, and 9; the general anesthesia was used because of the patients' severe cough under local anesthesia in the first session. It is unclear whether general anesthesia is preferable to topical (venous) anesthesia in such patients due to an increased risk of CO_2 narcosis and complications such as severe atelectasis and pneumonia [16]. A further large-scale study is needed to clarify this point.

One limitation of our study is that it was a small retrospective analysis. As the use of BT in clinical practice continues to increase in Japan, it will be necessary to create a large clinical dataset to establish the efficiency, safety, and adaptability of BT.

In conclusion, bronchial thermoplasty was effective for non-allergic and non-eosinophilic or allergic asthmatics, but it was insufficient for both allergic and eosinophilic asthma following mepolizumab treatment. The BT procedure might improve asthmatics' clinical condition by a mechanism different from those involving eosinophils and atopy factor.

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