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Indirect comparison of bronchial thermoplasty versus omalizumab for uncontrolled severe asthma

Robert M. Niven, MBChB, MRCP, FRCP, MD, MFOM^a, Michael R. Simmonds, MPhy^b, Michael J. Cangelosi, MA MPH^c, Dominic P. Tilden, MPH^d, Suzanne Cottrell, PhD^d, and Narinder S. Shargill, PhD^c

^aMAHSC, University of Manchester and University Hospital of South Manchester, Manchester, UK; ^bBoston Scientific, Sydney, NSW, Australia;

^cBoston Scientific, Marlborough, MA, USA; ^dThema Consulting Pty Ltd, Sydney, NSW, Australia

ABSTRACT

Objective: Bronchial thermoplasty (BT) as an add-on therapy for uncontrolled severe asthma is an alternative to biologic therapies like omalizumab (OM). We conducted an indirect treatment comparison (ITC) to appraise comparative effectiveness of BT and OM. **Methods:** A systematic literature review identified relevant randomized controlled trials. The ITC followed accepted methodology. **Results:** The ITC comprised a sham-controlled trial of BT (AIR2) and two placebo-controlled trials of OM (INNOVATE; EXTRA). Comparing the BT post-treatment period to ongoing treatment with OM, showed no significant differences in the rate ratios (RRs) for severe exacerbations (RR of BT versus OM = 0.91 [95% CI: 0.64, 1.30]; $p = 0.62$) or hospitalizations (RR = 0.57 [95% CI: 0.17, 1.86]; $p = 0.53$); emergency department visits were significantly reduced by 75% with BT (RR = 0.25 [95% CI: 0.07, 0.91]; $p = 0.04$); the proportions of patients with clinically meaningful response on the asthma quality-of-life questionnaire were comparable (RR = 1.06 [95% CI: 0.86, 1.34]; $p = 0.59$). The RR for exacerbations statistically favours OM over the total study period in AIR2 (RR = 1.50 [95% CI: 1.11, 2.02]; $p = 0.009$) likely reflecting a transient increase in events during the BT peri-treatment period. **Conclusions:** The ITC should be interpreted cautiously considering the differences between patient populations in the included trials. However, based on the analysis, BT compares well with a potentially more costly pharmacotherapy for asthma. Clinicians evaluating the relative merits of using these treatments should consider the totality of evidence and patient preferences to make an informed decision.

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Comparative effectiveness; GINA Step 5; systematic literature review; indirect treatment comparison; informed decision

Abbreviations

AQLQ	asthma quality-of-life questionnaire
BT	bronchial thermoplasty
ITC	indirect treatment comparison
OAT	optimized asthma therapy
OCS	oral cortical steroids
OM	omalizumab
RCT	randomized controlled trial
RR	rate ratio

Introduction

Treatment options for asthma include long-acting beta-agonists, short-acting beta-agonists, and corticosteroids, delivered in order according to the Global Initiative for Asthma (GINA) guidelines [1]. However, for approximately 5% of the patients, these options are insufficient to provide control of asthma symptoms [2]. For these patients, current GINA guidelines [1] specify other

treatment options, including bronchial thermoplasty (BT) and monoclonal antibody therapies such as omalizumab (OM) and mepolizumab, which are effective only in specific asthma phenotypes [3–5].

BT is a minimally invasive, once per lifetime intervention for the treatment of uncontrolled severe asthma. The BT procedure involves delivery of controlled thermal energy to the airway wall as a means of reducing excess airway smooth muscle mass and constriction of the airways. This has been shown to reduce the number and severity of asthma exacerbations and their associated treatment requirements. BT is currently indicated for both allergic and non-allergic asthma patients [6]. OM is a once- or twice-monthly subcutaneously injected monoclonal antibody therapy that targets serum-free immunoglobulin E (IgE) to interrupt the molecular signals that trigger the allergic inflammatory cascade in asthma. OM is indicated only for treating subtypes of allergic asthma [7]. The ideal patient population for BT remains unknown.

CONTACT Robert M. Niven  robert.niven@uhsm.nhs.uk  University of Manchester and University Hospital of South Manchester, Manchester, M23 9LT, UK. Color versions of one or more of the figures in the article can be found online at www.tandfonline.com/ijas.

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Both BT and OM therapies were evaluated and proven to be safe and effective in their own clinical trials and gained regulatory approval. In the pivotal trial for BT (Asthma Intervention Research 2 Trial – AIR2), BT was compared to sham treatment [6, 8], while in the OM registration trials, OM was compared to placebo injection [9–11]. Clinicians and patients who wanted to make informed decisions regarding treatment choices and payers who were required to take decisions regarding reimbursement may benefit from the comparison of BT and OM. Recently published allergist guidelines suggest consideration of BT and OM as part of a sustained ‘step-up’ of therapeutic options for asthma [12]. However, to date, no trial has directly compared BT and OM and, while a randomized controlled trial (RCT) comparing these two treatments would be ideal, there would be significant, perhaps intractable, challenges in maintaining subject blinding when comparing an interventional procedure with an injected drug. For this reason, the use of an indirect treatment comparison (ITC) should be considered as this would, at a minimum, afford the asthma community, currently grappling with a directional understanding of the comparative efficacy of these two treatments, some comparison of these two add-on treatment options. Thus, the objective of this study was to explore the comparative effectiveness of BT and OM utilizing an ITC.

Methods

The methodological approach was consistent with the health technology assessment guidelines for submissions to the Australian Medical Services Advisory Committee and Pharmaceutical Benefits Advisory Committee [13, 14]. Briefly, RCTs were identified through a rigorous systematic review of the published literature. Double-blinded randomized trials represent the study-type least susceptible to bias and are generally regarded as the best quality evidence available; non-blinded randomized trials were therefore identified but not included in the ITC. The treatments were then compared by an indirect meta-analysis of the study results, via a common non-therapeutic reference, following the method of Bucher, using fixed-effect models [15]. To examine the comparability of baseline characteristics of the trial populations, average means and pooled standard deviations were aggregated to BT-pooled and OM-pooled values and a T-test was used for the total study populations to generate the *p*-value.

Systematic literature review of trials and inclusion/exclusion criteria

The systematic literature review searched EMBASE, MEDLINE, Cochrane Library, and Clinical Trial Registries. Search terms included main concepts for

the population, disease area and intervention. The strategies used for the EMBASE + MEDLINE searches are provided in full in the Supplementary Material Online (e-Appendix 1). Included trials were RCTs which accepted patients with uncontrolled severe asthma despite treatment with asthma therapy consistent with Step 4 of the GINA guidelines. Identified trials were limited to those in which BT or OM was used as an add-on therapy option to a patient's existing optimized asthma therapy (OAT) and the comparator was given OAT alone or OAT with the addition of a non-therapeutic treatment (i.e., a sham procedure or placebo) for the purposes of blinding. No limitations were placed upon the inclusion of trials based on language of publication, or outcome(s) studied.

Outcomes

The outcomes of interest were as follows: the rate ratios (RRs) of severe asthma exacerbations and asthma exacerbation-related events (hospitalizations, emergency department visits, unscheduled doctor's office visits, etc.), and change in total score on the asthma-related quality-of-life questionnaire (AQLQ) [16]. A standardized form was used for the extraction of the data and all data were agreed upon consensus of two reviewers. No adjustment was made for potential differences in the definition of a severe asthma exacerbation in each trial (definitions of severe asthma exacerbation used in each trial included in the ITC are provided in e-Table 1).

ITC

The Bucher method examines the magnitude of treatment effect in studies of different treatments (against a common reference, usually placebo) and compares those treatment effects while preserving the randomization of the originally assigned patient groups. Adopting this approach, it is possible, even if control and treatment groups across trials differ in their baseline characteristics, to obtain an unbiased estimate of treatment effect. The only requirement is that the magnitude of treatment effect remains consistent across trials' differences in the populations' baseline characteristics [15].

Results

Results of the systematic literature review are shown in a PRISMA diagram (Figure 1). A total of 424 publications (citations and clinical trials' registry records) were identified from the initial searches. After a review of the publications and application of the inclusion and exclusion criteria, seven RCTs [6,17–22] were considered for further review (Table 1), of which the sham-controlled trial

Table 1. Main characteristics of randomized controlled trials identified in literature search.

Trial	Design characteristics	Compared interventions
<i>Trials of bronchial thermoplasty</i>		
AIR2 (6)	R, DB, MC, MN, PG Sham-controlled, 30 centres; 6 countries	BT (3 sessions 3 weeks apart) plus OAT (n = 190) Sham BT (3 sessions 3 weeks apart) plus OAT (n = 98) 12 months of follow-up (46 weeks after last BT/Sham session)
RISA (22)	R, MC, MN, PG, Open label 8 Centres; 3 countries	BT (3 sessions 3 weeks apart) plus OAT (n = 17) 3 control visits to the physician's office + OAT (n = 17) 12 months of follow-up (46 weeks after last BT session)
<i>Trials of omalizumab</i>		
INNOVATE (20)	R, DB, MC, MN, PG, Placebo-controlled 108 centres; 14 countries	OM plus OAT (n = 209) Placebo plus OAT (n = 210) Randomized treatment duration: 28 weeks with 16 weeks of follow-up
EXTRA (19)	R, DB, MC, MN, PG, Placebo-controlled 193 centres; 2 countries (US/Canada)	OM plus OAT (n = 427) Placebo plus OAT (n = 423) Randomized treatment duration: 48 weeks
EXALT (18)	R, MC, MN, PG, Open label 106 centres; 14 countries	OM (plus OAT (n = 271) OAT alone (n = 133) Randomized treatment duration: 32 weeks
IOA4 (21)	R, MC, MN, PG, Open label 49 centres, 5 European countries	OM plus OAT (n = 206; Severe subgroup n = 115) OAT alone (n = 106; severe subgroup n = 49) Randomized treatment duration: 12 months
ABR01 (NCT00567476) (17)	R, PG, Open label Multicentre; 1 country (Brazil)	OM plus OAT (n = 78) OAT alone (n = 38) Randomized treatment duration: 32 weeks

BT, bronchial thermoplasty; DB, double-blind; MC, multi-centre; MN, multi-national; OAT, optimized asthma therapy; OM, omalizumab; PG, parallel group; R, randomized.

of BT (AIR2 [NCT00231114]) [6] and the two placebo-controlled trials of OM (INNOVATE [NCT00046748]) [20] and EXTRA [NCT00314574]) [19] were included in the ITC, using the sham and placebo arms as a common reference (Figure 1). These three trials were selected for the ITC on the basis that they each were double-blinded trials and thus represented the least bias best quality data available for each treatment.

Comparability of trial populations and feasibility of ITC

Overall, the populations included in the BT and OM trials reflect patients with severe asthma which was uncontrolled despite treatment with GINA Step 4 asthma therapy including high dose inhaled corticosteroids and a long-acting beta-agonist. However, scrutiny of the trial entry criteria and the baseline characteristics of subjects indicates differences across the trials (Tables 2–4): the BT trials exclusively involved adult patients, whereas the OM trials included both adults and adolescents; the BT trials did not exclude subjects on the basis of atopy, whereas the OM trials included only allergic asthma; the populations included in the OM trials represent patients that could be interpreted to be more severely affected by their asthma than those included in the BT trials based on average baseline characteristics including slightly younger and greater proportion male subjects, lower FEV1, worse morning peak expiratory flow, a lower asthma symptom score comparable to minimal patient-perceptible difference, a lower AQLQ though the absolute difference not meeting minimal clinical relevance, higher maintenance dose of inhaled corticosteroids, more likely to be on maintenance corticosteroid therapy, more frequent asthma exacerbations requiring treatment with

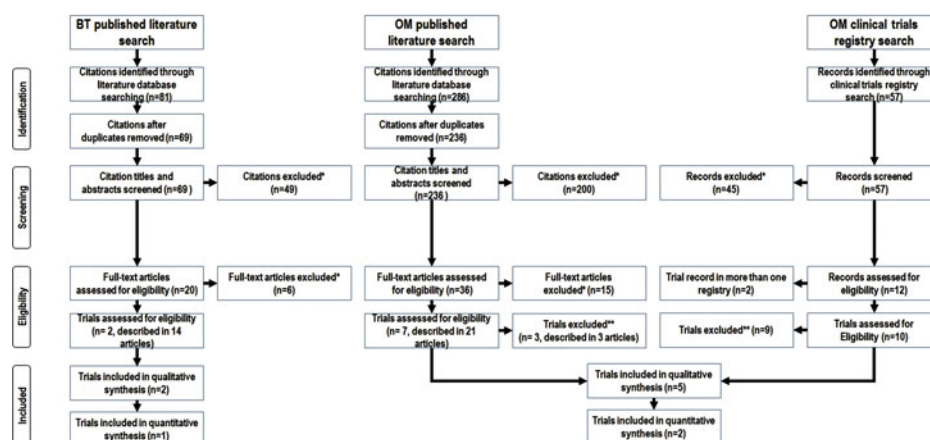


Figure 1. PRISMA flow diagram showing the results of the systematic literature search. BT, bronchial thermoplasty; OM, omalizumab. Searches of the clinical trials' registries identified no further trials meeting search inclusion criteria for which data were available. *Not RCT; wrong intervention and/or comparator; wrong population. **Small trial; outcome measures not relevant; population broader than specified by search criteria and no subgroup analysis reported; Limited information available—trial reported only as a conference abstract. Searches were conducted in June 2014.

Table 2. Key inclusion criteria in the sham/placebo-controlled trials.

Criterion based on:	TRIAL OF BT AIR2 (6)	TRIALS OF OMALIZUMAB	
		INNOVATE (20)	EXTRA (19)
Age	18–65 years	12–75 years	12–75 years
Asthma diagnosis	Severe asthma (all subjects were subsequently described as having inadequately controlled severe asthma)	Inadequately controlled severe persistent allergic asthma	Severe persistent allergic asthma; inadequately controlled
Pre-bronchodilator FEV1 (% of predicted)	≥ 60%	≥ 40% to < 80%	> 40% to < 80%
Asthma maintenance medication	ICS > 1000 µg/d BDP or equivalent LABA SABA as-needed	ICS > 1000 µg/d BDP or equivalent LABA SABA as-needed	ICS ≥ 500 µg fluticasone twice daily or equivalent LABA
Asthma exacerbation history (in the past 12 months)	No stipulation	In the past 12 months. ≥ 2 asthma exacerbations ^a OR ≥ 1 severe exacerbation resulting in hospitalization or ER treatment	In the past 12 months. ≥ 1 documented asthma exacerbation ^a

BDP, beclomethasone dipropionate; ER, emergency room; FEV1, forced expired volume in one second; FP, fluticasone propionate; ICS, inhaled corticosteroid therapy; LABA, long-acting beta-agonist; SABA, short-acting beta-agonist.

^aExacerbations requiring treatment with systemic corticosteroids.

systemic steroids, and a higher rate of hospitalizations and emergency department visits.

Results of the ITC

Severe asthma exacerbations and related event rates

As shown in Table 5, Figures 2–4 and the Supplementary Material Online (e-Figure 1A), when comparing the post-treatment period of the AIR2 BT trial (i.e., the

follow-up period after completion of all three BT procedures) to the ongoing treatment period with OM in the INNOVATE and EXTRA trials, there is a statistically significant difference (~75% reduction: $p = 0.035$) in favour of BT for the RR for asthma-related emergency department visits. There is no statistical difference between the treatments for the RRs of severe asthma exacerbations, asthma-related hospitalizations and unscheduled doctor's office visits. Notably, the comparative effect of OM

Table 3. Baseline characteristics of the subjects included in the sham/placebo-controlled trials.

Baseline variable	TRIAL OF BT		TRIALS OF OMALIZUMAB				BT pooled vs. OM pooled <i>p</i> -value
	AIR2 (6)		INNOVATE (20)		EXTRA (19)		
	BT + OAT (n = 190)	Sham + OAT (n = 98)	OM + OAT (n = 209)	PBO + OAT (n = 210)	OM + OAT (n = 427)	PBO + OAT (n = 421)	
Age: years - mean (SD)	40.27 (11.89)	40.6 (11.85)	43.4 (13.29)	43.3 (13.49)	43.7 (14.3)	45.3 (13.9)	<i>p</i> < 0.0001
Gender: n (%) Male	81 (42.63)	38 (38.78)	68 (32.54)	72 (34.29)	165 (38.6)	126 (29.9)	<i>p</i> < 0.05
Race/ethnicity: n (%) white	151 (79.47)	72 (73.47)	163 (77.99)	164 (78.10)	313 (73.3)	318 (75.5)	<i>p</i> = 0.512
Pre BD FEV1: % of predicted - mean (SD)	77.8 (16.65)	79.7 (15.14)	61 (14.42)	61.6 (13.83)	65.4 (15.2)	64.4 (13.9)	<i>p</i> < 0.0001
AQLQ baseline score: mean (SD)	4.3 (1.17)	4.32 (1.21)	3.9 (1.05)	3.9 (1.12)	4.0 (1.1)	3.9 (1.1)	<i>p</i> < 0.0001
Morning PEF: L/min - mean (SD)	383.8 (104.32)	386.3 (112.59)	299 (102.30)	311 (102.40)	NR	NR	<i>p</i> < 0.0001
Total symptom score; mean (SD) ^b	3.8 (2.34)	3.9 (2.53)	3.2 (2.12)	3.3 (2.04)	NR	NR	<i>p</i> < 0.001
Asthma related hospitalizations in last 12 months							<i>p</i> < 0.0001
Subjects with event: <i>n</i> (%)	8 (4.2)	6 (6.1)	83 (39.7)	79 (37.6)	NR	NR	
Asthma related ER visits in last 12 months							
Mean events per subject	0.79	1.19	1.68	1.48	NR	NR	<i>p</i> < 0.0001
Subjects with event: <i>n</i> (%)	55 (28.9)	31 (31.6)	118 (56.5)	116 (55.2)	NR	NR	
Asthma related unscheduled doctor office visits in last 12 months							
Mean events per subject	0.85	0.75	4.9	4.9	NR	NR	NR
Number of pulses of systemic OCS for asthma in last 12 months							
Mean events per subject	0.88	1.04	2.64	2.41	2.0 (2.2)	1.9 (1.5)	<i>p</i> = 0.0001
Subjects with event: <i>n</i> (%)	98 (51.6)	56 (57.1)	207 (99.0)	210 (100)	(100)	NR	

AQLQ, Asthma quality-of-life questionnaire; BT, bronchial thermoplasty; ER, emergency room; FEV1, forced expired volume in one second; L, litres; OAT, optimized asthma therapy; OCS, oral corticosteroids; OM, omalizumab; NR, not reported; PBO, placebo; PreBD, prebronchodilator; SD, standard deviation.

Table 4. Asthma medications at baseline in the sham/placebo-controlled trials.

Medication	TRIAL OF BT		TRIALS OF OMALIZUMAB				BT pooled vs. OM pooled <i>p</i> -value
	AIR2 (6)		INNOVATE (20)		EXTRA (19)		
	BT + OAT (n = 190)	BT + OAT (n = 190)	OM + OAT (n = 209)	PBO + OAT (n = 210)	OM + OAT (n = 427)	PBO + OAT (n = 421)	
<i>ICS and LABA</i>							
Proportion on ICS plus LABA: n (%)	190 (100)	98 (100)	209 (100)	210 (100)	(100)	209 (100)	<i>p</i> = 1
ICS: µg/d BDP or equivalent: mean (SD)	1960.7 (745.19)	1834 (659.35)	2359 (2000.0)	2301 (2000.0)	NR	NR	<i>p</i> < 0.001
<i>MOC</i>							
Proportion on MOCs: n (%)	7 (3.7)	1 (1.0)	49 (23.44)	42 (20.0)	73 (17.1)	71 (16.9)	<i>p</i> < 0.0001
Dose of MOCs mg/d: mean (SD)	6.4 (1.97)	5 (0.00)	NR	NR	10.0 (7.1)	13.4 (10.8)	<i>p</i> < 0.0001
<i>Rescue medication</i>							
Puffs per week: mean (SD)	13.4 (19.17)	11.8 (11.24)	46.2 (50.68)	38.5 (41.02)	28.0 (20.3)	28.7 (22.4)	<i>p</i> < 0.0001.

BDP, beclomethasone dipropionate; BT, bronchial thermoplasty; ICS, inhaled corticosteroids; LABA, long-acting beta-agonist; MOCs, maintenance oral corticosteroids; OAT, optimized asthma therapy; OM, omalizumab; NR, not reported.

and BT in preventing exacerbations is measured on the relative reduction in exacerbations.

Table 5 also shows results for the indirect comparison of events occurring during the total BT study duration in the AIR2 trial (peri-treatment period as well as the 46-week post-treatment follow-up period) to those during the ongoing treatment period in the OM trials. There is no statistical difference between the treatments in terms of the RRs of asthma-related hospitalizations and emergency department visits. However, there is a statistically significant difference which favours OM in terms of the RR for severe asthma-related exacerbations (~33% rate reduction compared to BT; *p* = 0.009).

Asthma-related quality of life

The indirect comparison of AQLQ outcomes with BT and OM shows similar, clinically significant improvements in the AQLQ total scores and comparability in terms of the proportions of patients achieving the minimal clinical important difference (Table 5 and e-Figure 1B and C).

Discussion

Clinicians, patients and payers frequently must choose between available treatment options, based on the relative clinical and cost effectiveness. The authors

Table 5. Results of the indirect treatment comparison.

Outcome	Rate ratio [95% CI]; Result < 1 favours active treatment			Indirect rate ratio [95% CI]; Result < 1 favours BT + OAT	
	BT + OAT Vs SHAM + OAT			BT + OAT Vs OM + OAT	
	Post BT treatment phase	Total BT study duration	OM + OAT Vs OAT	Vs Post BT treatment phase	Vs Total BT study duration
Exacerbation rate ratio	0.69 [0.50, 0.94] ^a	1.12 [0.87, 1.44] ^a	0.75 [0.63, 0.88] ^b	0.91 [0.64, 1.30]; <i>p</i> = 0.621	1.50 [1.11, 2.02]; <i>p</i> = 0.009
Hospitalization rate ratio	0.31 [0.13, 0.76] ^a	0.93 [0.48, 1.80] ^a	0.54 [0.25, 1.17] ^c	0.57 [0.174, 1.862]; <i>p</i> = 0.352	1.72 [0.623, 4.747]; <i>p</i> = 0.295
Emergency Dept. visit rate ratio	0.16 [0.09, 0.30] ^a	0.29 [0.18, 0.47] ^a	0.66 [0.21, 2.09] ^c	0.25 [0.07, 0.91]; <i>p</i> = 0.035	0.44 [0.13, 1.53]; <i>p</i> = 0.195
Unscheduled doctor's office visit	0.78 [0.51, 1.19] ^a	Not reported	0.55 [0.27, 1.10] ^c	1.41 [0.62, 3.22]; <i>p</i> = 0.408	—
Relative risk [95% CI]; Result > 1 favours active treatment					
Proportion with improvement in AQLQ total score ≥ 0.5	1.23 [1.04, 1.45] ^a		1.16 [1.02, 1.32] ^d	1.06 [0.86, 0.1.34]; <i>p</i> = 0.59	
Weighted mean/mean difference [95% CI]; Result > 0 favours active treatment					
Mean change from baseline in AQLQ total score	0.19 [−0.1, 0.48] ^a		0.20 [0.03, 0.37] ^b	−0.01 [−0.35, 0.33]; <i>p</i> = 0.953	

AQLQ, asthma quality-of-life questionnaire; BT, bronchial thermoplasty; CI, confidence interval; OAT, optimized asthma therapy; OM, omalizumab.

^aData from AIR2 [6]; results are presented for the post-treatment phase (46 weeks) and for the total study duration which additionally included the six-week peri-procedure period.

^bMeta-analysis of data for outcome from INNOVATE [20] and EXTRA [19] (see Supplemental Material Online: e-Figures 1A–C).

^cData for outcome available only from INNOVATE [20].

^dData for outcome available only from EXTRA [19].

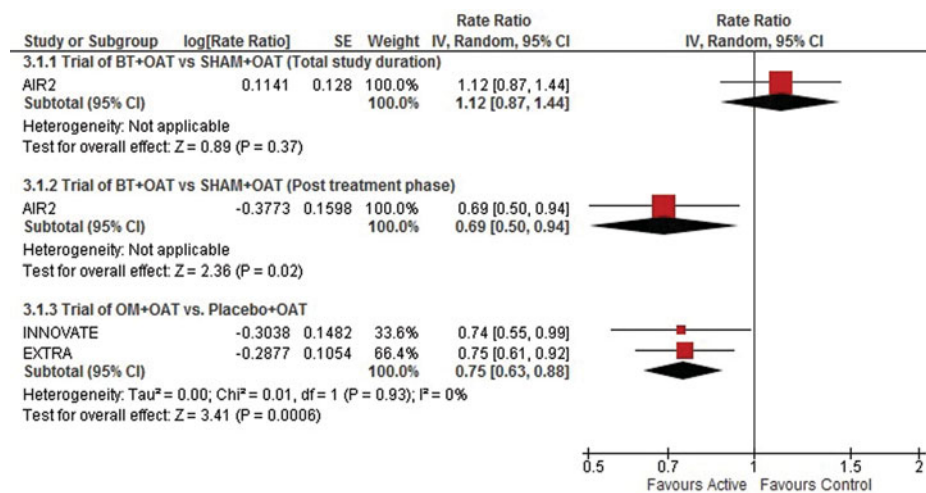


Figure 2. Asthma-related asthma exacerbations. BT, bronchial thermoplasty; OAT, optimized asthma therapy; OM, omalizumab.

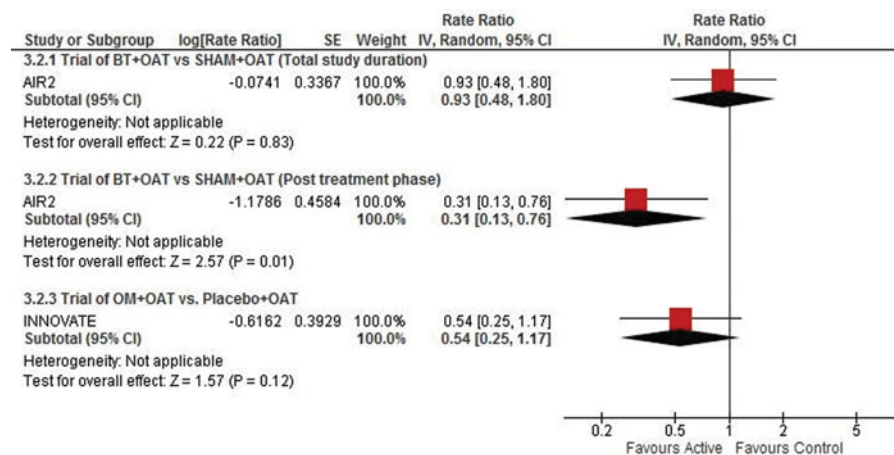


Figure 3. Asthma-related hospitalizations. BT, bronchial thermoplasty; OAT, optimized asthma therapy; OM, omalizumab.

acknowledge that the best supporting evidence would be an RCT, but this is not feasible with a SHAM trial of BT, now being considered unethical by most authorities. In addition, there would be insurmountable challenges

arising when attempting to compare a surgical intervention with a chronic drug treatment. Accordingly, there are situations when evidence derived from ITC methodologies must be considered to draw conclusions on

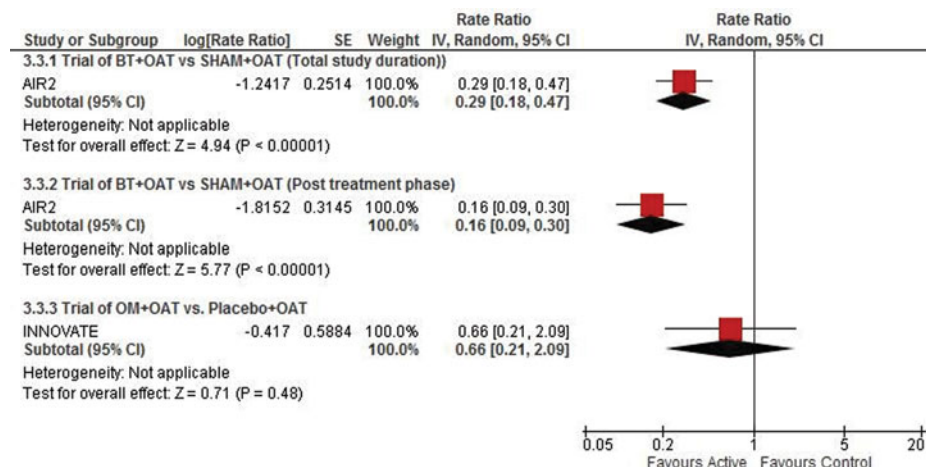


Figure 4. Asthma-related emergency department visits. BT, bronchial thermoplasty; OAT, optimized asthma therapy; OM, omalizumab.

comparative efficacy. In the absence of RCT data, ITCs are perhaps necessary in order to make informed decisions, despite inherent weaknesses in the methodology.

The analysis presented here suggests some favourable outcomes for BT over OM with regard to emergency room visits during the post-treatment period, with a statistically and clinically significant 75% reduction with BT compared to OM (RR = 0.25; $p = 0.04$). There were no significant differences in the RR for severe exacerbations or hospitalizations, and the proportions of patients achieving a clinically meaningful response on the AQLQ were comparable.

These analyses did not specifically examine events in the 'peri-procedure' period. However, statistically significant results observed in favour of OM in terms of the RR for asthma-related exacerbations when considering the total study period of the AIR2 BT trial likely reflect a transient increase in asthma-related exacerbations observed during the peri-procedure period. While the occurrence of these adverse events in the short term may detract from considering BT as the first treatment intervention, due consideration should be given also to the sustained reduction of these events over a protracted period in the longer term, for example, out to five years in published studies [8,23]. Extended follow-up post-OM is not available within the published data with the longest follow-up being two years and this was an open label study.

A key assumption of indirect comparisons is the similarity of relative treatment effect across the respective sets of clinical trials. However, when faced with differences in patient characteristics or study methods, the indirect comparison will remain valid when there is no treatment effect modification within each side of the indirect comparison or trials' populations [20].

In regard to the study designs of the BT and OM trials, both sides of the comparison included only randomized controlled double-blinded trials. In regard to the control arms, a non-therapeutic treatment (i.e., sham procedure or a placebo injection) was used in addition to patients' existing OAT for blinding purposes. For the purpose of this study, it has been necessary to consider these non-active elements sufficiently similar to allow the control arms of the trials to serve as an appropriate common reference for the ITC, although clearly this may be an imperfect assumption. The outcomes of interest were similarly defined across the trials, notwithstanding some minor differences between AIR2 and INNOVATE trials as to what constituted a severe asthma exacerbation: a worsening of asthma requiring treatment with oral or intravenous corticosteroids or a doubling of the baseline inhaled corticosteroid dose, or any temporary increase in

the dosage of oral corticosteroids (AIR2) [6]; a worsening of asthma symptoms requiring treatment with systemic corticosteroids (INNOVATE) [20]; a worsening of asthma symptoms requiring treatment with systemic corticosteroids or a 20 mg or more increase in the average daily dose of oral prednisone or a comparable dose of another systemic corticosteroid (EXTRA) [19]. Differences across the trials in terms of the duration of follow-up are acknowledged. In regard to the baseline characteristics of the patients, acknowledged differences, inferring that the patients in the BT trials were less severely affected by their asthma than the patients in the OM trial, may place potential limitations on the interpretation of the results of the analysis. However, it is important to note that asthma exacerbation-related events are compared as RRs, which means that the comparative effect of OM and BT in preventing events is on a relative scale. As outlined earlier, provided there is no modification of treatment effect due to greater asthma severity, the two treatments would be expected to be comparable on a relative scale.

The absence of a BT treatment modification effect either way cannot be confirmed based on the AIR2 trial data. Logistic regression analysis data from the AIR2 trial did not confirm any treatment effect modification based on baseline variables, including those indicative of baseline asthma severity. Moreover, evidence from the early RISA clinical trial [22] and several case series [24–29] shows BT to be similarly effective in patients more severely affected by their asthma than those included in the AIR2 trial. On the OM side of the comparison, a pooled analysis of data from seven RCTs involving 4308 patients, 93% of which had severe asthma, has shown that baseline characteristics do not reliably predict benefit with OM, although there was a suggestion of a greater treatment effect in patients with lower percentage-predicted FEV1 values and higher IgE [30–33], and more recently, in those with a higher serum eosinophil count, serum periostin or fractionated exhaled nitric oxide [34].

Given the assumption that the BT treatment effect is not reduced and the OM treatment effect is unchanged or increased with increased asthma severity, a conclusion of comparable efficacy between BT post-treatment and OM, based on the ITC, is reasonable, potentially biased against BT due to the OM trials' populations potentially skewing more to populations that may be associated with an enhanced treatment effect. Specifically, OM is used in patients with specific patient characteristics, which at least initially were believed to be indicative of a likely treatment response, whereas no such selection process occurs for patients receiving BT.

Treatment choice based on relative clinical merit is frequently hampered by the absence of direct comparative clinical trial evidence. ITCs may help clinicians and treatment providers to make more informed decisions regarding treatment choices and funding [35]. While it must be acknowledged that the findings of this ITC are best considered indicative rather than definitive, in the absence of RCT evidence which directly compares BT and OM or which allows an indirect or mix treatment comparison in more comparable severe asthma populations, it provides the best available quantitative assessment of the relative efficacy of these two therapies. Final treatment choice should therefore consider factors in addition to apparent relative efficacy, for example, toxicity, convenience and cost.

Conclusion

Based on the ITC of healthcare-utilization events which occurred during the post-treatment period alone, BT compares favourably to OM in terms of relative impact on exacerbation-related events including severe exacerbations, emergency department visits, and hospital admissions, as well as impact on asthma-related quality of life. Using the indirect comparison of severe exacerbations occurring during the total study duration in the AIR2 trial, the less favourable result for BT likely reflects the transient increase in events observed only during the peri-treatment period.

These data need to be interpreted with caution due to the indirect nature of the methodology. However, in the absence of an impractical, potentially unethical and time-consuming RCT, which would be the 'gold standard' for directly comparing these two treatments, and despite the inherent weakness of the indirect comparison as described here, our observations nevertheless provide one analysis of the potential relative benefits of OM and BT. Clinicians and treatment providers evaluating these two add-on treatments should consider the totality of evidence as well as patient preferences to make an informed decision.

Declaration of interests

Authors contributions

DPT and SC contributed to the performance of the systematic review, data extraction, meta-analysis, and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors contributed to the manuscript preparation, review, and response to peer-review comments.

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