Efficacy of bronchial thermoplasty in patients with severe asthma

Keywords: Bronchial thermoplasty, airway smooth muscle, quality of life, exacerbations, precision medicine, severe asthma

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Abstract

Objective: To investigate the efficacy and safety of bronchial thermoplasty (BT) in clinical practice in adults with severe, refractory asthma.

Methods: Prospective, single-center, open, observational study comprising patients with uncontrolled asthma (asthma control questionnaire (ACQ) >1.5) and/or frequent exacerbations despite treatment with at least high dose inhaled corticosteroids plus a second controller. Efficacy outcomes was change from baseline 4, 8, 12 and 24 months in FEV₁, FVC and FEV₁/FVC ratio, asthma control questionnaire (ACQ) score and asthma quality of life score (mini-AQLQ). Results are presented as median with interquartile ranges (IQR). The following were recorded as adverse events: Un-scheduled health care contacts, rescue courses of oral corticosteroid (OCS) and/or antibiotics for exacerbation for exacerbations/respiratory tract infections (RTI).

Results: Sixteen patients were enrolled (9 males, median age 50 years; 14 followed for 24 months). Compared to baseline, an improvement in FEV₁, FVC, FEV₁/FVC ratio, mini-AQLQ and ACQ was observed, i.e. FEV₁ (IQR) 1.98 L (1.65-2.45) vs. 2.45 L (2.09-2.93) (p=0.006), FVC (IQR) 3.23 L (2.76-4.05) vs. 3.75 L (3.22-4.36) (p=0.041), FEV₁/FVC 0.60 (IQR: 0.55-0.70) vs. 0.66 (IQR: 0.63-0.71) (p=0.016), mini-AQLQ 4.0 (IQR: 3.2-4.9) vs. 5.6 (IQR: 4.5-6.5) (p=0.008, and ACQ 2.9 (IQR: 2.1-3.7) versus 1.5 (IQR 1.0-2.4) (p=0.004). On the other hand, an increase was observed in unscheduled visits (p=0.005), as well as use of OCS and antibiotics (p=0.009 and p=0.003, respectively).

Conclusion: BT in adults with severe asthma improved ACQ, mini-AQLQ and lung function, but resulted in an increased frequency of unscheduled doctor-visits and rescue courses of OCS and antibiotics.
Introduction

Asthma is the most common chronic disease among children and young adults with a prevalence of up to 18% among adults (1, 2). The public health implications of asthma are significant, as the number of Disability-Adjusted Life Years (DALY) currently lost due to asthma has worldwide been estimated to be about 15 million per year (1). The majority of asthma patients can achieve good asthma control on standard therapy, but up 10% have difficult-to-control or severe asthma (3), and this minority of the patient population accounts for a large proportion of the resource expenditure (4).

Patients with severe persistent asthma, defined as GINA step 5, are challenging in terms of treatment. Several phenotypes of severe asthma are recognized, based on clinical, physiological and immunological variables, and these are used to classify asthma and to predict response to therapy. Type 2 asthma is closely associated with eosinophilic inflammation and predicts a favorable therapeutic response to biological agents targeting this pathway including interleukins (IL) such as IL-4, IL-5 and IL-13. On the other hand, non-eosinophilic asthma, often referred to as non-T2 asthma, have less favorable response to currently marketed therapies, but might respond to bronchial thermoplasty (BT). BT may be considered a treatment option for adults with severe asthma (2, 4, 5) provided that it is done in the context of an institutional review board approved independent systematic registration or clinical study (4).

BT is a non-pharmacological intervention, described firstly in a study published in 2004 of patients with moderate-to-severe asthma (6). BT refers to a technique of applying controlled heat using a radiofrequency catheter during flexible bronchoscopy to airways between 3 and 10 mm in size. The thermal injury is thought to reduce the increased mass of airway smooth muscle, thereby decreasing the bronchoconstrictor response in asthma (6). Overall, available studies of BT have shown a moderate improvement only in quality of life, together with a reduction in asthma exacerbations (7, 7, 8, 9, 10, 11). In controlled clinical trials, no significant effect has been reported with regard to measures of symptoms and pulmonary function parameters (8). However, uncontrolled, randomized studies have shown slight improvements in symptoms (7, 9) and lung function (9).

The positioning of BT in the management of severe asthma is uncertain and has so far been effective in only one half to three-quarters of treated patients (5). Despite the demonstrated effects of BT in some patients and only minor adverse events (10), BT has never been implemented more widely in clinical practice (12, 13).
This was the first Scandinavian study completed as a nationwide study in Denmark in collaboration with the Danish National Board of Health and also the first study, where it was possible to electronically control adherence on filled prescriptions. The aim of the present study was to investigate the efficacy and safety of BT in clinical practice (real life) and to address the barriers for implementing BT as a routine treatment option in adults with severe asthma.
Material and methods

Study design and follow-up

This is a prospective, non-randomized, uncontrolled real-life study of patients with severe asthma, who underwent BT treatment at a single center tertiary hospital.

Study population

Patients fulfilled the criteria of severe asthma according to Bel et al (14). We included adult patients with FEV$_1 \geq 50\%$ predicted with uncontrolled asthma (Asthma Control Questionnaire (ACQ) $>1.5$), and/or frequent exacerbations requiring step-up in medication and/or un-scheduled health care contacts despite treatment with high dose inhaled corticosteroids combined with long-acting-$\beta_2$-agonist (LABA) (GINA, step 4-5). Patients were included only if they had the asthma diagnosis objectively verified (2), and they had filled $\geq 80\%$ of their prescriptions for maintenance therapy. Adherence was assessed using unique electronic access for each patient at www.medicin-it.dk (now www.fmkk-online.dk) to obtain information on filled prescriptions (by using the unique personal identification number) at all pharmacies in Denmark. Thus, the asthmatic subgroup in this study filled prescription for high dose ICS and LABA during the study. Despite this they were uncontrolled with frequent exacerbations.

Recruited patients had to be eligible for bronchoscopy in the opinion of the investigator, and patients were excluded if they had an asthma exacerbation with emergency department (ED) visit, hospitalization, rescue course of increased oral corticosteroids (OCS), or un-scheduled health care visit for asthma during the four weeks prior to BT treatment, if they were on maintenance OCS therapy at doses $>10$ mg/day prednisone equivalent, or if they had had a step-up in dosage within the last two weeks. Also, they did not suffer from uncontrolled hypertension or other significant respiratory or cardiovascular disease. For a full list of exclusion criteria, please refer to Appendix 1.

Outcome measures

The main outcome measures were the seven-item asthma control questionnaire (ACQ7) (15) and the Mini Quality of Life Questionnaire (miniAQLQ) (16). These questionnaires were completed by the patients. Secondary outcome measures included fractional exhaled nitrogen oxid (FeNO) (17),
forced expiratory volume in 1 second (FEV₁), forced vital capacity (FVC), FEV₁ in % of predicted (FEV₁%), FVC in % of predicted (FVC%), and the percentage bronchodilator reversibility (400 µg salbutamol; ΔFEV₁%) (18, 19). The outcome measures were recorded at baseline and at 4, 8, 12 and 24 months after baseline.

The main safety outcome measures were total lung capacity (TLC) and hemoglobin-corrected diffusing capacity for carbon monoxide (DLCOc) at baseline and after 12 months (19). We also included the following secondary outcome measures: number of un-scheduled contacts to primary- and secondary care, an increase in use of bronchodilators and/or initiation of rescue courses of OCS.

Measurement of FeNO, spirometry, TLC and DLCOc were performed by specially trained pulmonary nurses.

**Bronchial thermoplasty (BT)**

The BT procedure was performed using the Alair Bronchial Thermoplasty System (Boston Scientific Inc, Inc., Marlborough, MA) (6, 9) in three bronchoscopy sessions (with midazolam and fentanyl as sedation) within 12 weeks, each separated by approximately three weeks. Prednisolone was administered orally for five days in relation to each procedure, starting on day -3. A systematic approach from distal to proximal airways was used, working methodically from airway to airway across each region of the lungs. All accessible airways, excluding the right middle lobe were carefully identified and treated once (7). The BT procedure was done by three specially trained doctors. The department was certified as Center of Excellence for BT after an on-site evaluation by an assessment team from the BT company. We used the exact same BT procedure as in previous clinical trials (7, 8, 9).

Blood samples were routinely obtained for haemoglobin, international normalised ratio (INR), blood glucose, thrombocytes and leucocytes, together with an ECG.

In compliance with Danish legislation, the study was approved by the Danish Data Protection Agency (J No 2008-58-0035). Data was collected as an independent systematic register in agreement with the Danish Health Authority.
Statistical analysis

Data are presented as medians with interquartile ranges (IQR) or as absolute values with proportions, as appropriate. We calculated changes from baseline to post-intervention after 4, 8, 12, and 24 months for each outcome measure variable. We used the two-sample proportion test for categorical data and Wilcoxon signed rank test for continuous data for within-group analyses. A p-value less than 0.05 were regarded as statistically significant.

Results

We had 1-year follow-up information on 16 patients (nine males, median age 50 years) and 2-year follow-up on 14 patients. The median FEV1% of predicted was 62% at baseline (IQR 48-73%), and six patients had allergic sensitization. Further characteristics, including comorbidities, are given in Table 1.

At two-year follow-up, we observed a significant improvement in all efficacy lung function measures compared to baseline. The FEV1 increased from 1.98 L (IQR 1.65-2.45) to 2.45 L (IQR 2.09-2.93) (p=0.006), the FEV1/FVC ratio from 0.60 to 0.66 (p=0.016) and the bronchodilator reversibility declined in FEV1% from 12.4 to 3.6 (p=0.003) (Table 2). Furthermore, we found a decrease in the ACQ score of 1.4 (p=0.004) together with an increase in mini-AQLQ of 1.6 (p=0.008), which was found to be clinically relevant in 10 (mini-AQLQ) and 11 (ACQ), respectively, of the patients (Table 2). However, as shown in Fig. 1, there was some variability in ACQ score over the study period, whereas the decline in mini-AQLQ appeared to be more stable (figure 2). No significant changes in FeNO was observed during the study period.

There were no major adverse events related to the BT procedures. Analysis of data on the main safety outcome measures, that is, TLC and DLCO, revealed no significant changes (Table 3).

With regard to the secondary outcome measures, we found an increased number of GP contacts, RTIs, and prescribed courses of antibiotics and OCS. During the first three four months periods and the last 12 months period, five to six patients had a rescue course of OCS and three to seven patients were treated with antibiotics. No significant changes were observed in prescribed bronchodilators,
inhaled corticosteroids, and hospital contacts, including outpatient visits, admissions to acute medical ward and intensive care unit, during the observation period (Table 3).

**Discussion**

In this first Scandinavian, prospective, single-center, uncontrolled real-life study with consecutively included patients with severe asthma, we found, that BT significantly improved lung function, asthma-related quality of life and bronchodilator reversibility. On the other hand, however, we observed an increased number of contacts to general practitioners and need for rescue courses of OCS and antibiotics. The study was an adherence controlled, nationwide and included all patients treated with BT in Denmark.

So far, only three randomized controlled trials have addressed the potential benefit of BT in severe asthma (7, 8, 9), and only one of these studies was placebo controlled with a sham procedure arm (8). In general, these studies have revealed a moderate improvement only in quality of life (AQLQ scores 0.28, 95% confidence interval 0.07 to 0.50) (10), and in the placebo-controlled study (8) also a reduction in ER visits caused by exacerbation of asthma from 15% to 8% over 12 months, whereas no effect has been reported with regard to asthma-related quality of life or lung function (8, 11). A five-year follow-up of the cohort showed that the positive results were still seen with regard to fewer exacerbations and ER visits (10). No serious safety concerns related to the BT procedures were reported from the studies (10, 11).

Compared to the randomized controlled trials (7, 8, 9), the patients in the present study were approximately 10 years older (median age 50 years). Furthermore, our patients had slightly lower FEV₁ (62% of predicted) compared to two of the randomized controlled trials (7, 8), and also compared to smaller observational studies (12), but similar to the patients included in the study by Pavord et al (9). The level of ACQ scores were similar in all studies, including the present study (7, 8, 9). Taken together, it appears unlikely that differences in recruited cohorts have had significant impact on the observations with regard to efficacy of BT.

In contrast to most other available studies (9,12,13), we observed a substantial increase in FEV₁ and FVC (Table 2). This might be caused by an increased need for rescue courses of OCS in our study (Table 3) and as a result of regression towards the mean, because the patients were required to be stable at baseline to allow for BT. In direct relation to the BT procedures, previous studies have
reported an increased risk of hospitalization for mild respiratory events, and by that, an expected increase in rescue courses of OCS (13). However, BT has been reported to decrease (12, 21), increase (20) or have no influence (13) on OCS use.

As assessed by the ACQ score, our patients overall changed from being uncontrolled to controlled, which is similar to the findings in the randomized, open-label studies (7, 9) and smaller observational studies comprising up to 20 patients (12), but in contrast to what was found in the placebo-controlled trial (8). Similar improvements were found in miniAQLQ score (Table 3). In line with this, an improvement was also reported from the sham-controlled trial (8), but this improvement was found in both the intervention (+1.36) and the control group (+1.16), although statistically significantly different between the two groups (8). In the present study, miniAQLQ score improved by +1.6. Our study, therefore, supports the notion that BT therapy may have positive impact on asthma-related quality of life.

A limitation of the present study is the lack of control group, and some bias might be due to the increased administration of prednisolone during the follow-up period. Thus, it cannot be ruled out that the improvement in miniAQLQ, ACQ and lung function parameters may in part be driven by the effect of systemic corticosteroid. An important strength is the fact that adherence with maintenance therapy can be assessed electronically (using the unique personal identification number assigned to all Danish citizens) allowing us to exclude non-adherent patients from the study. Thus, the add-on effect of BT to prescribed maintenance therapy was ascertained in the present study, which is important as low or suboptimal adherence is seen in up to half of the patients potentially eligible for novel therapies (20).

Before implementing BT on a national level in Denmark, we needed to reveal if there were any unexpected risks or side effects, and this was done in collaboration with the Danish National Board of Health. The study population was small (n=16), but was similar in size similar to one of the previous trials (n=15) (9).

Our study adds to existing studies supporting the overall assessment that there is still substantial uncertainty with regard to the risk-benefit ratio, and also related to the selection of patients likely to benefit the most from BT (12, 22). Despite 300 million people worldwide suffering from asthma (1), and among these at least 5% that can be classified as having severe asthma (3), less than 450 patients have been included in randomized trials of BT therapy and less than 375 have been followed for more than two years (12,13,23). There are a number of reasons for this small number
of patients. Firstly, the ideal BT asthma phenotype has been hard to identify in real-life (12, 22). Initially, it was thought, that BT reduced very specific structural abnormalities involved in airway narrowing and bronchial reactivity, particularly airway smooth muscles (21). But integrated in vitro and in silico modelling suggests, that the reduction in airway smooth muscle post-BT cannot be fully explained by acute heating, nor did this reduction confer a greater improvement in asthma control (24). So, at present, the mechanisms underlying the observed improvements in overall asthma control remain poorly understood (5). In this study not all the patients were truly non-T2-asthmaic as blood eosinophil counts range were above 0.3 $10^9$/L, but no biological therapies were available at starting time for this study in Denmark. Blood eosinophil count was not specified in the first BT studies (7, 8, 9). A small (n=15) recent study found decreased numbers of severe exacerbations, and in this study the patients had an eosinophil count below 0.3 $10^9$/L (21) suggesting an effect in non-T2-asthma, but these patients were also treated with a mean dose of prednisolone above 30 mg/d explaining the lower eosinophil count. Secondly, the BT procedure is costly in equipment and man-power (25, 26), although some have claimed the cost-effectiveness of BT to omalizumab and standard therapy (27) and even to standard therapy in patients with recurrent exacerbations (28). Finally, and probably the most important reason, is that BT have been overtaken by biological therapies. Several new and effective biological therapies have become available in recent years for primarily T2 phenotypes of severe and/or uncontrolled asthma, and these treatments are easy to administer, have few side effects and have been shown to reduce both exacerbations and exposure to systemic corticosteroid (5).

Thus, the identification of patients most likely to benefit from BT is crucial and will be of paramount importance in determining the role of BT in the management of severe asthma in the future. Especially further studies in non-T2-astmatics are needed.
Conclusion: Bronchial thermoplasty improved asthma-related quality of life and lung function in patients with severe asthma, but increased primary care contacts and the use of both oral corticosteroid and antibiotics.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.
References


Appendix 1

Exclusion criteria:

• Asthma exacerbation (ED visit, hospitalization, course of increased systemic steroids, or urgent health care visit for asthma) within the four weeks prior to the BT procedures.

• Three of more hospital admissions due to exacerbation of asthma in the previous year or one (or more) ICU admission for asthma in the previous two years.

• Maintenance therapy with oral corticosteroid at a dose >10 mg/day prednisone equivalent or adjustment of dose within the last two weeks.

• Respiratory tract infection within the past four weeks

• Known sensitivity to medications required to perform bronchoscopy, including lidocaine, atropine and benzodiazepines.

• Bleeding diathesis, platelet dysfunction, and/or thrombocytopenia (platelet count < 125 mia/L known coagulopathy (INR > 1.5).

• Other significant chronic respiratory disease, including interstitial lung disease, emphysema, cystic fibrosis, vocal cord dysfunction, mechanical upper airway obstruction, obstructive sleep apnea, eosinophilic granulomatosis with polyangiitis, and allergic bronchopulmonary aspergillosis.

• Chest x-ray with segmental atelectasis, lobar consolidation, significant infiltrate(s), or pneumothorax.

• Clinically significant cardiovascular disease, including myocardial infarction, angina, arrhythmias, conduction defects, cardiomyopathy, aortic aneurysm, or stroke.

• Uncontrolled hypertension.

• Pacemaker/ICD-unit.

• Any condition/adherence issue which in the opinion of the investigator may interfere with the study procedures.
Table 1 Baseline characteristics of patients undergoing bronchial thermoplasty treatment

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Study population (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR)</td>
<td>50 (31-57)</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>9 (56)</td>
</tr>
<tr>
<td>Female</td>
<td>7 (43)</td>
</tr>
<tr>
<td>Asthma diagnosis, n (%)</td>
<td></td>
</tr>
<tr>
<td>β₂-reversibility ≥12 % and ≥ 200 ml</td>
<td>11 (69)</td>
</tr>
<tr>
<td>Diurnal PEF variability ≥ 20 %</td>
<td>2 (13)</td>
</tr>
<tr>
<td>Pos. mannitol challenge test</td>
<td>3 (19)</td>
</tr>
<tr>
<td>Blood eosinophil count $10^9$/L, median (IQR)</td>
<td>0.25 (0.07-0.43)</td>
</tr>
<tr>
<td>FEV₁ %pred (IQR)</td>
<td>62 (48-73)</td>
</tr>
<tr>
<td>Allergy n (%)</td>
<td>6 (38)</td>
</tr>
<tr>
<td>Co-morbidity (%)</td>
<td>8 (50)*</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
</tr>
<tr>
<td>GINA 4 (%)</td>
<td>5 (31)</td>
</tr>
<tr>
<td>GINA 5 (%)</td>
<td>11 (69)</td>
</tr>
</tbody>
</table>

IQR inter-quartile range

*diabetes, attention deficit hyperactivity disorder, polycystic ovary syndrome, hypertension, back pain, gout and secondary adrenal insufficiency
Table 2

Efficacy measures, compared with measures at baseline, at 4, 8, 12 and 24 months in adult patients (n=16) with severe asthma undergoing bronchial thermoplasty treatment (BT)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Baseline (n=16)</th>
<th>4 months (n=15)</th>
<th>p-value</th>
<th>8 months (n=14)</th>
<th>p-value</th>
<th>12 months (n=16)</th>
<th>p-value</th>
<th>24 months (n=14)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1, median (IQR)</td>
<td>1.98 (1.65-2.45)</td>
<td>2.40 (1.80-3.00)</td>
<td>0.002</td>
<td>2.27 (1.39-2.83)</td>
<td>0.683</td>
<td>2.47 (1.61-2.84)</td>
<td>0.179</td>
<td>2.45 (2.09-2.93)</td>
<td>0.006</td>
</tr>
<tr>
<td>FVC, median (IQR)</td>
<td>3.23 (2.76-4.05)</td>
<td>3.67 (3.24-4.15)</td>
<td>0.061</td>
<td>3.56 (3.13-4.19)</td>
<td>0.875</td>
<td>3.83 (3.42-4.28)</td>
<td>0.148</td>
<td>3.75 (3.22-4.36)</td>
<td>0.041</td>
</tr>
<tr>
<td>FEV1/FVC, median (IQR)</td>
<td>59.9 (55.3-69.8)</td>
<td>64.1 (58.2-77.8)</td>
<td>0.132</td>
<td>63.6 (55.2-72.3)</td>
<td>0.300</td>
<td>61.0 (53.9-71.6)</td>
<td>0.897</td>
<td>66.1 (62.6-71.1)</td>
<td>0.016</td>
</tr>
<tr>
<td>ΔFEV1 %, median (IQR)</td>
<td>12.4 (7.9-23.0)</td>
<td>10.4 (6.4-13.8)</td>
<td>0.221</td>
<td>9.0 (7.6-11.3)</td>
<td>0.221</td>
<td>9.9 (5.6-14.8)</td>
<td>0.363</td>
<td>3.6 (1.8-7.3)</td>
<td>0.003</td>
</tr>
<tr>
<td>ACQ score, median (IQR)</td>
<td>2.9 (2.1-3.7)</td>
<td>1.7 (1.1-2.6)</td>
<td>0.001</td>
<td>2.0 (1.3-4.0)</td>
<td>0.140</td>
<td>1.4 (0.9-2.6)</td>
<td>0.032</td>
<td>1.5 (1.0-2.4)</td>
<td>0.004</td>
</tr>
<tr>
<td>Mini AQLQ score, median (IQR)</td>
<td>4.0 (3.2-4.9)</td>
<td>5.2 (4.3-5.5)</td>
<td>0.017</td>
<td>5.2 (3.5-5.9)</td>
<td>0.286</td>
<td>5.5 (5.0-6.4)</td>
<td>0.011</td>
<td>5.6 (4.5-6.5)</td>
<td>0.008</td>
</tr>
<tr>
<td>FeNO, median (IQR)</td>
<td>30.0 (15.0-37.0)</td>
<td>28.0 (15.0-35.0)</td>
<td>0.660</td>
<td>30.0 (20.0-38.0)</td>
<td>0.345</td>
<td>23.0 (13.0-58.0)</td>
<td>0.570</td>
<td>21.5 (16.0-30.0)</td>
<td>0.470</td>
</tr>
</tbody>
</table>

*P-values with baseline characteristics as comparison

FEV1 forced expiratory volume in 1. Second, FVC forced vital capacity, ΔFEV1 increase in % after salbutamol (expressed as change in percentage of predicted value), fractional exhaled nitrogen oxid (FeNO), ACQ Asthma Control Questionnaire, and AQLQ quality of life questionnaire
**Table 3**

Static lung volumes, diffusion capacity and adverse events during follow-up in adults with severe asthma (n=16) undergoing bronchial thermoplasty treatment

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Baseline (n=16)</th>
<th>4 months (n=15)</th>
<th>p-value</th>
<th>8 months (n=14)</th>
<th>p-value</th>
<th>12 months (n=16)</th>
<th>p-value</th>
<th>24 months (n=14)</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td><strong>Doctor contacts</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Hospital admission</td>
<td>0 (0-0)</td>
<td>0 (0-0)</td>
<td>0.158</td>
<td>0 (0-0)</td>
<td>0.084</td>
<td>0 (0-0)</td>
<td>0.084</td>
<td>0 (0-0)</td>
<td>0.158</td>
</tr>
<tr>
<td>General practitioner (GP)</td>
<td>0 (0-0)</td>
<td>0 (0-1)</td>
<td>0.046</td>
<td>1 (0-1)</td>
<td>0.009</td>
<td>0 (0-1)</td>
<td>0.026</td>
<td>1 (0-1)</td>
<td>0.005</td>
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<td>GP on call</td>
<td>0 (0-0)</td>
<td>0 (0-0)</td>
<td>0.157</td>
<td>0 (0-0)</td>
<td>0.157</td>
<td>0 (0-0)</td>
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<td>0.157</td>
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<tr>
<td>Emergency department</td>
<td>0 (0-0)</td>
<td>0 (0-0)</td>
<td>0.317</td>
<td>0 (0-0)</td>
<td>0.317</td>
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<tr>
<td>Admission to intensive care unit</td>
<td>0 (0-0)</td>
<td>0 (0-0)</td>
<td>.</td>
<td>0 (0-1)</td>
<td>0.317</td>
<td>0 (0-0)</td>
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<td>0 (0-1)</td>
<td>0.317</td>
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<tr>
<td>Admission to Acute medical ward</td>
<td>0 (0-0)</td>
<td>2 (1-2)</td>
<td>0.180</td>
<td>1 (1-3)</td>
<td>0.102</td>
<td>1 (1-3)</td>
<td>0.102</td>
<td>1 (1-1)</td>
<td>0.157</td>
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<td>Outpatient clinic</td>
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<td>0 (0-0)</td>
<td>0.157</td>
<td>0 (0-0)</td>
<td>0.317</td>
<td>0 (0-0)</td>
<td>0.317</td>
<td>0 (0-0)</td>
<td>0.157</td>
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<tr>
<td><strong>Medications</strong></td>
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<td></td>
<td></td>
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<tr>
<td>Increase in inhaled bronchodilator use</td>
<td>0 (0.0%)</td>
<td>3 (20.0%)</td>
<td>0.060</td>
<td>1 (7.1%)</td>
<td>0.277</td>
<td>1 (6.2%)</td>
<td>0.310</td>
<td>0 (0.0%)</td>
<td>.</td>
</tr>
<tr>
<td>Increase in inhaled corticosteroid use</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>.</td>
<td>1 (7.1%)</td>
<td>0.277</td>
<td>0 (0.0%)</td>
<td>.</td>
<td>1 (7.1%)</td>
<td>0.277</td>
</tr>
<tr>
<td>OCS rescue course</td>
<td>0 (0.0%)</td>
<td>6 (40.0%)</td>
<td>0.005</td>
<td>6 (42.9%)</td>
<td>0.003</td>
<td>6 (37.5%)</td>
<td>0.007</td>
<td>5 (35.7%)</td>
<td>0.009</td>
</tr>
<tr>
<td>Antibiotics short course</td>
<td>0 (0.0%)</td>
<td>3 (20.0%)</td>
<td>0.060</td>
<td>7 (50.0%)</td>
<td>0.001</td>
<td>4 (25.0%)</td>
<td>0.033</td>
<td>6 (42.9%)</td>
<td>0.003</td>
</tr>
<tr>
<td>Symptoms of RTI</td>
<td>0 (0.0%)</td>
<td>5 (33.3%)</td>
<td>0.012</td>
<td>5 (35.7%)</td>
<td>0.009</td>
<td>4 (25.0%)</td>
<td>0.033</td>
<td>6 (42.9%)</td>
<td>0.003</td>
</tr>
<tr>
<td><strong>Lung function</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TLC</td>
<td>5.82 (5.48-7.28)</td>
<td></td>
<td></td>
<td>6.14 (5.36-7.37)</td>
<td>0.955</td>
<td>6.09 (5.02-6.66)</td>
<td>0.197</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DLCOc</td>
<td>8.86 (7.94-10.91)</td>
<td></td>
<td></td>
<td>8.91 (7.14-10.41)</td>
<td>0.490</td>
<td>9.28 (7.08-10.68)</td>
<td>0.388</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* P-values were calculated with baseline as comparison

OCS oral corticosteroids, RTI respiratory tract infection, TLC total lung capacity, and DLCOc: haemoglobin corrected diffusing capacity for carbon monoxide.
Figure 1.
Asthma Control Questionnaire (ACQ) score at baseline and at 4, 8, 12, and 24 months following bronchial thermoplasty treatment (three treatment sessions) in adults with severe asthma, (with each line representing one patient).
Figure 2.

Mini-Asthma Quality of Life Questionnaire (mini-AQLQ) score at baseline and at 4, 8, 12, and 24 months following bronchial thermoplasty treatment (three treatment sessions) in adults with severe asthma, (with each line representing one patient).