Bronchial Thermoplasty Induced Airway Smooth Muscle Reduction and Clinical Response in Severe Asthma

TASMA research group; Goorsenberg, Annika W M; d'Hooghe, Julia N S; Srikanthan, Karthikan; Ten Hacken, Nick H T; Weersink, Els J M; Roelofs, Joris J T H; Kemp, Samuel V; Bel, Elisabeth H; Shah, Pallav L

Published in:
American Journal of Respiratory and Critical Care Medicine

DOI:
10.1164/rccm.201911-2298OC

ORIGINAL ARTICLE

Bronchial Thermoplasty Induced Airway Smooth Muscle Reduction and Clinical Response in Severe Asthma

The TASMA Randomized Trial

Annika W. M. Goorsenberg[1*], Julia N. S. d'Hooghe[1*], Karthikan Srikanthan[2], Nick H. T. ten Hacken[3], Els J. M. Weersink[1], Joris J. T. H. Roelofs[4], Samuel V. Kemp[2,5], Elisabeth H. Bel[1], Pallav L. Shah[2,5,6], Jouke T. Annema[1‡], and Peter I. Bonta[1‡]; on behalf of the TASMA Research Group

[1]Department of Respiratory Medicine and [4]Department of Pathology, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands; [2]Department of Respiratory Medicine, Royal Brompton Hospital, London, United Kingdom; [3]Department of Pulmonology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands; [5]National Heart & Lung Institute, Imperial College, London, United Kingdom; and [6]Department of Pulmonology, Chelsea & Westminster Hospital, London, United Kingdom

ORCID ID: 0000-0002-9052-4638 (P.L.S.).

Abstract

Rationale: Bronchial thermoplasty (BT) is a bronchoscopic treatment for severe asthma targeting airway smooth muscle (ASM). Observational studies have shown ASM mass reduction after BT, but appropriate control groups are lacking. Furthermore, as treatment response is variable, identifying optimal candidates for BT treatment is important.

Objectives: First, to assess the effect of BT on ASM mass, and second, to identify patient characteristics that correlate with BT response.

Methods: Patients with severe asthma ($n = 40$) were randomized to immediate ($n = 20$) or delayed ($n = 20$) BT treatment. Before randomization, clinical, functional, blood, and airway biopsy data were collected. In the delayed control group, reassessment, including biopsies, was performed after 6 months of standard clinical care, followed by BT. In both groups, post-BT data including biopsies were obtained after 6 months. ASM mass (% positive desmin or α-smooth muscle actin area in the total biopsy) was calculated with automated digital analysis software. Associations between baseline characteristics and Asthma Control Questionnaire and Asthma Quality of Life Questionnaire (AQLQ) improvement were explored.

Measurements and Main Results: Median ASM mass decreased by >50% in the immediate BT group ($n = 17$) versus no change in the delayed control group ($n = 19$) ($P = 0.0004$). In the immediate group, Asthma Control Questionnaire scores improved with −0.79 (interquartile range [IQR], −1.61 to 0.02) compared with 0.09 (IQR, −0.25 to 1.17) in the delayed group ($P = 0.006$). AQLQ scores improved with 0.83 (IQR, −0.15 to 1.69) versus −0.02 (IQR, −0.77 to 0.75) ($P = 0.04$). Treatment response in the total group ($n = 35$) was positively associated with serum IgE and eosinophils but not with baseline ASM mass.

Conclusions: ASM mass significantly decreases after BT when compared with a randomized non–BT-treated control group. Treatment response was associated with serum IgE and eosinophil levels but not with ASM mass.

Keywords: severe asthma; bronchial thermoplasty; airway smooth muscle; airway remodeling

(Received in original form November 29, 2019; accepted in final form July 28, 2020)

*These authors contributed equally to this work.

‡Share last authorship.

TASMA Research Group: C. Caneja, J. Hartman, S. Augustijn, M. van de Pol, S. Lone-Latif, O. de Boer, and T. Dirksen.

The TASMA study is funded by the Dutch Lung Foundation (grant number 5.2.13.064JO), the Netherlands Organization for Health Research and Development (ZonMw) (grant number 90713477), and Boston Scientific.

Author Contributions: A.W.M.G. and J.N.S.d'H. contributed to the acquisition, analysis, and interpretation of the data and drafting the manuscript. K.S., E.J.M.W., and S.V.K. contributed to the acquisition and interpretation of the data. J.J.T.H.R. contributed to the acquisition and analysis of the data. N.H.T.t.H., E.H.B., P.L.S., J.T.A., and P.I.B. contributed to the conception and design of the study and the acquisition and interpretation of the data. All authors critically revised and approved the final version of the manuscript.

Correspondence and requests for reprints should be addressed to Peter I. Bonta, M.D., Ph.D., Department of Respiratory Medicine, F5-144, Amsterdam UMC, University of Amsterdam, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands. E-mail: p.i.bonta@amsterdamumc.nl.

This article has a related editorial.

This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org.

Am J Respir Crit Care Med Vol 203, Iss 2, pp 175–184, Jan 15, 2021

Originally Published in Press as DOI: 10.1164/rccm.201911-2298OC on July 28, 2020
Internet address: www.atsjournals.org

At a Glance Commentary

Scientific Knowledge on the Subject: Bronchial thermoplasty (BT) is an endoscopic treatment for patients with severe asthma that uses radiofrequency energy to target airway wall remodeling. Observational studies have shown a decrease of airway smooth muscle (ASM) mass after treatment, but appropriate control groups are lacking and the responder profile is unclear.

What This Study Adds to the Field: This is the first randomized controlled trial reporting a reduction of ASM mass after BT treatment when compared with a nontreated control group. Clinically relevant improvements in Asthma Quality of Life Questionnaire and Asthma Control Questionnaire after BT were reported, but this treatment response was not associated with baseline or a reduction of ASM mass. However, baseline serum IgE and eosinophils were significantly associated with response, thereby adding important information to patient candidate selection for BT treatment.

Severe asthma is a disease characterized by persistent symptoms and frequent exacerbations despite optimal treatment with high doses of inhaled corticosteroids and long-acting bronchodilators (1, 2). Although only approximately 5% of patients with asthma fulfill the criteria for a diagnosis of severe asthma (3), the burden on healthcare costs is high owing to medication use and frequent hospitalizations (4, 5). Recent advances in treatment options for patients with severe asthma are the implementation of biologicals for specific asthma phenotypes such as anti-IgE treatment for allergic asthma and anti–IL-5 treatment for eosinophilic asthma (6–8). However, not all patients tolerate and/or respond to these treatments, and for nonallergic and noneosinophilic asthma phenotypes, no specific biological treatment is available. Bronchial thermoplasty (BT) is an endoscopic treatment, targeting airway smooth muscle (ASM) by heating the medium to larger-sized airways with radiofrequency energy (9). Observational studies have shown a reduction in ASM mass after BT; however, appropriate control groups are lacking and a relationship with treatment response is not clear (10–13). Although clinical studies have shown improvements in asthma control and quality of life and a reduction in exacerbation rate (14–17), not all patients respond equally well to BT. Identification of clinical and physiological characteristics associated with BT response is needed to optimize patient selection and further elucidate the mechanism of action of this treatment. In this study, we aimed to assess the effect of BT on ASM mass in the airways of patients with severe asthma using a randomized controlled design and the untreated right middle lobe (RML). Secondary outcomes included the evaluation of patient characteristics and biomarkers associated with BT response. Some of the results of this study have been previously reported in the form of abstracts (18–22).

Methods

Study Design

This study is an investigator-initiated, international multicenter randomized controlled trial (Clinical trials.gov NCT02225392). Patients were recruited between 2014 and 2018 in two centers in the Netherlands (Amsterdam University Medical Centers, location Academic Medical Center and University Medical Center in Groningen) and two centers in the United Kingdom (Royal Brompton Hospital and the Chelsea and Westminster Hospital, both in London). After informed consent, patients were screened and characterized using demographic data, medical history including exacerbation rate, asthma questionnaires, routine blood analysis including eosinophils and allergy tests, routine pulmonary function tests, methacholine challenge (PC20) tests, and a bronchoscopy for the detection of airway abnormalities and measurement of baseline airway smooth muscle mass in bronchial biopsies. After the bronchoscopy, patients were randomized into an immediate BT treatment group and a 6 months delayed treatment group, the control group. Additional visits, similar to those during screening, were scheduled for the delayed group after 6 months of standard clinical care, including a research bronchoscopy with endobronchial biopsy sampling. In both randomization groups, patients were in follow-up for 6 months after BT treatment, after which clinical and functional assessments, blood tests, and endobronchial biopsies were collected. Directly after each research bronchoscopy, patients were treated with 50 mg of prednisolone for 3 days. Asthma medication remained unchanged during the complete study period. The study design is shown in Figure 1.

Randomization and Sample Size Calculation

Patients were randomized into an immediate BT treatment and 6 months delayed BT treatment control group (1:1 ratio, $n = 20$ per group). Stratification factors used in the randomization were FEV_1 lower or higher than 70% of predicted value and eosinophil counts (in sputum $<$ or $\geq$3% or when sputum was not available in blood $<$ or $\geq 0.3 \times 10^9$/L). Power calculation for the primary endpoint was based on an estimated decrease of 20% in ASM mass after treatment and determined as 18 patients per group (23). Accounting for a 10% dropout rate, we aimed to include 20 patients per group, 40 patients in total.

Subjects

Patients with severe asthma between 18 and 65 years old, fulfilling the World Health Organization or modified Innovative Medicines Initiative criteria, were included (1, 24). *See* the online supplement for a detailed description of the definition of severe asthma. The diagnosis of asthma needed to be confirmed in the 5 years before inclusion by one of the following parameters: reversibility to β2-agonists in FEV_1 of $\geq$12% predicted and $\geq$200 ml, bronchial hyperresponsiveness to methacholine or histamine (PC20 $<$ 4 mg/ml), peak-flow variability of $>$20% over a 2-week period, or a fall in FEV_1 of $>$12% predicted and $>$200 ml after tapering down asthma treatment. Ethical approval was provided by the ethical committees of the four centers, and informed consent was obtained from all patients. The main exclusion criteria were prebronchodilator FEV_1 $<$50% predicted or $<$1.2 L, five or more hospitalizations in the year before inclusion or more than one intensive care admission for asthma requiring endotracheal intubation, oral corticosteroid

maintenance therapy of more than 20 mg/d, asthma exacerbation or a respiratory tract infection in the prior 4 weeks, unable to undergo multiple bronchoscopies because of allergies to the required medications, or comorbidities. Additionally, patients with body mass index ⩾35, those with relevant abnormalities on a high-resolution computed tomography scan, or current smokers and a pack-year history of more than 15 years were excluded from participating in this trial.

BT Treatment

Treatment procedures were performed according to current guidelines (25) with the Alair System (Boston Scientific) using general anesthesia or conscious sedation (remifentanil and propofol) (26). Treatment sessions of the right lower lobe, left lower lobe, and both upper lobes were performed with at least a 3-week interval between procedures. The RML remained untreated. Patients were treated with 50 mg of prednisolone 3 days before the treatment, during the procedure, and 1 day thereafter.

Response Assessment

Clinical response to BT was measured with asthma control questionnaires (ACQ-6) and asthma quality of life questionnaires (AQLQ) 6 months after BT. In addition, asthma exacerbations, defined as the need to increase the dose of systemic corticosteroids or a doubling dose of inhaled corticosteroids for more than 3 consecutive days, were assessed during the complete study period. Exacerbations after BT treatment were calculated from 6 weeks after the last treatment until the follow-up visit at 6 months and defined as exacerbation rate per 6 months. FEV_1, reversibility (post-salbutamol $FEV_{1\%}$ predicted minus pre-salbutamol $FEV_{1\%}$ predicted), and methacholine challenge tests were also evaluated after treatment.

Histology Processing and Analysis

Endobronchial biopsies were obtained with large cup forceps of predefined (sub) segmental airway carinas. During the research bronchoscopies before treatment, four biopsies were obtained. During the bronchoscopy after treatment, six biopsies were taken, including two biopsies (one segmental and one subsegmental) from the untreated RML. Biopsies were paraffin embedded, sectioned, attached to glass slides, and stained for ASM-specific desmin (clone-33; BioGenes GmbH) and α-smooth muscle actin (α-SMA) (clone 1A4; DAKO). From each biopsy, the two biopsy sections with the highest total surface area were included in the analysis and blindly measured, using automated digital image analysis software (ImageJ, NIH) (27). Sections without epithelium or mucosal layer or with artifacts were excluded from the analysis. ASM mass was measured as the percentage of positive stained desmin or α-SMA area as compared with the total biopsy area as previously described (11).

Study Endpoints

The primary endpoint of this study was the absolute difference in ASM change between the direct BT treatment group and the delayed control group (post-BT ASM% minus pre-BT ASM% in the direct group vs. delayed group ASM% at control visit minus pre-BT ASM%) (Figure 1). Secondary endpoints are the ASM mass change after BT in the total group and in the untreated RML. Additionally, response to BT was evaluated using ACQ-6 and AQLQ scores after BT, exacerbation rates, and lung function parameters. Associations between response to BT, as assessed with ACQ-6 and AQLQ questionnaires, and baseline patient characteristics were analyzed. Additional hypothesis-generating exploratory endpoints as mentioned on clinicaltrials.gov are not included in this manuscript because these research questions were investigated in one center only and need separate analysis (28).

Statistical Analysis

Statistical analyses were performed in GraphPad Prism version 5.01 (GraphPad Software Inc) or IBM SPSS Statistics version 25.0. Demographic parameters were provided as mean with SD or median with interquartile ranges. Mann-Whitney *U* tests were performed to assess the difference in change from baseline between the immediate group, 6 months after BT, and the delayed treatment group, 6 months after standard clinical care. The effect of BT in the total group of patients was calculated with paired *t* tests or Wilcoxon signed rank test. The Hodges-Lehman estimator (29) with 95% confidence interval is used to calculate median differences to quantify treatment effects (Rstudio Version 1.2.1335). Spearman rank correlation was used to explore associations between patient characteristics and ACQ or AQLQ change. An improvement of >0.5 points on ACQ-6 or AQLQ scores was considered clinically relevant (30, 31). Two-sided *P* values were used with a statistical significance at $P < 0.05$.

Results

Subjects

A total of 54 patients were screened for eligibility, and 14 patients were excluded. Reasons for exclusion were declining to participate ($n = 5$), negative methacholine challenge tests (PC20 < 4 mg/ml) ($n = 6$), prebronchodilator FEV_1 below 50% of predicted ($n = 2$), and age ($n = 1$). After screening, 40 patients were randomized between immediate and delayed BT treatment (Figure 1). Baseline demographic and clinical characteristics between both randomization groups were well matched except for a slightly higher ACQ score in the immediate treatment group (Table 1).

Procedural BT Information and Safety

A mean of 66 (±29) radiofrequency activations were given in the right lower lobe, 62 (±17) activations in the left lower lobe, and 98 (±42) activations in both upper lobes. No device-related complications occurred. After 43 of the 119 BT procedures (36%), patients experienced an asthma exacerbation. These exacerbations were all successfully treated with conventional asthma medication such as oral corticosteroids and nebulized bronchodilators. Patients required hospitalization following nine of these exacerbations with a median length of hospital stay of 4 days (interquartile range [IQR], 1–7). Other reported pulmonary adverse events were chest pain or discomfort (12%), dyspnea (15%), (productive) cough (16%), hemoptysis (7%), common cold (1%), bronchitis or sinusitis (3%), fever (1%), and lower respiratory tract infection (3%).

Clinical Effectiveness

Changes from baseline in asthma questionnaires were significantly different between the immediate BT group 6 months after treatment and the delayed group 6 months after standard clinical care (Table 2). In the immediate BT-treatment group, ACQ scores improved with −0.79 (IQR, −1.61 to 0.02), whereas in the delayed group, a difference of 0.09 (IQR,

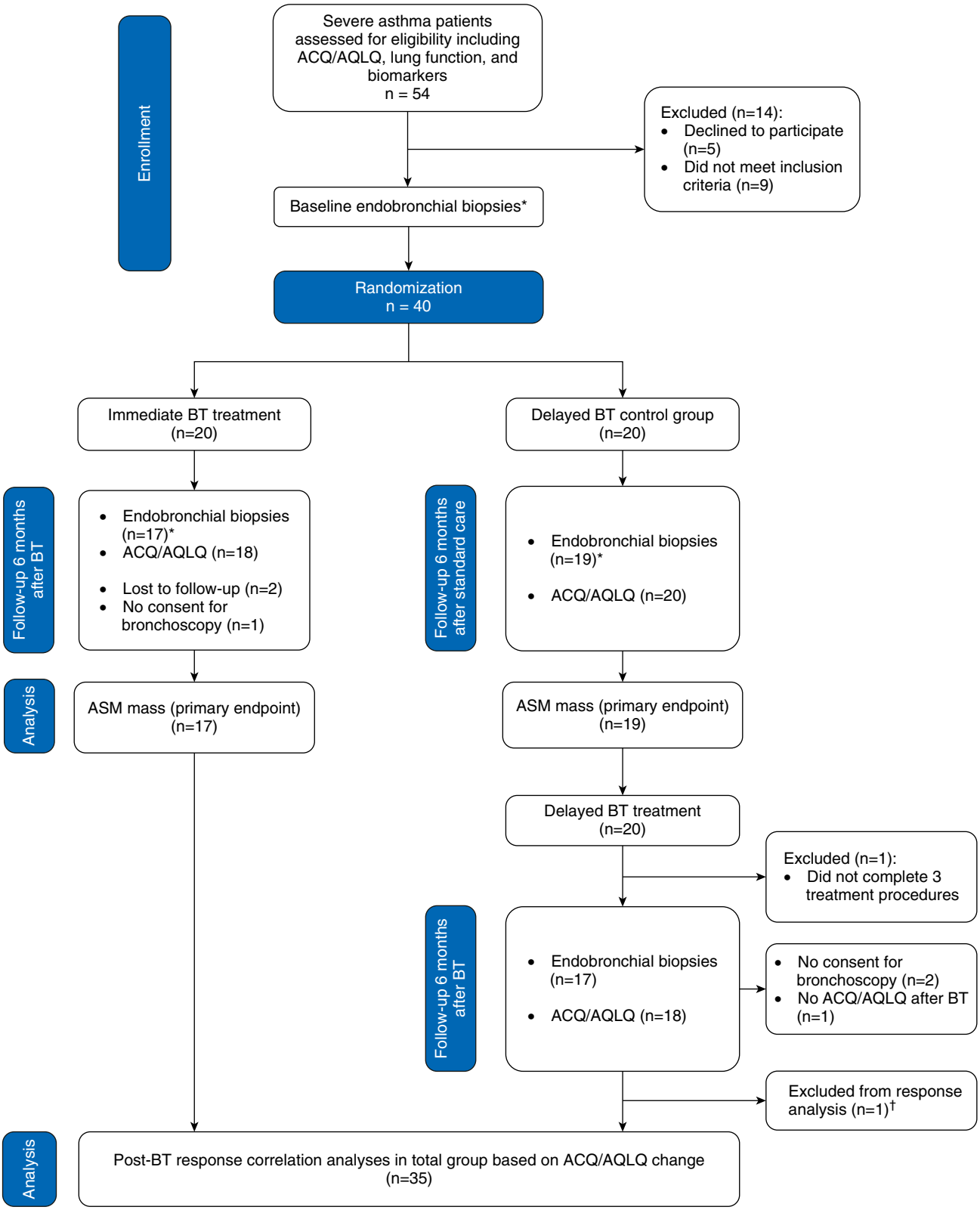

Figure 1. Flowchart of study design and participants (adapted from CONSORT [Consolidated Standards of Reporting Trials]). The primary endpoint of this study is the comparison between the change in ASM mass after BT in the immediate BT treatment group and the change in the delayed BT treatment group after 6 months of standard clinical care. Time points of primary endpoint data collection are highlighted with an asterisk (*). Response analysis was performed in the total group ($n = 35$) of patients in which ACQ and AQLQ were collected 6 months after BT. †Excluded from response analysis because this patient started anti–IL-5 treatment during follow-up. ACQ = Asthma Control Questionnaire; AQLQ = Asthma Quality of Life Questionnaire; ASM = airway smooth muscle; BT = bronchial thermoplasty.

Table 1. Baseline Characteristics

Characteristics	Immediate BT Group (*n* = 20)	Delayed Control Group (*n* = 20)
Sex, M/F, *n*	3/17	8/12
Age, yr	45 ± 14	46 ± 10
Age of asthma onset, yr	20 ± 18	21 ± 14
BMI, kg/m^2	29 ± 4	27 ± 5
Patients with a history of smoking, pack-years, *n* (mean ± SD)	4 (9 ± 5)	10 (8 ± 9)
Medication		
Dose of LABA, μg/d salmeterol equivalents	140 ± 81	146 ± 61
Dose of ICS, μg/d fluticasone equivalents	1,038 ± 609	1,159 ± 592
Patients on maintenance use of OCS (dose in mg/d), *n* (mean ± SD)	4 (9.3 ± 1.5)	6 (15 ± 6.3)
Patients on omalizumab, *n*	2	3
Asthma control		
Exacerbation rate/6 mo	1.25 (0.5–4.5)	2.0 (1.5–3.0)
ACQ-6 score	2.97 ± 0.62	2.53 ± 0.66
AQLQ score	3.74 ± 0.91	4.18 ± 1.01
Total serum IgE, kU/L	117 (35–210)	43.2 (9.9–106)
Blood eosinophil count, 10^9/L	0.15 (0.06–0.34)	0.11 (0.06–0.29)
Lung function		
Pre-BD FEV_1, % predicted	80.9 ± 20	85 ± 27
Post-BD FEV_1, % predicted	91.7 ± 20	100 ± 23
Reversibility FEV_1, %	8.5 (4.0–12.8)	12 (7.0–23.0)
PC_{20}, mg/ml	0.24 (0.03–2.91)	0.20 (0.03–2.83)
F_{ENO}, ppb	14.5 (9.5–59.5) (*n* = 15)	23.8 (13.5–45) (*n* = 12)
ASM mass assessed with desmin staining, %	7.99 (5.6–11.9)	7.14 (5.5–10.5)
ASM mass assessed with α-SMA staining, %	19.69 (15.8–23.9)	18.68 (13.7–23.3)

Definition of abbreviations: α-SMA = α smooth muscle actin; ACQ = Asthma Control Questionnaire; AQLQ = Asthma Quality of Life Questionnaire; ASM = airway smooth muscle; BD = short-acting bronchodilation; BMI = body mass index; BT = bronchial thermoplasty; F_{ENO} = fractional exhaled nitric oxide; ICS = inhaled corticosteroids; IgE = total IgE; LABA = long-acting β_2-agonist; OCS = oral corticosteroids; PC_{20} = methacholine provocation test. Data are presented as mean ± SD or median (interquartile range) unless otherwise noted.

−0.25 to 1.17) was found (median difference, −1.08; 95% confidence interval [95% CI], −1.75 to −0.33; $P = 0.006$). AQLQ improved in the immediate BT-treatment group with 0.83 (IQR, −0.15 to 1.69) in comparison with −0.02 (IQR, −0.77 to 0.75) in the delayed group (median difference, 0.81; 95% CI, 0.06 to 1.75; $P = 0.04$). No significant differences were found in changes in fractional exhaled nitric oxide, pre–short-acting bronchodilator FEV_1 (% predicted), and FEV_1 reversibility. A nonsignificant change of PC20 values after BT was found in the immediate BT group (0.19 [IQR, 0.00 to 0.85]) as compared with the non–BT-treated delayed group (0.0 [IQR, −0.03 to 0.43]) (median difference, 0.09; 95% CI, −0.18 to 0.64; $P = 0.08$). Asthma maintenance medication remained unchanged in both groups as requested during the study period.

In the total group of patients that completed the three BT procedures and clinical follow-up ($n = 35$), ACQ scores improved from 2.67 (±0.64) to 2.00 (±1.05) ($P = 0.0005$) and AQLQ scores improved from 3.99 (±1.00) to 4.73 (±1.24) ($P = 0.0023$). Twenty-one of the 35 patients (60%) showed a clinically meaningful improvement of more than 0.5 points on ACQ or AQLQ questionnaires (30, 31). In addition, exacerbation rates per half year declined from 1.5 (IQR, 1.0–3.0) before treatment to 0 (IQR, 0–1) after treatment ($P < 0.0001$). FEV_1 (% predicted) before short-acting bronchodilation did not significantly change after BT (83% [±25] before BT vs. 87% [±24] after BT; $P = 0.14$), whereas reversibility declined from 10.5 (IQR, 4–16) before BT versus 3.5 (IQR, 2–14) after BT ($P = 0.03$) ($n = 32$). Bronchial hyperresponsiveness, assessed with methacholine challenge tests, did not significantly change (0.25 mg/ml [IQR, 0.03–2.42] before BT vs. 0.42 mg/ml [IQR, 0.04–4.0] after BT; $n = 29$; $P = 0.11$) (Table 3). Median differences in these clinical parameters in the total group of patients are shown in Table 3.

Primary Endpoint

In the direct treatment group ($n = 17$), desmin-positive ASM mass decreased by 53% from 8.75% (IQR, 5.25 to 12.0) to 4.14% (IQR, 2.73 to 6.29) ($P = 0.0015$), whereas in the delayed group ($n = 19$), ASM mass did not change: 7.08% (IQR, 5.40 to 9.98) at randomization to 7.56% (IQR, 5.53 to 10.44) after 6 months of standard care ($P = 0.43$) (Figures 2 and 3A and 3B). The absolute change in desmin-positive ASM mass % between both randomization groups was significantly different: −4.44 (IQR, −8.3 to −1.02) in the direct treatment group versus 0.62 (IQR, −2.30 to 3.41) in the delayed control group (median difference, −5.0; 95% CI, −7.88 to −2.56; $P = 0.0004$) (Figure 3C). For α-SMA–positive ASM mass, similar results were found (Figure E1 in the online supplement).

Secondary Endpoints

ASM mass in the total group after BT. BT reduced ASM mass in the total group ($n = 34$) from 8.6% (IQR, 5.3 to 11.6) before BT to 4.02% (IQR, 2.7 to 5.8) after BT, with a median difference of −4.07% (95% CI, −2.49 to −5.78; $P < 0.0001$). A difference

Table 2. Immediate BT Treatment Group and Delayed Control Group Changes after 6 Months

Characteristics	Immediate Treatment Group (*n* = 18)			Delayed BT Control Group (*n* = 20)			*P* Value
	At Inclusion	6 mo after BT	Change	At Inclusion	After 6 mo Standard Care	Change	
ACQ-6 score	2.97 ± 0.62	2.13 ± 1.13	−0.79 (−1.61 to 0.02)	2.53 ± 0.66	2.86 ± 0.92	0.09 (−0.25 to 1.17)	0.006*
AQLQ score	3.74 ± 0.91	4.63 ± 1.05	0.83 (−0.15 to 1.69)	4.18 ± 1.0	4.06 ± 0.96	−0.02 (−0.77 to 0.75)	0.04*
Dose of LABA, μg/d salmeterol equivalents	127.7 ± 56.0	127.7 ± 56.0	—	143.4 ± 57.1	140.9 ± 50.6	0 (0 to 0)	—
Dose of ICS, μg/d fluticasone equivalents	1,069 ± 629	1,097 ± 613	0 (0 to 0)	1,209 ± 660	1,209 ± 660	—	—
Patients on maintenance use of OCS (dose in mg/d), *n* (mean ± SD)	3 (9.2 ± 1.4)	2 (8.8 ± 1.8)	0 (0 to 0)	6 (15.0 ± 6.3)	7 (14.3 ± 6.1)	0 (0 to 0)	0.17
Prebronchodilator FEV_1, % predicted	80.9 ± 20.1	82.1 ± 23.4	4.5 (−2.0 to 8.0)	85.5 ± 27 (*n* = 19)	86.0 ± 26 (*n* = 19)	−1.0 (−7.25 to 7.25) (*n* = 19)	0.26
Reversibility FEV_1, %	8.5 (4.0 to 12.8)	3.0 (2.0 to 13.5)	−2.0 (−7.75 to 1.25)	12.0 (7 to 23) (*n* = 19)	13.0 (4 to 21) (*n* = 19)	1.0 (−5.25 to 9.25) (*n* = 19)	0.19
PC_{20}, mg/ml†	0.24 (0.03 to 2.91)	1.33 (0.06 to 4.0)	0.18 (0.0 to 0.85)	0.20 (0.03 to 2.83) (*n* = 18)	0.09 (0.03 to 2.60) (*n* = 18)	0.0 (−0.03 to 0.43) (*n* = 18)	0.08
FE_{NO}, ppb	14.5 (9.5 to 59.5) (*n* = 14)	18.0 (11.3 to 40.0) (*n* = 14)	−0.50 (−3.38 to 7.38) (*n* = 14)	23.8 (13.5 to 45.0) (*n* = 12)	25.0 (15.3 to 46.5) (*n* = 12)	1.75 (−5.38 to 12.0) (*n* = 12)	0.60

Definition of abbreviations: ACQ = Asthma Control Questionnaire; AQLQ = Asthma Quality of Life Questionnaire; BT = bronchial thermoplasty; FE_{NO} = fractional exhaled nitric oxide; ICS = inhaled corticosteroids; LABA = long-acting β_2-agonist; OCS = oral corticosteroids; PC_{20} = methacholine provocation test.

Data are presented as mean ± SD or median (interquartile range) unless otherwise noted. Differences in change from baseline between both groups were analyzed using Mann-Whitney *U* test. Median changes within groups are shown.

*Significant difference with $P < 0.05$. Medication use needed to be stable during the entire study period including follow-up.

†Values were log-transformed for statistical analysis.

Table 3. Clinical Characteristics before and after BT in the Total Group ($n = 35$)

Characteristics	Before BT	After BT	Median Difference (95% CI)	*P* Value
ACQ-6 score	2.67 ± 0.64	2.00 ± 1.05	−0.67 (−0.17 to −1.17)	0.0005*
AQLQ score	3.99 ± 1.00	4.73 ± 1.24	0.85 (0.19 to 1.41)	0.0023*
Exacerbation rate/6 mo	1.5 (1.0 to 3.0)	0 (0 to 1)	−1.0 (−0.50 to −1.50)	<0.0001*
Pre–short-acting bronchodilator FEV_1, % predicted†	83 ± 25	87 ± 24	4.00 (−10.00 to 16.00)	0.14
Reversibility FEV_1, %†	10.5 (4 to 16)	3.5 (2 to 14)	−5.00 (-6.61×10^{-6} to −8.00)	0.03*
PC_{20}, mg/ml‡	0.25 (0.03 to 2.42)	0.42 (0.04 to 4.0)	0.02 (−0.18 to 1.12)	0.11
ASM mass desmin, %§	8.6 (5.3 to 11.6)	4.0 (2.7 to 5.8)	−4.07 (−2.49 to −5.78)	<0.0001*
ASM mass α-SMA, %§	19.5 (15.9 to 23.9)	11.8 (8.9 to 13.9)	−7.54 (−5.07 to −10.09)	<0.0001*

Definition of abbreviations: α-SMA = α smooth muscle actin; ACQ = Asthma Control Questionnaire; AQLQ = Asthma Quality of Life Questionnaire; ASM = airway smooth muscle mass; BT = bronchial thermoplasty; CI = confidence interval; PC_{20} = methacholine provocation test.
Within-group analyses performed with paired *t* tests or Wilcoxon signed rank test depending on the distribution of the variables. Median differences with 95% CIs are calculated using the Hodges-Lehmann estimator. Data are presented as mean ± SD or median (interquartile range) unless otherwise noted.
*Significant difference with $P < 0.05$.
†Data available in $n = 32$.
‡Values were log-transformed for statistical analysis and not available in six patients because of the inability to withhold asthma medications for the methacholine challenge test.
§Data available in $n = 34$.

between pre-BT ASM mass and the untreated post-BT RML ($n = 33$) was also found: ASM mass at baseline was 8.2% (IQR, 5.5 to 11.4) compared with 5.4% (IQR, 3.7 to 8.2) in the untreated RML (median difference, −2.31; 95% CI, −0.63 to −4.20; $P = 0.0024$). In addition, post-BT ASM mass in the treated areas (4.14% [IQR, 2.7 to 5.8]) was different when compared with the untreated RML (5.4% [IQR, 3.7 to 8.2]) (median difference, 1.35; 95% CI, 0.11 to 2.66; $P = 0.0012$) (Figure 4A). When dividing the untreated RML biopsies in subsegmental ($n = 29$) and segmental ($n = 31$) biopsies, a difference was only found between subsegmental RML biopsies and the treated areas. No difference was found between the segmental RML biopsies and the treated areas (Figure 4B).

Associations between clinical response and baseline characteristics (n = 35). Associations were explored between ACQ and AQLQ change (post-BT minus pre-BT scores) and baseline patient characteristics in the total group (Table 4). ASM mass at baseline, ASM mass after BT, and ASM change were not associated with ACQ and/or AQLQ improvement. Associations were found between ACQ improvement and baseline blood eosinophil count and total IgE count (rho = −0.46, $P = 0.006$, and rho = −0.53, $P = 0.001$, respectively). This association between total IgE level and ACQ improvement remained statistically significant after exclusion of patients who were treated with omalizumab during the study (rho = −0.46, $P = 0.009$). For AQLQ change, only blood eosinophil counts were associated (rho = 0.48, $P = 0.004$).

In addition, no associations were found between improvements on asthma questionnaires and changes in lung function such as FEV_1, reversibility, and methacholine challenge tests (PC20) or with the amount of activations during treatment.

Discussion

This study is the first to show a reduction in ASM mass 6 months after BT when compared with an appropriate non–BT-treated control group. Clinical response analysis could not reveal an association between ASM reduction and response. However, baseline blood eosinophils and total IgE counts were associated with improvements in ACQ and AQLQ scores after BT. These findings suggest that

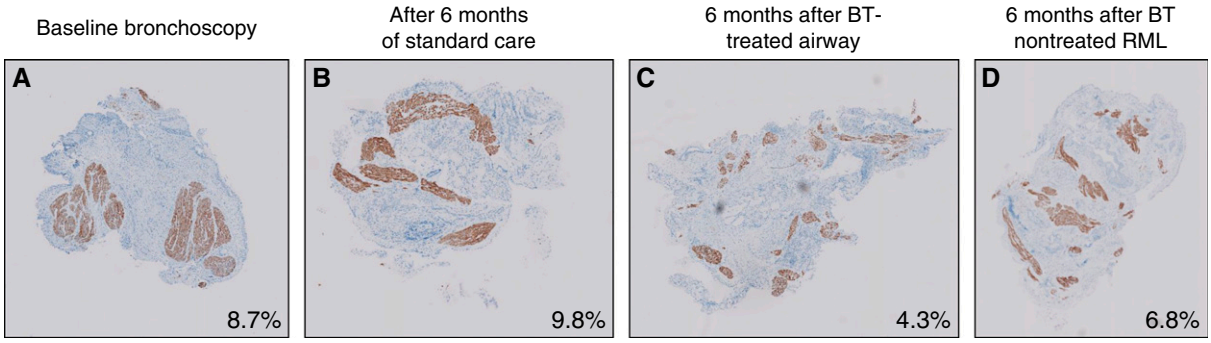

Figure 2. Airway smooth muscle mass percentage in the airways of one patient during the study. Airway smooth muscle mass percentage assessed with desmin staining (*A*) before BT at randomization; (*B*) after 6 months of standard care; (*C*) after BT in treated airways; and (*D*) after BT in the untreated RML. BT = bronchial thermoplasty; RML = right middle lobe.

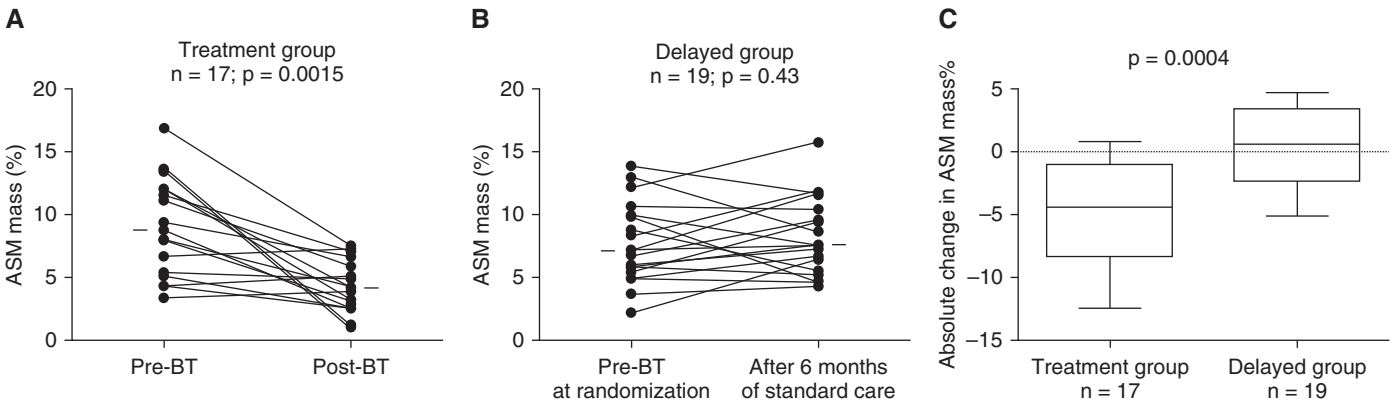

Figure 3. ASM decrease after BT as compared with the randomized control group. (*A*) ASM mass percentage in the immediate group before and after BT showing a median ASM mass percentage of 8.75% before BT versus 4.14% after BT (53% decrease). (*B*) ASM mass percentage in the delayed group before and after 6 months of standard care with a median ASM mass percentage of 7.08% at randomization versus 7.56% after 6 months of standard care (7% increase). (*C*) Difference in absolute ASM mass percentage change between both randomization groups (post-BT − pre-BT ASM percentage in the immediate BT group, and for the delayed control group, the difference between baseline and 6 months of standard care biopsies). ASM mass was assessed with desmin staining. Median values are denoted by dashes. ASM = airway smooth muscle; BT = bronchial thermoplasty.

patients with high blood eosinophil counts and/or IgE levels are more likely to respond to BT treatment.

In this study, ASM mass reduction after BT has been investigated in a randomized controlled design using desmin and α-SMA stain. The results showed similar amounts of ASM mass at baseline as found in other severe asthma populations (13, 32) and confirm previously published results in observational studies (10, 12, 13, 32). The reduction of ASM mass in the untreated RML adds novel information to the discussion about the mechanism of action of BT. Whereas imaging studies using computed tomography (33–35) and optical coherence tomography (36) showed immediate effects of BT in nontreated parts of the lungs, biopsy studies including the RML were conflicting (12, 13). The present results suggest that the effect of BT extends to untreated parts of the lungs as well but does not result in ASM reduction in the more distal subsegmental parts of these airways. Several theories have been published regarding the possible extending effect of BT such as a heat shock effect along the bronchial tree, heat extension through (incomplete) fissures, or through the distribution of mucus, blood, and secretions to the lower lobes as a result of BT treatment in the upper lobes (34). The decreasing effect of BT on ASM mass in more distally located parts of the RML adds to the hypothesis that indeed a heat shock effect can be distributed to the distal airways. A clinically relevant improvement in ACQ or AQLQ scores was found in the majority of patients and exacerbation rates were reduced in almost all patients during 6 months of follow-up after BT. The results in this study confirm the safety profile and clinical benefit of BT that has also been reported by several other research groups (14–17). The optimal patient responder profile, however, remains under debate. One novel and potentially important finding in this study was the correlation between BT response, as assessed by ACQ and AQLQ score changes, and baseline blood eosinophils and total IgE. The correlations found in this study are in line with results from a retrospective multicenter study with 47 patients in which atopic patients showed a better response to BT than nonatopic patients (37). Currently, BT is mainly provided to patients who are not eligible or not responding to biological treatments (38). Our results suggest that the same patients who are eligible for biological treatment might also be good candidates for BT. Although these results need to be confirmed in larger cohorts, it might be both clinically and health-economically beneficial for some patients to be treated with BT before starting with lifelong biological treatment.

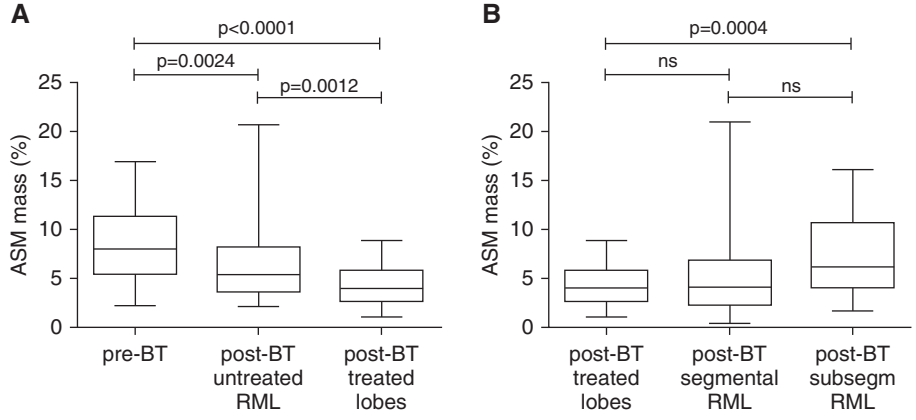

Figure 4. ASM mass reduction in the untreated RML as compared with BT-treated airways. Paired analyses showed (*A*) a significant but less profound reduction in ASM mass after BT in the untreated RML and that (*B*) subsegmental airways of the untreated RML have significantly more ASM mass as compared with the treated airways after BT. ASM was assessed with desmin staining. ASM = airway smooth muscle; BT = bronchial thermoplasty; ns = nonsignificant; RML = right middle lobe.

Table 4. Associations between ACQ-6 and AQLQ Improvement and Baseline Characteristics ($n = 35$)

	ACQ-6 Change		AQLQ Change	
	Rho	*P* Value	Rho	*P* Value
Asthma age of onset, yr	−0.20	0.25	0.30	0.08
Total IgE, kU/L*	−0.53	0.001†	0.24	0.17
Blood eosinophils, $\times 10^9$/L*	−0.46	0.006†	0.48	0.004†
Pre-SABA FEV_1, % predicted‡	−0.02	0.89	0.20	0.26
Reversibility FEV_1‡	−0.13	0.48	0.21	0.25
PC_{20}, mg/ml§	0.30	0.08	−0.09	0.61
FE_{NO}, ppb‖	−0.28	0.19	0.21	0.33
ASM mass desmin, %	0.07	0.69	−0.009	0.96
ASM mass α-SMA, %	0.18	0.29	−0.05	0.79

Definition of abbreviations: α-SMA = α smooth muscle actin; ACQ = Asthma Control Questionnaire; AQLQ = Asthma Quality of Life Questionnaire; ASM = airway smooth muscle; FE_{NO} = fractional exhaled nitric oxide; PC_{20} = methacholine provocation test; SABA = short-acting β agonist.
Associations analyzed with spearman rho correlation coefficient.
*Data available in $n = 34$.
†Significant correlation with $P < 0.05$; *P* value after Bonferroni correction for multiple comparisons $P < 0.006$.
‡Data available in $n = 33$.
§Values were log-transformed for statistical analysis.
‖Data available in $n = 24$.

The amount of ASM mass at baseline and the change in ASM after BT did not correlate with BT response. Patient selection for BT based on airway remodeling as assessed in ASM mass analysis is therefore probably not optimal. Consequently, the exact mechanism of action of BT is not yet understood. Other studies have shown decreasing submucosal nerves and neuroendocrine cells in the epithelium after BT (13, 39), possibly correlating with BT response, indicating that the effect of BT might be more targeted at other components than the ASM layer. We hypothesize that because BT results in denudation of the epithelium (36) and because there is no correlation between ASM reduction and response, the epithelium might be the primary target of BT. As a consequence, the mechanism of action of BT might be comparable to nitrogen cryospray in chronic bronchitis (40). In this therapy, it has been shown that after destroying the epithelium layer, the new regenerated epithelial cells might function as normal cells. Future studies should explore this hypothesis further.

One of the strengths of the present study is the randomized design. By using a control group with patients remaining on their regular asthma medication and management for 6 months, a proper control group was implemented. A sham treatment group was not included in the study design considering the already high burden of multiple sampling bronchoscopies implemented in the TASMA (Unravelling Targets of Therapy in Bronchial Thermoplasty in Severe Asthma) study and the previously published BT sham randomized controlled trial (14). In addition, the multicenter international design, with two centers in the Netherlands and two centers in the United Kingdom both including and treating patients, strengthens the generalizability. Also, the relatively large group of 40 patients with severe asthma, thorough characterization of the patients, and the use of two different staining techniques strengthen the quality of the current findings.

Several limitations need to be addressed. First, biopsies in this study were taken from different predefined (sub) segmental airway carinas. Although this could potentially bias the results, variation between different lobes has been shown to be small (12), and by using different sites, the risk of analyzing the effect of the previously taken biopsy instead of the BT treatment itself is mitigated. In addition, during each bronchoscopy, biopsies were taken from both the lower and upper lobes, thereby limiting bias due to variations between lobes. Second, even though patients were randomized into two groups, the immediate treatment group seemed to have a higher ACQ and lower AQLQ score at baseline compared with the delayed control group. This comparison did not reach the minimally clinically relevant difference of 0.5 points and remained stable in the delayed non-BT control group. Furthermore, by comparing the change from baseline between both groups, the statistical test partially corrected for this potential influence. In addition, the questionnaires were not associated with ASM mass, and an influence on the primary outcome of this study is therefore not likely. Third, this study was powered for the assessment of ASM mass reduction but not for a response analysis. Although the results regarding response add important information to the discussion about the optimal patient for BT, the results need to be confirmed in a larger cohort.

Conclusions

BT significantly reduces ASM mass in patients with severe asthma when compared with non–BT-treated controls and seems to affect the proximal parts of the untreated RML as well. No correlation was found between ASM mass and BT response. Importantly, significant correlations were found between blood eosinophil counts and total IgE at baseline and BT response, implicating that patients with higher blood eosinophil counts and/or IgE levels are potentially the most appropriate candidates for BT treatment. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Acknowledgment: The authors thank all the patients participating in this study, O. de Boer and T. Dirksen from the Pathology department of the Amsterdam University Medical Centers, location Academic Medical Center, for their committed and professional work, and J. Hartman, S. Augustijn, C. Caneja, M. van de Pol, and S. Lone-Latif for coordinating patient visits in the participating centers.

References

1. Bel EH, Sousa A, Fleming L, Bush A, Chung KF, Versnel J, *et al*.; Unbiased Biomarkers for the Prediction of Respiratory Disease Outcome (U-BIOPRED) Consortium, Consensus Generation. Diagnosis and definition of severe refractory asthma: an international consensus statement from the Innovative Medicine Initiative (IMI). *Thorax* 2011;66:910–917.
2. 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.
3. Hekking PP, Wener RR, Amelink M, Zwinderman AH, Bouvy ML, Bel EH. The prevalence of severe refractory asthma. *J Allergy Clin Immunol* 2015;135:896–902.
4. Serra-Batlles J, Plaza V, Morejón E, Comella A, Brugués J. Costs of asthma according to the degree of severity. *Eur Respir J* 1998;12: 1322–1326.
5. Settipane RA, Kreindler JL, Chung Y, Tkacz J. Evaluating direct costs and productivity losses of patients with asthma receiving GINA 4/5 therapy in the United States. *Ann Allergy Asthma Immunol* 2019;123:564–572, e3.
6. Busse W, Corren J, Lanier BQ, McAlary M, Fowler-Taylor A, Cioppa GD, *et al*. Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. *J Allergy Clin Immunol* 2001;108:184–190.
7. Castro M, Zangrilli J, Wechsler ME, Bateman ED, Brusselle GG, Bardin P, *et al*. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. *Lancet Respir Med* 2015;3:355–366.
8. Pavord ID, Korn S, Howarth P, Bleecker ER, Buhl R, Keene ON, *et al*. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *Lancet* 2012;380:651–659.
9. Castro M, Musani AI, Mayse ML, Shargill NS. Bronchial thermoplasty: a novel technique in the treatment of severe asthma. *Ther Adv Respir Dis* 2010;4:101–116.
10. Denner DR, Doeing DC, Hogarth DK, Dugan K, Naureckas ET, White SR. Airway inflammation after bronchial thermoplasty for severe asthma. *Ann Am Thorac Soc* 2015;12:1302–1309.
11. d'Hooghe JNS, Goorsenberg AWM, Ten Hacken NHT, Weersink EJM, Roelofs JJTH, Mauad T, *et al*.; TASMA research group. Airway smooth muscle reduction after bronchial thermoplasty in severe asthma correlates with FEV_1. *Clin Exp Allergy* 2019;49:541–544.
12. 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;190:1452–1454.
13. 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;139:1176–1185.
14. Castro M, Rubin AS, Laviolette M, Fiterman J, De Andrade Lima M, Shah PL, *et al*.; AIR2 Trial Study Group. Effectiveness and safety of bronchial thermoplasty in the treatment of severe asthma: a multicenter, randomized, double-blind, sham-controlled clinical trial. *Am J Respir Crit Care Med* 2010;181:116–124.
15. Chupp G, Laviolette M, Cohn L, McEvoy C, Bansal S, Shifren A, *et al*.; Other members of the PAS2 Study Group. Long-term outcomes of bronchial thermoplasty in subjects with severe asthma: a comparison of 3-year follow-up results from two prospective multicentre studies. *Eur Respir J* 2017;50:1700017.
16. 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;356:1327–1337.
17. Pavord ID, Cox G, Thomson NC, Rubin AS, Corris PA, Niven RM, *et al*.; RISA Trial Study Group. Safety and efficacy of bronchial thermoplasty in symptomatic, severe asthma. *Am J Respir Crit Care Med* 2007;176:1185–1191.
18. d'Hooghe JNS, Roelofs JJTH, Annema JT, Bonta PI. Reduction of airway smooth muscle mass in airway biopsies following bronchial thermoplasty; the TASMA randomized controlled trial [abstract]. *Eur Respir J* 2016;48:OA3014.
19. d'Hooghe JNS, ten Hacken NHT, Roelofs JJTH, Annema JT, Bonta PI. Airway smooth muscle mass reduction after bronchial thermoplasty; the TASMA randomized controlled trial [abstract]. *Eur Respir J* 2017;50: PA3027.
20. d'Hooghe JNS, Weersink EJM, ten Hacken NHT, Annema JT, Bonta PI. Clinical response of severe asthma patients following bronchial thermoplasty [abstract]. *Eur Respir J* 2017;50:PA3029.
21. Goorsenberg AWM, d'Hooghe JNS, ten Hacken NHT, Weersink EJM, Bel EH, Shah PL, *et al*. Towards optimal patient selection for bronchial thermoplasty treatment in severe asthma: results from the TASMA randomized trial [abstract]. *Eur Respir J* 2019;54:PA2537.
22. Goorsenberg AWM, d'Hooghe JNS, ten Hacken NHT, Weersink EJM, Roelofs JJTH, Srikanthan K, *et al*. Bronchial thermoplasty induced reduction of airway smooth muscle: results from the randomized controlled TASMA trial [abstract]. *Eur Respir J* 2019;54:OA1616.
23. Benayoun L, Druilhe A, Dombret MC, Aubier M, Pretolani M. Airway structural alterations selectively associated with severe asthma. *Am J Respir Crit Care Med* 2003;167:1360–1368.
24. Bousquet J, Mantzouranis E, Cruz AA, Aït-Khaled N, Baena-Cagnani CE, Bleecker ER, *et al*. Uniform definition of asthma severity, control, and exacerbations: document presented for the World Health Organization Consultation on Severe Asthma. *J Allergy Clin Immunol* 2010;126:926–938.
25. Bonta PI, Chanez P, Annema JT, Shah PL, Niven R. Bronchial thermoplasty in severe asthma: best practice recommendations from an expert panel. *Respiration* 2018;95:289–300.
26. d'Hooghe JNS, Eberl S, Annema JT, Bonta PI. Propofol and remifentanil sedation for bronchial thermoplasty: a prospective cohort trial. *Respiration* 2017;93:58–64.
27. Collins TJ. ImageJ for microscopy. *Biotechniques* 2007;43:25–30.
28. Goorsenberg AWM, d'Hooghe JNS, Slats AM, van den Aardweg JG, Annema JT, Bonta PI. Resistance of the respiratory system measured with forced oscillation technique (FOT) correlates with bronchial thermoplasty response. *Respir Res* 2020;21:52.
29. Hodges JL, Lehmann EL. Estimates of location based on rank tests. *Ann Math Stat* 1963;34:598–611.
30. Juniper EF, Guyatt GH, Willan A, Griffith LE. Determining a minimal important change in a disease-specific Quality of Life Questionnaire. *J Clin Epidemiol* 1994;47:81–87.
31. Juniper EF, Svensson K, Mörk AC, Ståhl E. Measurement properties and interpretation of three shortened versions of the asthma control questionnaire. *Respir Med* 2005;99:553–558.
32. Chakir J, Haj-Salem I, Gras D, Joubert P, Beaudoin EL, Biardel S, *et al*. Effects of bronchial thermoplasty on airway smooth muscle and collagen deposition in asthma. *Ann Am Thorac Soc* 2015;12:1612–1618.
33. Debray MP, Dombret MC, Pretolani M, Thabut G, Alavoine L, Brillet PY, *et al*. Early computed tomography modifications following bronchial thermoplasty in patients with severe asthma. *Eur Respir J* 2017;49: 1601565.
34. d'Hooghe JNS, Bonta PI, van den Berk IAH, Annema JT. Radiological abnormalities following bronchial thermoplasty: is the pathophysiology understood? *Eur Respir J* 2017;50:1701537.
35. d'Hooghe JNS, van den Berk IAH, Annema JT, Bonta PI. Acute radiological abnormalities after bronchial thermoplasty: a prospective cohort trial. *Respiration* 2017;94:258–262.
36. Goorsenberg AWM, d'Hooghe JNS, de Bruin DM, van den Berk IAH, Annema JT, Bonta PI. Bronchial thermoplasty-induced acute airway effects assessed with optical coherence tomography in severe asthma. *Respiration* 2018;96:564–570.
37. Sierra M, Fernandez-Bussy S, Mehta H, Kheir F, Barry M, Jantz M, *et al*. Bronchial thermoplasty in severe uncontrolled asthma with different phenotypes [abstract]. *Chest* 2017;152:A29.
38. Global Initiative for Asthma. Global strategy for asthma management and prevention; 2019 [accessed 2019 Nov]. Available from: www.ginasthma.org.
39. Facciolongo N, Di Stefano A, Pietrini V, Galeone C, Bellanova F, Menzella F, *et al*. Nerve ablation after bronchial thermoplasty and sustained improvement in severe asthma. *BMC Pulm Med* 2018;18:29.
40. Slebos DJ, Breen D, Coad J, Klooster K, Hartman J, Browning R, *et al*. Safety and histological effect of liquid nitrogen metered spray cryotherapy in the lung. *Am J Respir Crit Care Med* 2017;196:1351–1352.