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ORIGINAL ARTICLE

Bronchial thermoplasty versus mepolizumab: Comparison of outcomes in a severe asthma clinic

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ABSTRACT

Background and objective: **BT and interleukin-blocking monoclonal antibodies are both effective therapies for severe asthma, but there have been no direct comparisons between the two treatments. The aim of this study was to compare the efficacy and safety of BT and mepolizumab, in a real-world setting.**

Methods: **Patients with severe asthma despite optimized inhaler therapy were drawn from a severe asthma clinic in a tertiary hospital. Every patient commencing therapy with BT or mepolizumab was prospectively included in a national registry. At predetermined assessment points over a 12-month period, assessments were made of ACQ, spirometry, oral corticosteroid requiring exacerbations, reliever medication and maintenance oral corticosteroid use.**

Results: **A total of 91 patients with severe asthma participated: mean ACQ score 3.5 ± 1.0, FEV_1 51.4 ± 17.7%, maintenance oral steroids 48.3% and 11.5 ± 10.0 inhalations/day reliever therapy. Forty-seven patients received mepolizumab and 44 received BT. Baseline characteristics were similar except significantly higher blood eosinophil count in the mepolizumab group. At 12 months, there were no differences between treatment outcomes for ACQ (1.9 ± 1.3 mepolizumab vs 1.7 ± 1.3 BT), exacerbation rate (0.9 ± 1.1 vs 0.9 ± 1.5), reduction in reliever use (−6.3 ± 10.5 vs −5.0 ± 8.8 puffs/day) or reduction in oral corticosteroids (−3.3 ± 7.5 vs − 5.8 ± 6.7 mg/day). The FEV_1 improved equally (160 ± 290 vs 150 ± 460 mL). Readmission or prolonged admission was observed in 18.2% of BT patients, whilst 25.5% of mepolizumab patients had discontinued treatment at 12 months, 14.9% due to an adverse event or non-compliance.**

Conclusion: **The results suggest that BT is as efficacious as mepolizumab for the treatment of severe asthma.**

SUMMARY AT A GLANCE

This is the first study to directly compare BT to the monoclonal antibody mepolizumab for the treatment of severe asthma. The findings suggest that BT is equally as effective as mepolizumab in reducing symptoms, exacerbations and oral steroid use, without being limited to patients with an eosinophilic phenotype.

Key words: asthma, bronchial thermoplasty, mepolizumab, therapy.

INTRODUCTION

Severe asthma, whilst only affecting 5–10% of all asthma patients, remains a leading cause of morbidity and healthcare utilization.[1,2] Delivering individualized therapy to target-specific phenotypes is now the accepted standard in the management of severe asthma. The Global Initiative for Asthma recommends monoclonal antibodies and/or bronchial thermoplasty (BT) as add-on treatment options for step 5 asthma, that is, those with uncontrolled symptoms despite maximal inhaled corticosteroids and long-acting bronchodilators.[3]

BT is an endoscopic procedure that delivers radiofrequency energy to the airway smooth muscle. Its efficacy and safety were shown in three randomized controlled studies.[4–6] Its applicability and effectiveness in the severe asthma group have also been described in real-world data.[7–9] Mepolizumab is a monoclonal antibody that inhibits interleukin-5 bioactivity. In eosinophilic asthma, it has been demonstrated to decrease exacerbations and improve quality of life.[10–12]

To date, no direct comparisons of outcomes between BT and biologic treatment have been performed. An indirect treatment comparison of BT and omalizumab was recently published using randomized studies, but the results were limited by variability in patient selection of the two individual treatments.[13] Therefore, whilst current consensus is that BT may have a role in those who do not qualify for a biologic or those who fail to respond, evidence for this has not been established.[14]

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In this study, we compare the effectiveness of BT and mepolizumab from a single-centre severe asthma service and hypothesize that BT is non-inferior to mepolizumab.

METHODS

Study population and design

This was a single-centre, observational cohort study undertaken at a university teaching hospital in Victoria, Australia. Patients were recruited from the Severe Asthma Clinic, a tertiary referral service providing specialized therapies including monoclonal antibodies and BT. Patients under the care of a respiratory specialist were referred to the clinic if the physician was convinced that (i) the diagnosis was asthma; (ii) the disease was uncontrolled despite optimized inhaled triple therapy, including high-dose inhaled corticosteroids; and (iii) common comorbidities, such as gastro-oesophageal reflux and obstructive sleep apnoea, had been evaluated and treated. In the clinic itself, inhaler technique was evaluated and medication compliance checked against pharmacy records. The diagnosis of asthma was reconfirmed with lung function testing, and chest computed tomography (CT) scanning. A multidisciplinary discussion was then held to determine patient suitability for treatment with either BT or mepolizumab. All patients receiving BT or mepolizumab at our site were included, and patients were enrolled consecutively into national registries with prospective data collection. BT patients were enrolled between June 2014 and June 2019, whilst mepolizumab patients were enrolled from January 2017, when this drug was funded through the Australian Pharmaceutical Benefits Scheme. Approval to collate and audit data as part of quality assurance was provided by the Peninsula Health Human Research Ethics Committee. All participants provided informed consent for data collection, registry inclusion and for treatment. Specific permission to use the Asthma Control Questionnaire (5-item version) (ACQ) in this project was granted by its author, Elizabeth Juniper.

Patient assessments were conducted by experienced clinical research nursing staff, using a standardized assessment tool, developed for each registry. Quality of life and asthma control were assessed using the ACQ.[15] Exacerbations were recorded if oral corticosteroids had been initiated in a steroid-naïve patient or increased by >10 mg/day in a patient taking maintenance prednisolone. Current asthma medication usage was assessed at each visit. Lung function testing was performed in an accredited laboratory using the Jaeger Masterscreen Body (Carefusion, Hoechberg, Germany), in accordance with the European Respiratory Society/American Thoracic Society (ERS/ATS) guidelines for spirometry.[16] The Global Lung Initiative predicted references values were used.[17]

In patients receiving mepolizumab, assessments were undertaken at baseline, and then at 3–4, 6 and 12 months after therapy initiation, as dictated by the Australian Mepolizumab Registry.[18] In patients receiving BT, assessments were undertaken at baseline, 6 weeks, 6 months and 12 months post therapy, as part of the Australian BT Register.[9]

Procedures

Mepolizumab injections were administered by experienced research nurses in the clinic setting. BT procedures were performed under general anaesthesia, and all patients were electively admitted for at least 24 h post-procedure. The majority of patients received BT in three treatment sessions, but in six patients the treatment was compressed to two treatment sessions as part of another research study. All BT patients received 1 week of oral corticosteroids to cover the perioperative treatment period.

Outcomes

Measured over 12 months, mepolizumab and BT were compared across the following outcomes: (i) change in ACQ from baseline, (ii) change in 1-s forced expiratory volume (FEV_1) % predicted, (iii) frequency of oral steroid requiring exacerbations, (iv) requirement for short-acting beta-agonist (SABA) reliever therapy, measured in puffs per day and (v) requirement for maintenance oral corticosteroid therapy. Adverse events and therapy withdrawals were also recorded for both treatment groups. In the case of BT, an adverse event was recorded for any patient who remained in hospital longer than the planned elective 24-h stay, or any patient readmitted to hospital for any reason within 30 days of a procedure.

Statistical analysis

SPSS version 25 (IBM Corporation, Armonk, NY, USA) was used for all statistical analyses. Statistical significance was taken throughout as $P < 0.05$ for a two-tailed test. Grouped data are reported as mean $\pm$ SD, unless specifically indicated otherwise. A paired t-test was used for paired sets of data, whilst an unpaired t-test was used to compare groups. Analysis of variance was used to compare baseline data with repeated tests over time. Piecewise latent growth modelling was used to evaluate time trends in repeated measures observations.

RESULTS

Participants

During the period June 2014 to June 2019, 44 patients at the severe asthma clinic underwent BT and 47 patients commenced treatment with mepolizumab. All patients were included in the analysis. The baseline characteristics of the two cohorts of patients are compared in Table 1. Overall, this was a group of severe asthmatic patients with very obstructed lung function, high symptom burden and frequent exacerbations, despite high-dose inhaled steroid use plus long-acting bronchodilators. Many patients were being treated with maintenance oral corticosteroids. All patients met the ERS/ATS definition for severe asthma.[19]

Table 1 Baseline characteristics of participants

	BT group	Mepolizumab group	*P*
n	44	47	
Age (years)	56.3 ± 13.2	61.3 ± 12.6	0.07
Male sex	45.5%	44.7%	0.74
BMI (kg/m^2)	29.7 ± 6.9	30.5 ± 6.0	0.56
ACQ score	3.3 ± 1.0	3.7 ± 1.0	0.06
Smoking (pack-years)	5.0 ± 9.7	8.4 ± 13.4	0.17
SABA (puffs/day)	9.9 ± 8.9	13.0 ± 11.0	0.15
LABA use	98%	98%	0.90
LAMA use	100%	96%	0.95
ICS (μg/day)	1811 ± 653	1540 ± 799	0.12
OCS (mg/day)	7.9 ± 11.2	4.5 ± 7.1	0.08
OCS maintenance	57%	40%	0.11
Exacerbations/6 months	3.8 ± 3.7	2.8 ± 2.3	0.11
IgE (IU/mL)	288 ± 595	n/a	
Eosinophils (cells/μL)	280 ± 290	570 ± 290	0.001
FEV_1 (% predicted)	52.0 ± 17.5	50.8 ± 18	0.75
VC (% predicted)	82.2 ± 15.9	75.5 ± 15.9	0.049
FER (%)	51.5 ± 11.6	53.0 ± 13.3	0.56
FEV_1 reversibility (%)	17.8 ± 17.2	11.8 ± 13.2	0.06

ACQ, Asthma Control Questionnaire; BMI, body mass index; BT, bronchial thermoplasty; FER, forced expiratory ratio; FEV_1, 1-s forced expiratory volume; ICS, inhaled corticosteroid beclomethasone equivalent dose; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist; n/a, not available; OCS, oral prednisolone; SABA, short-acting beta-agonist; VC, vital capacity.

The two cohorts of patients were clinically similar, with one essential difference, namely that the mepolizumab group had a significantly higher peripheral blood eosinophil count. This is consistent with clinicians exercising a choice in favour of mepolizumab therapy for patients with an eosinophilic phenotype. This was tested further by comparing the baseline characteristics of patients undergoing BT prior to the availability of mepolizumab, with those undergoing BT after the availability of mepolizumab (Table S1 in Supplementary Information). In the post mepolizumab era, the baseline eosinophil count in BT patients was 190 ± 200 cells/μL, compared to 380 ± 320 cells/μL prior to mepolizumab availability ($P < 0.05$).

Adverse events and withdrawals

In the BT group, there were three instances out of 126 procedures (2.4%), when patients remained in hospital longer than the planned 24-h stay. All were for wheezing and resolved within a few days. There were six instances of readmission within 30 days of a procedure (4.7%) and the reasons included pneumonia, asthma, gastrointestinal bleeding and urinary retention. All resolved uneventfully with treatment. The frequency of a BT patient experiencing either a readmission, or a prolonged admission, was 18.2% over the whole treatment period. No patients were lost to subsequent follow-up.

Of the 47 patients initiated with mepolizumab, five patients (10.6%) withdrew owing to a treatment-related adverse event. Each event was verified by withholding treatment and then rechallenging the patient. Two patients experienced severe headaches, two patients experienced severe arthralgias and one patient developed an allergic rash. A further five patients withdrew from treatment (10.6%) when there was no evidence of clinical improvement (improvement in ACQ is a requirement for continued funding of mepolizumab in Australia). Two patients chose not to continue with their injections, finding them a nuisance. All patients were followed up for 12 months, but by the 12-month reassessment, 12 patients (25.5%) had discontinued mepolizumab treatment.

Response to treatment: ACQ

Following BT, the ACQ score improved from a baseline value of 3.3 ± 1.0 to 1.9 ± 1.3 at 6 weeks post BT, 1.8 ± 1.2 at 6 months and 1.7 ± 1.3 at 12 months ($P < 0.001$). Post hoc comparisons revealed the significant change occurred between baseline and the first time point, and thereafter the ACQ results remained stable.

Following mepolizumab treatment, the ACQ improved from a baseline value of 3.7 ± 1.0 to 2.2 ± 1.1 at 3–4 months, 2.0 ± 1.2 at 6 months and 1.9 ± 1.3 at 12 months ($P < 0.001$). Piecewise latent growth modelling demonstrated that the ACQ measurements between the second and fourth assessments continued to show significant improvement (slope: −0.145, $P < 0.001$).

The responses to the two therapies are compared graphically in Figure 1. At the 12-month assessment, there was no statistically significant difference in the improvement in ACQ in the two cohorts ($P = 0.251$, unpaired t-test). The overall probability of responding to BT at 12 months with an improvement in ACQ ≥0.5 was 77% in the BT group and 75% in the mepolizumab group.

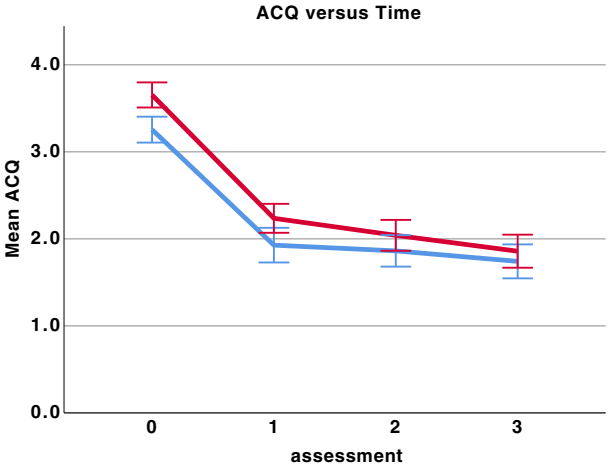

Figure 1 Comparison of ACQ responses: BT (I) versus mepolizumab (I). Timepoint: 0 = baseline, 1 = 6–12 weeks, 2 = 6 months, 3 = 12 months. ACQ, Asthma Control Questionnaire; BT, bronchial thermoplasty.

Response to treatment: FEV_1

The mean FEV_1 at baseline in the BT group was 52.0 ± 17.4% predicted. This increased to 56.3 ± 21.0% at the 6-month reassessment and 59.0 ± 21.7% at 12 months (P = 0.005) (Fig. 2). In the mepolizumab group, the FEV_1 at baseline was 50.2 ± 17.9% predicted, and this increased to 55.9 ± 21.9% at 6 months and 56.5 ± 20.7% at 12 months (P = 0.003) (Fig. 2). The improvements from baseline at the 12-month mark were not statistically different in the two groups (P = 0.92): 6.6 ± 14.2% or 150 ± 460 mL in the BT group, and 6.9 + 11.2% or 160 ± 290 mL in the mepolizumab group.

Response to treatment: Exacerbations

In the 6 months prior to BT, patients had experienced an average of 3.8 ± 3.7 oral corticosteroid requiring exacerbations. This reduced to 0.8 ± 1.2 exacerbations

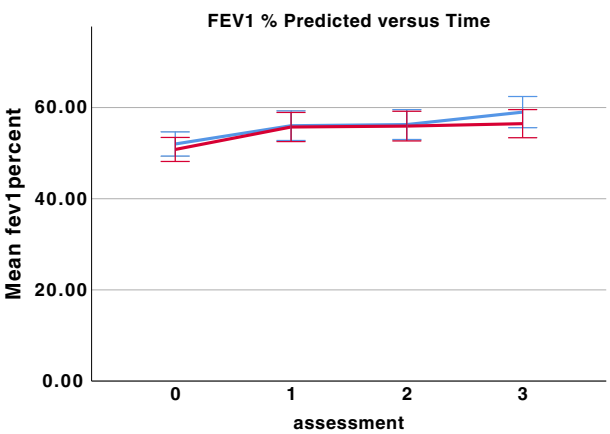

Figure 2 Comparison of FEV_1% predicted: BT (I) versus mepolizumab (I). Timepoint: 0 = baseline, 1 = 6–12 weeks, 2 = 6 months, 3 = 12 months. BT, bronchial thermoplasty; FEV_1, 1-s forced expiratory volume.

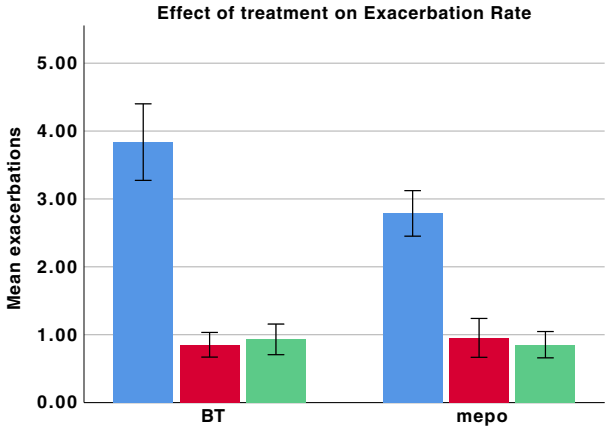

Figure 3 Exacerbation frequency: BT versus mepolizumab. Assessment: ■, baseline; ■, 6 months; ■, 12 months. BT, bronchial thermoplasty.

in the first 6 months after BT, and 0.9 ± 1.5 in the following 6 months (P < 0.001) (Fig. 3). In the 6 months prior to mepolizumab treatment, patients experienced an average of 2.8 ± 2.3 exacerbations. This reduced to 1.0 ± 1.9 exacerbations in the 6 months following therapy initiation, and 0.9 ± 1.1 in the next 6 months to the 12-month reassessment (P < 0.001) (Fig. 3). There were no differences between the two treatment groups in terms of exacerbation frequency at either the 6- or 12-month assessments. The probability of experiencing a 50% reduction in exacerbations at 12 months was 80% for BT and 64% for mepolizumab.

Response to treatment: Reliever medication usage

At baseline, patients in the BT group used an average of 9.9 ± 8.9 inhalations per day of SABA. At the 6-month reassessment, this had reduced to 4.4 ± 6.6 inhalations per day, and this was maintained at the 12-month assessment, 4.0 ± 6.4 inhalations per day (P = 0.001) (Fig. 4).

Patients treated with mepolizumab used 13.0 ± 11.0 inhalations per day of SABA at baseline. This reduced to 7.1 ± 9.8 inhalations per day at 6 months and 7.1 ± 9.8 at 12 months (P = 0.001) (Fig. 4). There was no significant difference between the magnitude of the improvement in SABA usage at 12 months in the two treatment groups (BT: −5.0 ± 8.8 puffs/day, mepolizumab: −6.3 ± 10.5 puffs/day, P = 0.57).

Response to treatment: Oral corticosteroids

Amongst BT patients, 25 (57%) were taking maintenance oral prednisolone at baseline (mean dose: 13.8 ± 12.0 mg/day). After 12 months, 11 patients (44%) had been weaned completely from oral steroids. The group mean prednisolone dose at 12 months was 4.4 ± 7.5 mg/day (P < 0.001).

Amongst the mepolizumab patients, 19 (40%) were taking maintenance oral prednisolone (mean dose: 11.1 ± 7.5 mg/day). Of these patients, five (26%) were completely weaned from oral steroids at 12 months,

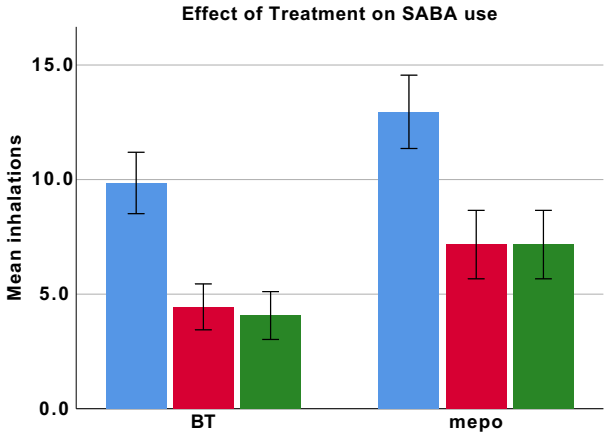

Figure 4 SABA requirement: BT versus mepolizumab. Assessment: ■, baseline; ■, 6 months; ■, 12 months. BT, bronchial thermoplasty; SABA, short-acting beta-agonist.

and the prednisolone dose for the group was 7.1 ± 11.4 mg/day (P = 0.07).

Subgroup analysis

Once mepolizumab became available, the clinical characteristics of patients selected for BT altered, becoming lower in blood eosinophil count (Table S1 in Supplementary Information). Therefore, we compared outcomes from BT in the 26 patients with an eosinophil count <300 cells/μL, with the 18 BT patients with a baseline eosinophil count ≥300 cells/μL. These data are shown in Table 2. There were no significant differences in response to BT across the range of outcome variables, including improvement in (i) ACQ, (ii) FEV_1% predicted, (iii) exacerbation frequency, (iv) maintenance oral steroid dose and (v) SABA use. Furthermore, the improvements observed following BT in the 18 eosinophilic patients were statistically indistinguishable from the improvements observed in the 47 eosinophilic patients treated with mepolizumab.

DISCUSSION

This study presents comparative outcomes from a group of very severe asthmatic patients treated at a tertiary centre either by BT or mepolizumab. The striking observation is the similarity in treatment response demonstrated in Figures 1–4. It would be difficult to argue that either one of these treatments was superior to the other across the range of parameters measured including improvement in ACQ, FEV_1, exacerbation frequency, reliever medication use or prednisolone dosage.

Further analysis of the BT group showed that the presence or absence of eosinophilic inflammation had no bearing on the ACQ outcome, with comparable results sustained over 12 months. This is consistent with the recently published, more rigorous analysis of predictive factors underlying response to BT.[20] This is

Table 2 Outcomes following BT in patients defined by baseline blood eosinophils

	Baseline blood eosinophils <300 (cells/μL)	Baseline blood eosinophils ≥300 (cells/μL)
n	26	18
Eosinophil count (cells/μL)	92 ± 16	550 ± 61*
Age (years)	58.1 ± 14.0	53.7 ± 11.9
BMI (kg/m^2)	30.5 ± 7.5	28.5 ± 5.8
ACQ baseline	3.3 ± 0.9	3.2 ± 1.1
ACQ 6 months	1.9 ± 1.1	1.9 ± 1.5
ACQ 12 months	1.7 ± 1.2	1.8 ± 1.5
FEV_1 baseline (% predicted)	52.7 ± 20.8	51.0 ± 11.7
FEV_1 6 months (% predicted)	56.0 ± 21.1	57.2 ± 21.2
FEV_1 12 months (% predicted)	58.0 ± 21.9	60.4 ± 21.4
Exacerbations base (per 6 months)	3.5 ± 2.7	5.6 ± 9.0
Exacerbations 6 months (per 6 months)	0.7 ± 1.0	1.1 ± 1.5
Exacerbations 12 months (per 6 months)	0.7 ± 1.0	1.2 ± 2.0
OCS (mg/day)	9.3 ± 11.8	5.9 ± 10.4
OCS (mg/day)	5.0 ± 7.2	3.9 ± 7.3
OCS (mg/day)	3.4 ± 5.8	5.8 ± 9.1
SABA base (puffs/day)	10.6 ± 9.6	8.8 ± 7.8
SABA 6 months (puffs/day)	4.6 ± 6.1	4.1 ± 7.6
SABA 12 months (puffs/day)	4.1 ± 5.2	4.3 ± 7.7

*P < 0.05.

ACQ, Asthma Control Questionnaire; BMI, body mass index; BT, bronchial thermoplasty; FEV_1, 1-s forced expiratory volume; OCS, oral prednisolone; SABA, short-acting beta-agonist.

an important observation for clinicians with significant implications for their patients.

During this study, it is clear that clinical practice shifted towards using mepolizumab in preference to BT for eosinophilic patients, in line with current expert recommendations.[21] This decision probably also reflects the prevailing medical mindset. For 100 years, asthma has been a disease treated with medication, and the initiation of a new pharmacological agent is likely a more familiar therapeutic step for most physicians than the initiation of a surgery. However, from the patient perspective, the impost of recurrent lifelong injections and the associated time commitments may not be viewed as favourably.[22] Cessation of biologics have been extensively reported in other diseases such as rheumatoid arthritis, with common patient concerns including injection discomfort or reaction, treatment duration and frequency.[23] Notably, there was a 25.5% withdrawal rate in our mepolizumab cohort.

It is important to note that the very high cost of anti-interleukin monoclonal antibodies therapy precludes their availability in many countries. The current study suggests that BT is an equally efficacious treatment option, which therefore could be used where monoclonal antibody therapy was not available. Furthermore, whilst the current model of practice is to consider BT after biologics, it might also be considered appropriate to proceed to BT prior to biologics, regardless of eosinophilic profile, if that was the patient's preference.

This study is good news for patients with a low blood eosinophil phenotype, where treatment options are more limited. The most recent addition to the therapeutic armamentarium for these patients has been the use of macrolide therapy.[24] In the AMAZES study, azithromycin significantly reduced exacerbation frequency but had modest effects on quality of life. The magnitude of the responses to BT in this current observational study compare favourably to the effects observed with macrolides, acknowledging the much stronger level of evidence in the randomized trial. In comparison with macrolide therapy, the safety of BT beyond 12 months has a strong evidence base, and BT does avoid the potentially significant issue of long-term antibiotic resistance.[25,26]

It must be acknowledged that this is an observational study—it is not a randomized control trial. There is demonstrated selection bias in the choice of treatments for individual patients, and there is the potential for bias in the recording of outcomes. On the other hand, there are no other published data directly comparing outcomes from BT with a biological agent, and there are no such clinical trials in progress.[27] The concordance in results between the two treatments in the current study is striking, thus providing insight into the outcomes from these two treatments in severe asthmatic patients treated in a real-world setting.

In conclusion, the outcomes from BT were comparable to mepolizumab, regardless of eosinophilic profile in this cohort of patients with severe asthma.

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Abbreviations: ACQ, Asthma Control Questionnaire; BT, bronchial thermoplasty; ERS/ATS, European Respiratory Society/American Thoracic Society; FEV_1, 1-s forced expiratory volume; Ig, immunoglobulin; OCS, oral prednisolone; SABA, short-acting beta-agonist.

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Supplementary Information

Additional supplementary information can be accessed via the *html* version of this article at the publisher's website.

Table S1 Characteristics of patients treated with bronchial thermoplasty: before and after mepolizumab availability.

