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ORIGINAL RESEARCH

A Retrospective Real-World Evaluation of the Clinical Outcomes of Biologic Therapy and Bronchial Thermoplasty in a Tertiary Severe Asthma Clinic

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Introduction: Asthma biologics and bronchial thermoplasty (BT) are both effective therapies for severe asthma but there are no direct comparisons between the two treatments. The aims of this study are to described the outcomes of patients with severe asthma managed at a tertiary centre severe asthma clinic with either biologics, BT, or both, and to compare the effectiveness of BT with currently available biologics.

Methods: Data was retrospectively collected at pre-specified timepoints—baseline, prior to BT (for patients undergoing BT), and at a follow-up clinic visit in July 2025. Data collected included demographics, serum biomarkers, lung function, asthma control questionnaire (ACQ), frequency of oral corticosteroid (OCS) requiring exacerbations, maintenance OCS dose, initial treatment prescribed and treatment changes over time.

Results: One hundred and fifteen consecutive patients' data were reviewed. Significant improvements in ACQ (3.4 (3–4.2) vs 1.8 (0.8–2.6), P<0.001) and number of OCS-requiring exacerbations (2 (1–4) vs 1 (0–1), P<0.001) were noted at follow-up compared to baseline. Sixty percent of patients who were on OCS at baseline were able to be successfully weaned off and 50% of the remaining patients were able to reduce their dose. Patients who underwent BT were either ineligible for (27%), or failed to respond to biologic therapy (73%). Despite this, significant reductions in ACQ (2.9 (2.2–3.5) vs 1.8 (1.2–2.5), P<0.001), OCS-requiring exacerbations (3.5 (2–6) vs 0 (0–1.3), P<0.001), and maintenance OCS dose were observed post BT. No significant difference was noted in the magnitude of change in key clinical outcomes between patients treated with biologics and those who underwent BT.

Conclusion: In this retrospective real-world study, patients treated with BT had comparable clinical outcomes to those treated with asthma biologics. This included a subset of patients who were ineligible for, or failed to respond to biologic therapy. These results support the ongoing role of BT in the era of biologic therapy.

Keywords: asthma control, bronchial thermoplasty, exacerbations, monoclonal antibodies, severe asthma

Introduction

Asthma is a common disease that affects approximately 250 million people worldwide and accounts for >20 million disability-adjusted life years.[1] Majority of patients with asthma will be able to achieve good symptom control and minimal exacerbations with combination inhalers although approximately 5–10% of them will require additional and expensive specialist therapies such as monoclonal antibodies and bronchial thermoplasty. This group of individuals is said to have severe asthma.[2]

Recent advances in our understanding of the pathobiology of asthma have led to the recognition of two main inflammatory endotypes – type 2 (T2) high and T2-low – and the subsequent development of monoclonal antibodies targeting the biological pathways which drive these endotypes.[3] Briefly, T2-high asthma is mediated by interleukin (IL)-

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4, IL-5, and IL-13 and characterized by elevated blood or sputum eosinophils, serum immunoglobulin E (IgE) levels and fractional exhaled nitric oxide (FeNO). These are the targets of omalizumab (anti-IgE), mepolizumab/reslizumab (anti-IL-5), benralizumab (anti-IL5 receptor alpha subunit), and dupilumab (anti-IL4 and IL-13). In contrast, T2-low asthma remains poorly understood and is often neutrophilic or pauci-granulocytic.[4]

Accurately defining the patient's inflammatory phenotype is a crucial step in deciding which of these monoclonal antibodies, known more commonly as asthma biologics, to use. The possibility of T2-high asthma should be considered if any of the following are found while the patient is receiving optimal inhaler therapy and/or maintenance oral corticosteroids (OCS): (i) blood eosinophil >150/uL; (ii) FeNO ≥20 ppb; (iii) sputum eosinophils ≥2%; and (iv) asthma is clinically allergen-driven.[5] Importantly, these criteria are suggested for initial assessment and may not be the same criteria used in determining the eligibility for asthma biologics, which may differ based on local regulatory and payer criteria. Furthermore, these biomarkers, in addition to the individual's clinical phenotype, are associated with predictors of response. For example, good predictors of response to omalizumab include childhood-onset asthma and a clinical history of allergen-driven symptom whereas patients with adult-onset asthma (often females with obesity), nasal polyps and higher blood eosinophil counts tend to benefit more with mepolizumab and benralizumab. Similarly, higher blood eosinophil counts and higher FeNO are associated with a greater response to dupilumab and tezepelumab despite the latter acting upstream in the inflammatory cascade and being approved for patients with both T2-high and T2-low severe asthma.[4,5]

Bronchial thermoplasty (BT) is a bronchoscopic procedure that delivers radiofrequency energy to thermally ablate the airway smooth muscle layer.[6] Its safety and efficacy have been shown in numerous randomized controlled trials and real-word registries,[7,8] including in patients with severe asthma.[9–11] Current guidelines reflect a cautious approach to BT, with many preferring asthma biologics, leaving BT as a treatment of last resort.[5] Furthermore, the lack of head to head comparative trials have given rise to concerns that BT may be less effective than asthma biologics, despite a recent network meta-analysis suggesting otherwise.[12]

Therefore, the aims of this single-centre real word study are to (i) describe the outcomes of patients with severe asthma who are being managed at a tertiary centre Severe Asthma Clinic, and (ii) compare the effectiveness of BT and omalizumab, mepolizumab, benralizumab and dupilumab over time.

Methods

This was a single-centre, retrospective chart-based study undertaken at an Australian university teaching hospital. Data from all patients seen in the Severe Asthma Clinic from inception (2011) to December 2024 were reviewed. For context, the Severe Asthma Clinic is a tertiary referral service providing specialized therapies including asthma biologics and BT. All patients seen in this clinic had to have a diagnosis of severe uncontrolled asthma as defined by the European Respiratory Society/American Thoracic Society.[2] Specifically, patients needed to show evidence of either frequent asthma exacerbations (≥ 2 OCS requiring episodes), or high symptom burden (5-item Asthma Control Questionnaire (ACQ) ≥ 2) in the preceding 12 months despite receiving Global Initiative for Asthma (GINA) Step 4 treatment for at least 6-months.[5]

All patients attending were assessed and optimized for adherence and management of co-morbidities. Patients were considered for add-on therapies depending on their asthma phenotype, endotype, and what was available in Australia at the time of their consultation – omalizumab (2011), BT (2013), mepolizumab (2017), reslizumab (2017), benralizumab (2018), and dupilumab (2021). Omalizumab, mepolizumab, benralizumab and dupilumab are all subsidized by the Australian Pharmaceutical Benefits Scheme for patients who fulfil strict criteria as listed in Table 1. Patients who did not meet these criteria were considered ineligible for asthma biologics. Additionally, patients were required to demonstrate a reduction in ACQ ≥0.5, or a 25% decrease in maintenance OCS with a ≤0.5 increase in ACQ in order to qualify for ongoing government subsidy. Patients who failed to fulfil these criteria were considered to have a suboptimal response. Although reslizumab is also approved for use in Australia, it remains unsubsidized and cost prohibitive and therefore not prescribed at our centre. Tezepelumab is currently not approved for use in Australia.

In general, omalizumab was the asthma biologic of choice for patients with severe non-eosinophilic allergic asthma, high serum IgE levels and at least one sensitization to a perennial allergen. Conversely, mepolizumab, benralizumab and

Table 1 Australian Pharmaceutical Benefits Scheme Criteria for Accessing Asthma Biologics

General requirements for biologic therapies
• Age ≥12 years at time of application • Confirmed asthma diagnosis for at least 12 months • Under the care of a respiratory physician, clinical immunologist, allergist or general physician experienced in the management of severe asthma • Failure to achieve adequate asthma control despite being adherent to optimal asthma therapy including: (i) high dose inhaled corticosteroids (equivalent to 1600mcg/day); (ii) long-acting beta$_2$-agonist; and (iii) daily oral corticosteroid for at least six weeks or a cumulative dose of at least 500mg prednisolone equivalent in the last 12 months* • Failure to achieve adequate asthma control despite optimal asthma therapy evidenced by (i) at least one asthma exacerbation requiring hospitalisation or systemic corticosteroid; and (ii) Asthma Control Questionnaire-5 score of ≥2
Additional requirements for specific biologic agents
• Elevated blood eosinophil counts ≥300 cells/uL or ≥150 cells/uL while receiving oral corticosteroids (mepolizumab, benralizumab, dupulimab) • Evidence of atopy on skin prick testing or radioallergosorbent test accompanied by total serum IgE ≥30 IU/mL (omalizumab, dupilumab) • Maintenance oral corticosteroid in the last 6 months with a stable daily dose of 5–35mg prednisolone equivalent in the 4 weeks prior to commencement treatment (dupilumab)

Note: * Criteria (iii) was removed in the 2024 update.
Abbreviation: IgE, serum immunoglobulin E levels.

dupilumab were selected in patients who exhibited severe eosinophilic asthma. The presence of comorbid conditions such as nasal polyps or severe eczema may also influence treatment decision, as does the number and frequency of injections. Ultimately, the final decision was made between the treating clinician in conjunction with patient preferences. Biologic switches were considered in the event of a suboptimal response after a 6-month period, or due to treatment side effects. Therapeutic switches were performed directly without a washout period. Patients considered for BT were those that were ineligible for, or did not respond to asthma biologics, or were unwilling to undergo treatment with asthma biologics for life.

For each patient, we collected the following baseline data: (i) demographics including whether asthma was diagnosed as a child (<18years) or an adult (≥18 years); (ii) serum biomarkers (serum total IgE level, blood eosinophil count, skin prick or serum specific IgE test results); (iii) clinical (ACQ, frequency of OCS requiring exacerbations in the prior 12 months, maintenance OCS dose); (iv) lung function (forced expiratory volume in 1 second (FEV1), FeNO); and (iv) initial biologic prescribed. Patients were routinely reviewed every 3–6 months, and follow-up data was collected from either the clinic visit closest to July 2025, or the last recorded clinic review for patients who discontinued care. Data recorded from this visit included (i) treatment changes over time (biologic switches or BT); (ii) ACQ; (iii) number of OCS requiring exacerbations in the preceding 12 months; and (iv) current maintenance OCS dose. Additional pre-treatment data were also collected for patients who underwent bronchial thermoplasty.

Ethical approval and patient consent to review their medical records for this study had been waived by Eastern Health institutional review board because of its retrospective nature and the use of data that had been collected as part of standard clinical care. All data, including patient data confidentiality, was handled in accordance with the National Health and Medical Research Council Guidelines Ethical Considerations in Quality Assurance and Evaluation Activities (2014).

Statistical Analysis

Statistical analysis was performed using SPSS Version 29 (IBM corporation, New York, USA). Continuous data was summarised using mean, median, standard deviation or interquartile range depending on the normality of their distribution. Categorial data were presented as number and percentage. Between group comparisons were performed using Mann Whitney U-test for continuous variables and χ^2 or Fisher's exact test for categorical variables. Dependent group measurements were tested for significance using Wilcoxon signed-rank test for two groups, and Friedman test for three or more groups. The Bonferroni correction was used to correct for multiple comparisons. The effect size for Wilcoxon signed-rank test and Mann Whitney U-test was calculated using the formula $r = Z/\sqrt{N}$ where Z refers to the

Z-statistic and N the total number of observations, while the Kendall's W was used for Friedman test. The magnitude of the effect size was interpreted using the scale proposed by Sawilowsky et al, where effect sizes are classified as very small (0.01), small (0,2), medium (0.5), large (0.8), very large (1.2) and huge (2.0).[13] A P value of <0.05 was considered statistically significant.

Results

Baseline Demographics and Characteristics

Overall, 115 consecutive patients were included. Among these, 61% (70) were female and the mean age was 60.7 ± 15.4 years. The median serum IgE level was 169 (65–401) IU/mL, with just under 80% (90) of patients showing evidence of atopy defined as either a positive skin prick test to common allergens or a positive serum specific IgE test. The median blood eosinophil count was 360 (130–560) cells/uL, with 57% (65) of patients considered to have eosinophilic asthma based on a blood eosinophil count of ≥300 cells/uL. Forty-one percent (47) of patients exhibited both atopic and eosinophilic endotype. Baseline FEV1 was 59.4 ± 20.0% predicted and FeNO was 31 (18–50) ppb. The average duration of follow-up was 54.0 ± 32.0 months. A summary is provided in Table 2.

Patients had uncontrolled asthma evidenced by high symptom burden and frequent exacerbations. The median ACQ was 3.4 (3–4.2) and the median number of OCS requiring exacerbations was 2 (1–4). Forty-one percent (47) of patients were taking maintenance OCS with a group median dose of 10 (5–12.5) mg/day.

Seven percent (8) of patients were ineligible for an asthma biologic. Of the 93% (107) who were eligible, 51% (55) were commenced on omalizumab, 28% (30) on benralizumab, 18% (19) on mepolizumab and 3% (3) on dupilumab.

Follow-Up Outcomes

Significant improvements in ACQ, number of OCS-requiring exacerbations and maintenance OCS dose were noted at follow-up compared to baseline (Table 3). Median ACQ was reduced from 3.4 (3–4.2) to 1.8 (0.8–2.6) (P<0.001, effect size −0.56), along with a reduction in the median number of OCS-requiring exacerbations from 2 (1–4) to 1 (0–1) (P<0.001, effect size −0.52). Sixty percent (28) of patients who were on maintenance OCS at baseline were able to be completely weaned off. Of the remaining 19 patients who continued to require maintenance OCS, 47% (9) were able to decrease their dose, 37% (7) experienced no dose changes, and 16% (3) required a slight increase in dose by 2.5–7.5mg.

Table 2 Baseline Characteristics

Variable	Entire Cohort (N=115)	Biologic Only (N=85)	BT (N=30)	P value†
Age (years)	60.7 ± 15.4	62.3 ± 14.5	56.1 ± 17.0	0.06
Female / Male (%)	70 (61) / 45 (39)	51 (60) / 34 (40)	19 (63) / 11 (37)	0.75
Childhood asthma (%)	67 (58)	48 (56)	19 (63)	0.51
Atopy (%)	90 (78.3)	65 (76.5)	25 (83)	0.43
IgE (IU/mL)	169 (65–401)	186 (77–412)	114 (39–372)	0.17
Blood eosinophil count (cells/uL)	360 (130–560)	0.4 (0.2–0.63)	0.2 (0.1–0.3)	0.005
FEV1 (% predicted)	59.4 ± 20.0	59.4 ± 18.8	59.0 ± 22.0	0.93
FeNO (ppb)*	31 (18–50)	31 (20–51)	26 (18–49)	0.61
Duration of follow-up (months)	54.0 ± 32.0	49.5 ± 31.5	66.9 ± 30.3	0.009

Note: *N=106. † Comparison between biologic only and BT groups. Values presented as number (%), mean ± SD or median (IQD).
Abbreviations: BT, bronchial thermoplasty; FEV1, forced expiratory volume in 1 second; FeNO, fractional exhaled nitric oxide; IgE, serum immunoglobulin E levels.

Table 3 Changes in Key Outcome Measures for Entire Cohort

Clinical Variables (N=115)	Baseline	Follow-Up	P value	Effect Size
ACQ	3.4 (3–4.2)	1.8 (0.8–2.6)	<0.001	−0.56
OCS dose (mg/day)*	10 (5–12.5)	0 (0–5)	<0.001	−0.53
Exacerbation	2 (1–4)	1 (0–1)	<0.001	−0.52
Asthma biologic distribution (N=115)				
Not on biologic	8 (7)	22 (19)		
On biologic	107 (93)	93 (81)		
Omalizumab	55 (51)	34 (37)		
Mepolizumab	19 (18)	19 (20)		
Benralizumab	30 (28)	21 (23)		
Dupilumab	3 (3)	19 (20)		

Notes: *Within group analysis of N=47 patients who were on OCS at baseline. Values presented as number (%) or median (IQD).
Abbreviations: ACQ, asthma control questionnaire; OCS, oral corticosteroids.

As a group, 82% (92) of patients experienced a ≥0.5-point decrease in ACQ between baseline and follow-up, with 45% of patients reporting an ACQ of <1.5 at follow-up. This represented a significant reduction in the number of patients with poorly controlled asthma (defined as ACQ ≥1.5) given the lowest ACQ recorded at baseline was 1.6.

Changes in the distribution of asthma biologics were also noted (Figure 1 and Table 3). Sixty-two percent (66) of the 107 patients who were receiving an asthma biologic at baseline continued with their initial biologic throughout the follow-up period. Twenty-one percent (22) undertook one biologic switch, with 8% (9) switching twice. Majority of the switches involved patients who were initially treated with omalizumab, with dupilumab the biologic of choice for most of the switches. Thirteen percent (14) of patients discontinued their biologic due to a lack of treatment efficacy. Expectedly, none of the 8 patients who were ineligible for an asthma biologic at baseline commenced biologic therapy during the follow-up period.

Subgroup Analysis of Patients Who Underwent Bronchial Thermoplasty

Twenty-six percent (30) of patients underwent BT. Apart from a lower blood eosinophil count, there were no significant differences in baseline characteristics between patients who underwent BT and those who did not (Table 2). Of the 30 patients who received treatment with BT, 27% (8) were ineligible for biologic therapy; 23% (7) were previously on biologic therapy but discontinued due to lack of efficacy, including 4 patients who switched once; and 50% (15) were actively receiving treatment with biologic therapy at the time of their procedure. Among the 15 patients on biologic therapy, 33% (5) had switched once and 20% (3) had switched twice before a decision was made to proceed with BT.

Changes in clinical outcomes were also analysed in this subgroup (Table 4). The median ACQ showed a non-significant improvement from 3.5 (2.6–4.4) at baseline to 2.9 (2.2–3.5) prior to BT. Post treatment, a significant reduction in ACQ was observed from 2.9 (2.2–3.5) to 1.8 (1.2–2.5) at follow-up. From a different perspective, the median change in ACQ between baseline and pre-BT was −0.2 (−0.8–0), with 33% (10) patients achieving a ≥0.5-point decrease in ACQ. Despite this, all patients continued to have poorly controlled asthma with no patient having an ACQ <1.5. Post BT, the median change in ACQ was −1.0 (−1.8- −0.2), with 63% (19) of patients reporting a ≥0.5-point decrease in ACQ and 37% (11) achieving an ACQ<1.5.

The number of OCS-requiring exacerbations also showed a similar pattern with 3 (1–4) exacerbations at baseline, 3.5 (2–6) prior to BT, and 0 (0–1.3) at follow-up. Thirty-three percent (10) of patients in this group were on maintenance OCS at baseline. Four patients were successfully weaned off prior to BT but an additional 2 patients were commenced on

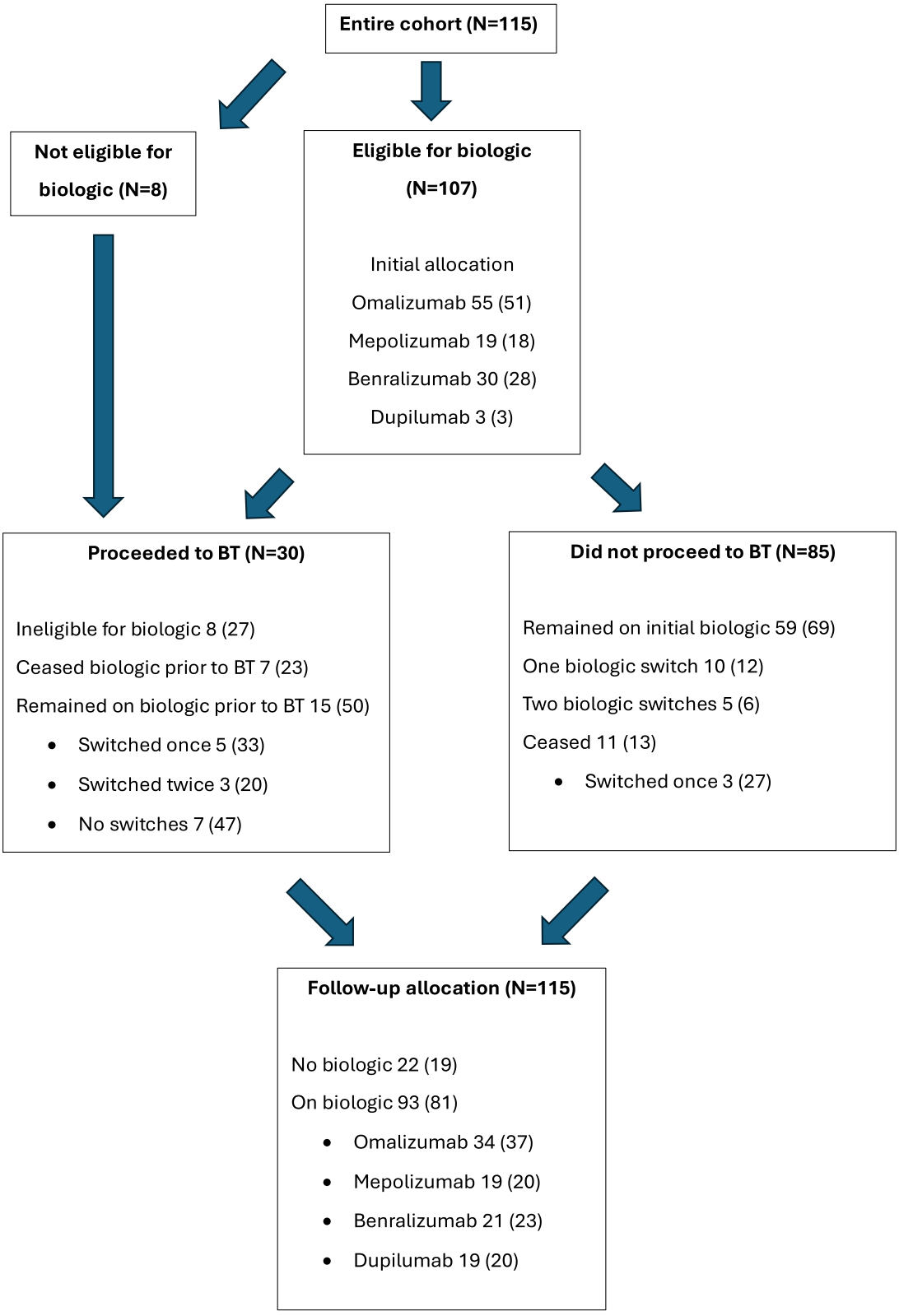

Figure 1 Flowchart showing treatment allocation and treatment changes over time. Values presented as number with their % of the group, or the subgroup in brackets. **Abbreviation**: BT, bronchial thermoplasty.

Table 4 Changes in Key Clinical Outcomes for Patients Treated with Only an Asthma Biologic and Those Who Underwent Bronchial Thermoplasty

BT (N=30)	**Baseline**	**Pre-BT**	**Follow-Up**	**P value**	**Effect Size**
ACQ	3.5 (2.6–4.4)	2.9 (2.2–3.5)	1.8 (1.2–2.5)	<0.001*	−0.53
Exacerbations	3 (1–4)	3.5 (2–6)	0 (0–1.3)	<0.001*	−0.46
OCS dose (mg/day)†	10 (10–12.5)	10 (5–30)	5 (5–10)	0.026‡	−0.52
Biologic only (N=85)	**Baseline**	**Pre-BT**	**Follow-up**	**P value**	**Effect size**
ACQ	3.4 (3–4)	-	1.6 (0.8–2.8)	<0.001	−0.56
Exacerbations	2 (1–4)	-	1 (0–1)	<0.001	−0.50
OCS dose (mg/day) †	10 (5–11.3)	-	5 (3.5–8.5)	0.009	−0.35
Variable	**Entire cohort (N=115)**	**Biologic only (N=85)**	**BT (N=30)**	**P value§**	**Effect size**
Delta ACQ¶	−1.6 (−2.7 - −0.7)	−1.8 (−2.8- −0.8)	−1.5 (−2.4- −0.6)	0.24	0.11
Delta exacerbations¶	−1 (−3- −1)	−1 (−3- −1)	2 (−3- −1)	0.48	−0.07

Notes: *Friedman test with Bonferroni correction and Kendall W effect size †Within group analysis of patients who were on OCS at various timepoints: For BT group: N=10 at baseline, N=8 pre-BT, and N=7 at follow-up; for biologic only group: N=37 at baseline, N=17 at follow-up. ‡Mann Whitney *U*-test between baseline and follow-up. §Mann Whitney *U*-test between biologic only and BT groups. ¶Delta refers to the change in variable between follow-up and baseline.

Abbreviations: ACQ, asthma control questionnaire; BT, bronchial thermoplasty; OCS, oral corticosteroids.

OCS over the same period. Fifty percent (4) of patients who required maintenance OCS prior to BT were able to reduce their OCS dose at follow-up including 2 that were weaned off completely. The remaining 50% (4) had no changes to their OCS dose.

There was no significant difference in the median change in ACQ between baseline and follow-up when comparing the 30 patients who underwent BT with the 85 patients who were treated with asthma biologics (−1.5 (−2.4- −0.6) vs −1.8 (−2.8- −0.8), P=0.24, effect size 0.11) (Figure 2). Likewise, the reductions in number of OCS-requiring exacerbations were similar in both groups (−2 (−3- −1) vs −1 (−3- −1), P=0.48, effect size −0.07). In terms of maintenance OCS use, 60% of patients who underwent BT were able to be weaned completely off maintenance OCS at follow-up compared to baseline. An additional 20% had a >50% reduction in maintenance OCS dose. This is comparable to that achieved in patients only treated with asthma biologics.

Nineteen out of 30 patients (63%) who underwent BT had an improvement in ACQ by >0.5 (between pre-BT and follow-up) and were classified as responders. The 11 non-responders were compared with their counterparts across a range of demographic, clinical and lung function variables (Table 5). Responders were found to have a significantly higher baseline FEV1%predicted (65.2 ± 21.0 vs 48.3 ± 20.4, p=0.04) compared to non-responders. No other significant differences were observed.

Additional comparisons were performed between the 15 patients who were on a biologic at the time of their BT procedure and the 15 patients who were not. Apart from baseline IgE which was significantly higher in those on a biologic at the time of their BT procedure (169 (113.5–620) vs 54 (27.5–121), p=0.01), the groups were otherwise comparable in regards to baseline characteristics, percentage of BT responders, and magnitude of clinical benefit (Table 6).

Discussion

In this retrospective real world study of severe refractory asthma patients treated at a tertiary referral centre, we showed that patients treated with BT had comparable outcomes to those treated with a range of currently available asthma biologics. Furthermore, we demonstrated the effectiveness of BT in a subset of patients who were ineligible for asthma biologics, or failed to achieve adequate asthma control despite biologic treatment.

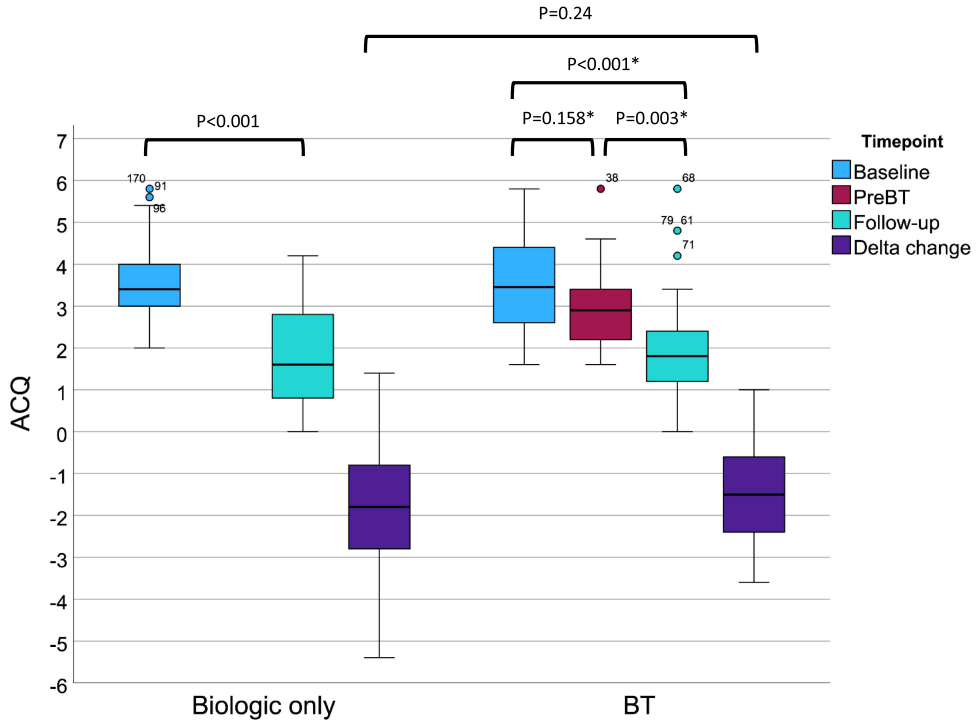

Figure 2 Box and whisker plots showing the changes in ACQ over time for patients who were only treated with an asthma biologic (N=85) (left) and those who underwent BT (N=30) (right). Delta change refers to the change in ACQ at follow-up compared to baseline. *Friedman test with P-values adjusted by Bonferroni correction for multiple tests. **Abbreviations**: ACQ, asthma control questionnaire; BT, bronchial thermoplasty.

All patients had severe refractory asthma at the time of referral to our Severe Asthma Clinic as evidenced by persistent airflow obstruction on lung function, high symptom burden and frequent exacerbations despite being on GINA step 4 treatment. This included 41% of patients requiring maintenance OCS. Following treatment with either asthma biologics or BT, significant and substantial improvements in ACQ, OCS-requiring exacerbation and maintenance OCS dose were reported over the mean follow-up period of 4.5 years.

On a more granular level, our data showed that majority of patients would be able to achieve good asthma control with asthma biologics alone, even if this necessitated biologic switches. However, this was not the case for 26% of patients in our cohort who proceeded to undergo BT. Importantly, the overwhelming majority (~75%) of these patients

Table 5 Difference Between BT Responders and Non-Responders

Baseline Variable	Responder (N=19)	Non-Responder (N=11)	P value
Age (years)	55.8 ± 16.0	56.6 ± 19.2	0.90
Female / Male (%)	12 (63) / 7 (37)	7(64) / 4 (36)	0.98
Childhood asthma (%)	13 (68)	6 (55)	0.45
Atopy (%)	16 (84)	9 (82)	0.87
IgE (IU/mL)	158 (75–549)	54 (28–210)	0.13
Blood eosinophil count (cells/uL)	0.2 (0.11–0.35)	0.14 (0.09–0.24)	0.21
FEV1 (% predicted)	65.2 ± 21.0	48.3 ± 20.4	0.04
FeNO (ppb)*	26 (14–50)	28 (23–47)	0.37

(*Continued*)

Table 5 (Continued).

Baseline Variable	Responder (N=19)	Non-Responder (N=11)	P value
Biologic use†	10 (53)	5 (46)	0.71
OCS (mg/day)	0 (0–5)	0 (0–7.5)	0.38
ACQ	3.4 (2.6–4.3)	3.5 (2.5–4.2)	0.95
Exacerbations	3 (1–4)	2 (1.5–4)	0.91
Delta ACQ	−1.6 (−2- −1)	0 (−0.25–0.1)	<0.001

Notes: *N=29. †Refers to patients who were on an asthma biologic at the time of BT. Values presented as number (%), mean ± SD or median (IQD).
Abbreviations: ACQ, asthma control questionnaire; BT, bronchial thermoplasty; Delta ACQ, change in ACQ between follow-up and pre bronchial thermoplasty; FEV1, forced expiratory volume in 1 second; FeNO, fractional exhaled nitric oxide; IgE, serum immunoglobulin E levels; OCS, oral corticosteroid.

Table 6 Difference Between Patients Who Were on a Biologic at the Time of BT and Those Who Were Not

Baseline Variable	On Biologic (N=15)	Not on Biologic (N=15)	P value
Age (years)	55.3 ± 16.1	56.8 ± 18.3	0.76
Female / Male (%)	8 (53) / 7 (47)	11 (73) / 4 (27)	0.26
Childhood asthma (%)	10 (67)	9 (60)	0.70
Atopy (%)	14 (93)	11 (73)	0.14
IgE (IU/mL)	169 (113.5–620)	54 (27.5–121)	0.01
Blood eosinophil count (cells/uL)	0.2 (0.13–0.47)	0.12 (0.1–0.29)	0.15
FEV1 (% predicted)	56.7 ± 19.7	61.4 ± 24.7	0.72
FeNO (ppb)	34.5 (22–50)*	25 (17–42)	0.40
Responders (%)	10 (67)	9 (60)	0.71
Delta ACQ	−1 (−2- −0.4)	−1 (−1.6- −0.2)	0.53
Delta Exacerbations	−2 (−7.5- −0.5)	−4 (−5- −1)	0.82
Delta OCS (mg/day) †	0 (−10- 0)	−2.5 (−16.25–1.25)	-

Notes: *N=14. †On biologic N=5; Not on biologic N=4. Sample size too small for statistical analysis.
Abbreviations: ACQ, asthma control questionnaire; BT, bronchial thermoplasty; Delta variable, change in variable between follow-up and pre bronchial thermoplasty; FEV1, forced expiratory volume in 1 second; FeNO, fractional exhaled nitric oxide; IgE, serum immunoglobulin E levels; OCS, oral corticosteroid.

had either previously been, or are currently being treated with an asthma biologic, including a proportion who underwent one or more biologic switches. Furthermore, 27% of patients who underwent BT had a T2 low endotype, with limited treatment alternatives. Although azithromycin and tezepelumab are potential add-on therapies for this group,[14] the former is not commonly prescribed at our institution due to cost and ongoing concerns about long-term antibiotics resistance; while the latter is yet to be approved for use in Australia. Additionally, despite being approved for use in severe asthma regardless of T2 status, tezepelumab's magnitude of effect is much lower in those with T2 low endotype.[15] Compared to BT, whose safety and efficacy has been proven for up to 10 years, longer term data for these alternative therapies are limited.

Regardless, our data suggests that BT is not only comparable to asthma biologics in terms of improving asthma symptoms and exacerbations, but may be the only treatment option for a subgroup of patients who are not eligible for, or fail to respond to asthma biologics. Given the prevalence of T2 low endotype has been estimated to be up to 50%,[16,17] and between 15–44% of patients receiving treatment with an asthma biologic required BT in a nationwide Japanese study,[18] this represents a large number of patients who would potentially benefit from this procedure. The results of this study also have particular relevance for countries where the high cost of asthma biologics poses a significant barrier to access, as data presented here suggest that BT is an equally efficacious treatment option, which therefore could be used where biological therapies are not available. Furthermore, a once off three-session procedure is likely to be more cost effective than a lifetime of expensive asthma biologics.[19] Similarly, patients may baulk at the idea of requiring recurrent lifelong injections, which are not without side effects.[4] Against this backdrop, it may be appropriate to consider BT prior to asthma biologics after an informed discussion with the patient. This approach will be clarified in an ongoing randomised controlled trial comparing BT to standard of care (including biologics) in severe asthma.[20]

Unlike asthma biologics, predictors of BT response have not been well established. Responder analysis showed that BT responders had better baseline lung function (FEV1%predicted) than non-responders, a finding consistent with the published literature.[21,22] Our 63% response rate is also in keeping with the 60–80% reported by others.[23–25] Several other predictors of BT response such as airway smooth muscle mass,[26,27] number of radiofrequency activations,[28,29] asthma control,[6,22] and inflammatory status (IgE and blood eosinophil count) [22,30] have been suggested by others although findings have not always been consistent, with baseline ACQ and markers of T2-inflammation not significantly different between responders and non-responders in the current study. More recently, imaging biomarkers such as ventilation heterogeneity [21,31] and degree of lung stiffness [32] assessed using functional lung imaging have been proposed as potential predictors of BT response but require further validation. In contrast to predictors of BT response, age, gender, body mass index and presence of bronchodilator responsiveness have not been found to be predictive of treatment response.[22,33] It has been suggested that age dictates a steroid-resistant cascade of airway inflammation leading to the differential development of airway remodelling.[34] This would be consistent with observations that patients with adult-onset asthma are more steroid-resistant than those with childhood-onset asthma.[35] Whether this has any impact on BT response remains unknown. In this study, age of asthma onset did not appear to be significantly different between BT responders and non-responder although this needs to be examined in a larger population.

Targeting specific and/or multiple pathobiological pathways is the cornerstone of modern asthma management, particularly for patients with severe disease, and is an important factor in guiding treatment decisions. Unlike currently available asthma biologics, which are immunomodulatory in nature, BT works by addressing the structural end-organ abnormality ie hypertrophied remodelled airway smooth muscle. This mechanistic difference may provide additional insights into the benefit of BT in patients who did not respond to biologics.

This study is limited by its retrospective nature and the lack of a control group. It is not a randomized controlled trial and hence biases involved in patient selection, treatment decisions and reporting of subjective outcomes such as the ACQ have to be acknowledged. Similarly, there is a lack of control for possible confounders, which may be partially mitigated with propensity score matching in future studies. On the other hand, there are limited data comparing different asthma biologics and BT in a real-world setting. A single centre observational study of 91 patients found BT to be as efficacious as mepolizumab for the treatment of severe asthma.[36] A subsequent real-life retrospective study reported similar findings in patients with severe asthma treated with omalizumab, mepolizumab, benralizumab and BT.[37] The present study not only confirms the efficacy of BT compared to asthma biologics in a real-world setting, but also extends it to patients treated with dupilumab, and beyond a 12-month period.

In conclusion, although asthma biologics are considered first-line step-up therapy in patients with severe refractory asthma, BT has a specific and crucial role in patients who have failed, or are not candidates for asthma biologics, as well as those who prefer a non-pharmacological, long term therapeutic option. The proven durability of a once off treatment (BT) compared to the lifelong impost of ongoing biologic use should be carefully considered in the decision-making process. This retrospective real-world study provides evidence to support the ongoing role of BT in the era of biologic therapy. Moving forward, there is an urgent need for prospective studies to guide optimal treatment selection and sequencing, especially for patients who are eligible for multiple treatment options.

Abbreviations

ACQ, Asthma control questionnaire; BT, Bronchial thermoplasty; FeNO, Fractional exhaled nitric oxide; FEV1, Forced expiratory volume in 1 second; GINA, Global Initiative for Asthma; IgE, Immunoglobulin E; IL, Interleukin; OCS, Oral corticosteroids; T2, Type 2.

Data Sharing Statement

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

Ethical approval for this study had been waived by Eastern Health institutional review board because of its retrospective nature and the use of data that had been collected as part of standard clinical care. For similar reasons, patient consent was not required. All data was handled in accordance with the National Health and Medical Research Council Guidelines Ethical Considerations in Quality Assurance and Evaluation Activities (2014).

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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