

Journal of Asthma

ISSN: 0277-0903 (Print) 1532-4303 (Online) Journal homepage: http://www.tandfonline.com/loi/ijas20

Long-term efficacy and safety of bronchial thermoplasty in patients with moderate-to-severe persistent asthma: a systemic review and meta-analysis

Jian Ping Zhou MD, Yun Feng MD, PhD, Qiong Wang MD, Li Na Zhou MD, Huan Ying Wan MD & Qing Yun Li MD, PhD

To cite this article: Jian Ping Zhou MD, Yun Feng MD, PhD, Qiong Wang MD, Li Na Zhou MD, Huan Ying Wan MD & Qing Yun Li MD, PhD (2015): Long-term efficacy and safety of bronchial thermoplasty in patients with moderate-to-severe persistent asthma: a systemic review and meta-analysis, Journal of Asthma, DOI: 10.3109/02770903.2015.1065424

To link to this article: http://dx.doi.org/10.3109/02770903.2015.1065424

Accepted author version posted online: 24 Aug 2015.
Published online: 18 Sep 2015.

Submit your article to this journal

Article views: 120

View related articles

View Crossmark data

Full Terms & Conditions of access and use can be found at
http://www.tandfonline.com/action/journalInformation?journalCode=ijas20

Download by: [University of Liverpool] **Date:** 27 October 2015, At: 06:42

http://informahealthcare.com/jas
ISSN: 0277-0903 (print), 1532-4303 (electronic)

Journal of ASTHMA

J Asthma, Early Online: 1–7
© 2015 Taylor & Francis. DOI: 10.3109/02770903.2015.1065424

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

Long-term efficacy and safety of bronchial thermoplasty in patients with moderate-to-severe persistent asthma: a systemic review and meta-analysis

Jian Ping Zhou, MD[1], Yun Feng, MD, PhD*[1], Qiong Wang, MD[1], Li Na Zhou, MD[1], Huan Ying Wan, MD[1], and Qing Yun Li, MD, PhD[1]

Department of Respiratory Medicine, Ruijin Hospital, School of Medicine, Shanghai Jiaotong University, Shanghai, P.R. China

Abstract

Objective: To evaluate the long-term efficacy and safety of bronchial thermoplasty (BT) in the treatment of patients with moderate-to-severe persistent asthma. *Methods*: We therefore performed a systematic literature review of peer-reviewed studies focusing on BT intervention in asthma control published between January 2000 and June 2014. Three randomized controlled studies and extension studies met the inclusion criteria ($n = 6$). Outcomes assessed after BT included spirometric data, adverse respiratory events, emergency room (ER) visits and hospitalization for respiratory illness. One-year and 5-year follow-up data were defined as V1 and V5, respectively. *Results*: There were 249 BT-treated subjects in total who had a 1-year follow-up (V1), whereas 216 of them finished a 5-year follow-up (V5). No evidence of significant decline was found in pre-bronchodilator FEV_1 (% predicted) (WMD = 0.75; 95% CI: 3.36 to 1.85; $p = 0.57$), or in post-bronchodilator FEV_1 (% predicted) (WMD = 0.62; 95% CI: 3.32 to 2.08; $p = 0.65$) between V1 and V5. In addition, the frequency of respiratory adverse events was reduced significantly during the follow-up (RR = 3.41, 95% CI: 2.96–3.93, $p < 0.00001$). The number of ER visits for adverse respiratory events remained unchanged (RR = 1.06, 95% CI: 0.77–1.46, $p = 0.71$) after BT treatment. There was no statistically significant increase in the incidence of hospitalization for respiratory adverse events (V5 vs. V1, RR = 1.47, 95% CI: 0.69–3.12, $p = 0.32$). *Conclusions*: These data demonstrate long-term benefits of BT with regard to both asthma control and safety for moderate-to-severe asthmatic patients.

Keywords

Bronchial thermoplasty, asthma, efficacy, safety

History

Received 11 April 2015
Revised 5 June 2015
Accepted 20 June 2015
Published online 17 September 2015

Downloaded by [University of Liverpool] at 06:42 27 October 2015

Introduction

Asthma is a chronic inflammatory airway disease that affects 300 million people worldwide, and its prevalence increases by 50% every decade [1,2]. Despite current standardized treatment, it has been estimated that approximately 5% of patients who suffer from severe persistent asthma continue to experience asthma symptoms [3]. Poorly, and not-well controlled asthma can cause a significant social and economic burden [4]; increase healthcare expenses, and have negative effects on quality of life in asthmatic patients.

Bronchial thermoplasty (BT) is an innovative approach for the management of severe asthma that specifically targets airway smooth muscles (ASMs) in order to control airway hyperresponsiveness. This is accomplished by radio-frequency-generated heat delivered through a flexible bronchoscope [5]. Controlled heat could decrease bronchial smooth muscle mass, contractility and bronchoconstrictor response to relieve the symptoms of asthma including shortness of breath [6]. It has been demonstrated that BT can achieve significant improvements in lung function and decrease the incidence of ER visit and hospitalization in severe asthmatic patients, as a non-pharmacologic intervention [7]. An increasing amount of evidence suggests that BT could be potential treatment for asthma [8–12], but information of long-term response to BT in asthmatic patients is limited by small sample size of current clinical trials. Thus, the present systematic review was carried out, along with a meta-analysis of the currently available clinical trials, to evaluate the long-term safety and effectiveness of BT for patients with moderate-to-severe persistent asthma.

Materials and methods

Search strategy

The methods used in this study followed the protocol of Cochrane Collaboration [13]. We performed a systematic literature review of peer reviewed studies focusing on BT

*Dr. Yun Feng, as co-first author, contributed equally to this article.

Correspondence: Qing Yun Li, Department of Respiratory Medicine, Ruijin Hospital, School of Medicine, Shanghai Jiaotong University, Shanghai 200025, P.R. China. Tel: +86 2164370045. Fax: +86 2164674301. E-mail: liqingyun68@hotmail.com

intervention in asthma control published between January 2000 and June 2014. All basic data were searched in multiple databases, including the Cochrane Library, ClinicalTrials.gov, MEDLINE®, EMBASE®, Ovid and PubMed. The search terms included ''bronchial thermoplasty'', or ''thermoplasty'' and ''asthma'' or ''bronchial asthma''. Trials were not excluded on the basis of language.

Inclusion criteria

The following criteria were used to select qualified clinical trials for inclusion in this study.

(i) *Target population*: All subjects should be between 18 and 65 years old and diagnosed with moderate-to-severe persistent asthma according to the guidelines of the Global Initiative for Asthma [14]. All subjects should require daily therapy with inhaled corticosteroid (ICS) equivalent to a dose of $\geq$200 μg of beclomethasone and long-acting β-adrenergic agonist (LABA), at a dose of $\geq$100 μg of salmeterol or the equivalent.

(ii) *Intervention*: All subjects should receive BT procedures at least once, performed by delivering radiofrequency energy to the airway wall using the Alair® system [9,15,16].

Methodological criteria

Three randomized clinical trials and extension studies were finally included for the analysis ($n = 6$). Outcomes of interest assessed after BT included spirometric data, adverse respiratory events, emergency room (ER) visits and hospitalization for respiratory illness. One-year and 5-year follow-up data were defined as V1 and V5, respectively. There were 249 BT-treated subjects in total who had a 1-year follow-up, whereas 216 of them finished a 5-year follow-up. The differences in outcomes of interest between V1 and V5 were analyzed.

Critical appraisal and quality control of study inclusion

Clinical trials were appraised by internal and external validity assessment using a checklist of factors by questionnaire [13,17]. Parameters included in this questionnaire were the method of allocation and concealment of the randomization schedule, the blinding of trial performers, outcome assessors, follow-up, method of analysis and quality of results obtained. The quality of randomized controlled study reporting was assessed using the Jadad scale [18,19]. A Jadad scale score <3 is considered to indicate a low-quality trial [20,21].

Data extraction and statistical analyses

Two physicians independently extracted the data from all included clinical trials. Intention-to-treat results were used whenever available. A meta-analysis was conducted to quantify the efficacy and safety of BT using Review Manager, version 5.3 (The Nordic Cochrane Center, The Cochrane Collaboration 2008, Copenhagen, Denmark) for all the statistical analyses.

Trial heterogeneity is estimated using the Cochrane Q statistic. The I2 statistic, which is the proportion of total variation among studies that is likely to be explained by between-study heterogeneity rather than chance [22], is reported and rejected. When the hypothesis of homogeneity has not been rejected, a fixed-effects model is used to calculate summary relative risk (RR), weighted mean difference (WMD) and 95% confidence intervals (CI). Otherwise, a random-effects model with inverse variance weighting will be used [23,24]. A p-value <0.05 is considered to be a statistically significant publication bias.

Results

Study Inclusion

Three randomized clinical trials and extension studies were included for the analysis ($n = 6$) (Figure 1). There were 249 BT-treated subjects in total who had a 1-year follow-up, whereas 216 of them finished a 5-year follow-up. The characteristics and demographic data of all included BT-treated subjects are presented in Tables 1 and 2 [9–12,15,25]. All clinical trials were of high quality and had the same follow-up duration of 5 years.

Efficacy of BT in patients with moderate-to-severe asthma

Maintenance medication changes for worsening of asthma

Overall, most of the subjects have presented different level of reduction of ICS and LABAs doses. More than 10% (Ranges: 12–49%) patients were completely weaned off LABA treatment, without further maintenance medication for symptom control.

Spirometric stability

The effect of treatment with BT was assessed using spirometry during 5 years follow-up. No evidence of significant decline was found in pre-bronchodilator FEV_1 (% predicted) (WMD = 0.75; 95% CI: 3.36 to 1.85; $p = 0.57$) (Figure 2), or in post-bronchodilator FEV_1 (% predicted) (WMD = 0.62; 95% CI: 3.32 to 2.08; $p = 0.65$) between V1 and V5 (Figure 3). This result suggested that BT might prevent moderate-to-severe persistent asthmatic patients from rapid deterioration in lung function.

Tolerability and safety of BT treatment reflected by adverse respiratory events

Total adverse respiratory events

During the follow-up period, there was no statistically significant decrease in the incidence of respiratory adverse events between V1 and V5 (RR = 3.41, 95% CI: 2.96–3.93, $p < 0.00001$) (Figure 4). The most frequently observed respiratory adverse events during post-treatment period were coughing, chest discomfort and dyspnea.

ER visits for adverse events

During the follow-up period, no statistically significant difference was found in the number of ER visit for respiratory adverse events between V1 and V5 (RR = 1.06, 95% CI: 0.77–1.46, $p = 0.71$) (Figure 5).

Downloaded by [University of Liverpool] at 06:42 27 October 2015

Downloaded by [University of Liverpool] at 06:42 27 October 2015

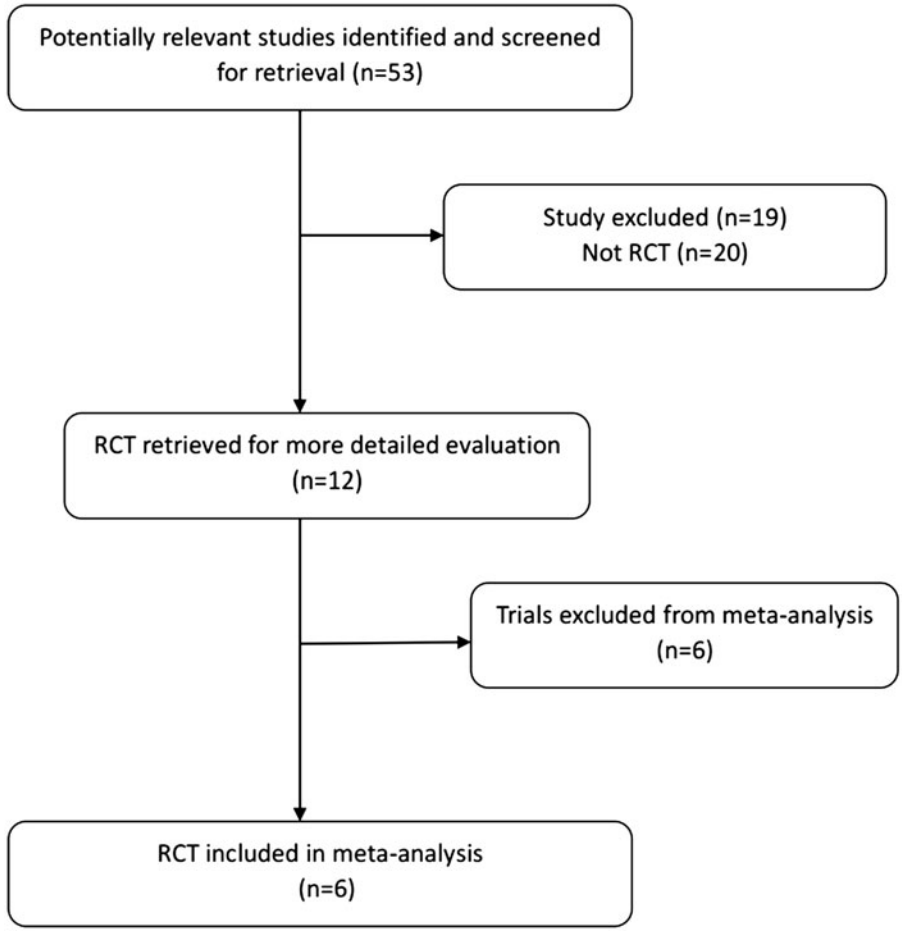


Figure 1. The flowchart of identifying studies through systemic search in multiple databases.

Table 1. Designed characteristics of each included study.

Study [Ref.]	Design	Sample size	JADAD scale 16–18	Variables	Inclusion criteria	Follow-up (years)
Pavord et al. [25]	Multicentre, randomized, controlled, parallel-group study	14	3	Safety; AE; FEV_1	Target population (BT group)	1
Pavord et al. [12]	Extension study	12	–	Safety; AE; FEV_1	Target population (BT group)	5
Cox et al. [15]	Multicentre, randomized, controlled, parallel-group study	45	3	Safety; AE; FEV_1	Target population (BT group)	1
Cox et al. [11]	Extension study	42	–	Safety; AE; FEV_1	Target population (BT group)	5
Castro et al. [9]	Multicentre, randomized, double-blind, study	190	3	Safety; AE; FEV_1	Target population (BT group)	1
Castro et al. [10]	Extension study	162	–	Safety; AE; FEV_1	Target population (BT group)	5

AE, adverse events; FEV_1, forced expiratory volume in the 1st second (% predicted).

Hospitalization for adverse respiratory events

During the period in the post-treatment course, no statistically significant increase was found in the incidence of hospitalization for respiratory adverse events (V5 vs. V1, RR = 1.47, 95%CI: 0.69–3.12, $p = 0.32$) (Figure 6).

Discussion

Bronchial thermoplasty is a device-based non-pharmacologic procedure that applies controlled heat to reduce the mass of the ASM. Such mechanism indicates a potential application of BT intervention in patients with severe asthma, where ASM constriction was a common patho-physiological change. The effectiveness and safety of BT has been evaluated in a series of studies enrolling subjects with mild to severe-refractory asthma [8–12,15,25,26].

In this meta-analysis, we examined the long-term safety and efficacy of BT treatment in asthma control by combining evidence from several comparative clinical trials. Previously published data have demonstrated the clinical benefits of BT in 1 year [27]. Our results have demonstrated the benefits of

Table 2. Demographics and clinical characteristics of included BT-treated patients.

	Pavord et al. [12,25]		Cox et al. [11,15]		Castro et al. [9,10]	
Study (Ref.)	V1 ($n=14$)	V5 ($n=12$)	V1 ($n=45$)	V5 ($n=42$)	V1 ($n=190$)	V5 ($n=162$)
Age (years)[a]	38.6 ± 13.3	–	40.0 ± 11.2	–	40.7 ± 11.8	41.5 ± 11.0
Sex, *n* (%)						
Male	6 (43)	–	19 (42)	–	81 (42.6)	68 (42.0)
Female	8 (57)	–	26 (58)	–	109 (57.4)	94 (58.0)
Race, *n*(%)						
White	14 (100)	–	41 (91)	–	151 (79.5)	134 (82.7)
African American/black	–	–	3 (7)	–	19 (10.0)	13 (8.0)
Other	–	–	1 (2)	–	20 (10.5)	15 (9.3)
Weight (kg)[b]	90.5 ± 19.5	–	76.3 ± 23.3	–	81.7 ± 18.4	81.4 ± 17.1
ICS dose (μg)[c]	1179 ± 421	–	1305 ± 880	–	1960.7 ± 745.2	1958.9 ± 757.9
LABA dose (μg)[d]	127 ± 62	–	109 ± 34	–	116.8 ± 34.4	120.8 ± 47.7
ACQ score[e]	2.8 ± 1.0	–	1.3 ± 0.6	–	2.1 ± 0.87	2.1 ± 0.84
AQLQ score[f]	4.1 ± 1.3	–	5.6 ± 0.9	–	4.30 ± 1.17	4.32 ± 1.17
SFD (%)[g]	5.6 ± 14.1	–	33.3 ± 34.3	–	16.4 ± 24.0	16.1 ± 24.1
Total respiratory events	118 (14)	29 (12)	202 (38)	46 (22)	366 (132)	126 (77)
ER visits for respiratory events in prior 12 months (no. of subjects)	5 (4)	1 (1)	3 (3)	2 (2)	141 (55)	115 (47)
Hospitalization for respiratory events in prior 12 months (no. of subjects)	10 (6)	1 (1)	3 (3)	1 (1)	10 (8)	10 (8)
Lung function measures[h]						
FEV_1 pre-BD% predicted	63.5 ± 12.5	70.3 ± 11.4	72.5 ± 10.9	73.2 ± 11.7	77.8 ± 15.7	77.8 ± 15.8
FEV_1 post-BD% predicted	75.2 ± 11.9	81.1 ± 10.8	84.4 ± 13.8	85.2 ± 12.5	86.1 ± 15.8	85.9 ± 15.8

BT, bronchial thermoplasty; Ref., reference; ICS, inhaled corticosteroid; LABA, long-acting β2-agonist; ACQ, asthma control questionnaire; AQLQ, Asthma Quality Of Life Questionnaire; SFD, symptom-free days; ER, emergency room visit; FEV_1, forced expiratory volume in the first second (% predicted); pre-BD, pre-bronchodilator; post-BD, post-bronchodilator; –, data not available. The following values are expressed by mean ± SD:
[a]Age,
[b]Weight,
[c]CS dose,
[d]LABA dose,
[e]ACQ score,
[f]AQLQ score,
[g]SFD and
[h]Lung function measures.

Downloaded by [University of Liverpool] at 06:42 27 October 2015

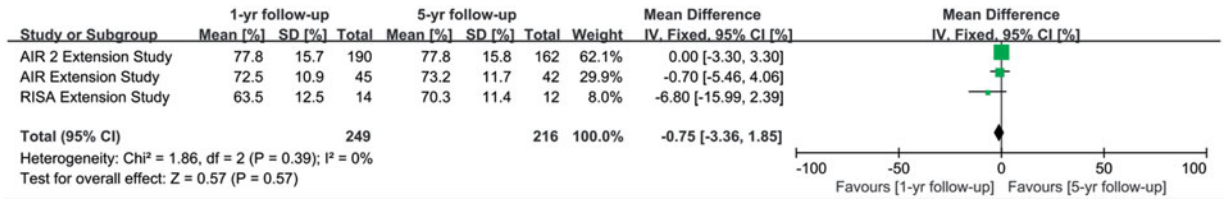


Figure 2. No evidence of significant decline in pre-bronchodilator FEV_1 (% predicted) during the long-term follow-up (WMD −0.75; 95% CI: −3.36 to 1.85; $p=0.57$).

BT observed at 1 year remained at 5 years. The long-term efficacy of BT was further supported by the absence of decline in lung function, which might imply the protective role of BT in lung function stability [28–31]. In addition, the incidence of ER visits and hospitalization for respiratory adverse events in subjects receiving BT treatment remained unchanged. All these results indicate that the integrity of the airways is not compromised over the long term as a result of BT treatment. This study confirms the persistent benefits of BT treatment up to at least 5 years and has intensified the previously established safety and efficacy profiles by other studies [10–12,25,32,33].

Despite of beneficial role of BT treatment in asthma control, one might also challenge that BT intervention could cause potential and transient damage to the airway walls with initial target only on ASM [34], which appears to play a versatile role in underlying mechanism for asthma. ASM hyperplasia increases contractility of ASM, and leads to intermittent airway obstruction. The recurrent episodes of ASM constriction could possibly initiate an inflammatory reaction by activating the release of smooth muscle agonists in a feed-forward loop fashion, and thus airway inflammation may persist [5]. The BT-induced reduction in the ASM mass could cause a physical change of the airway, which would be expected to be of long-term or even permanent [35]. However, such hypothesis was not supported by the findings from animal studies, which suggested an absence of scar formation in the treated area after BT intervention, but with a complete epithelial re-growth instead [5]. The only residual disruption of airway morphology was the replacement of ASM at the treatment site by loose connective tissue [5]. All other tissue elements remained intact or returned to normal

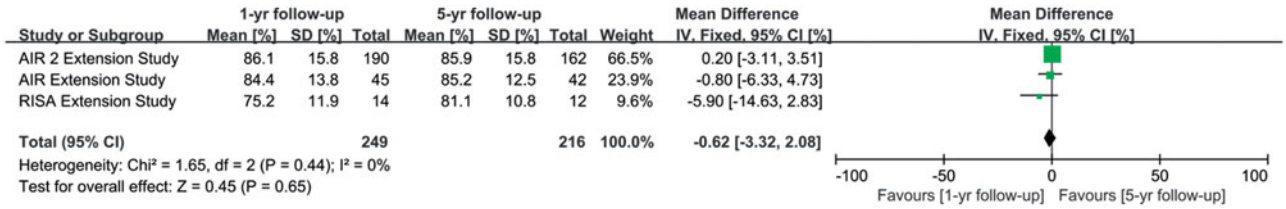


Figure 3. No evidence of significant decline in post-bronchodilator FEV_1 (% predicted) during the period in the post-treatment course (WMD −0.62; 95% CI: −3.32 to 2.08; $p = 0.65$).



Figure 4. A statistically significant reduction in the frequency of respiratory adverse events after BT treatment (RR = 3.41, 95% CI: 2.96–3.93, $p < 0.00001$).

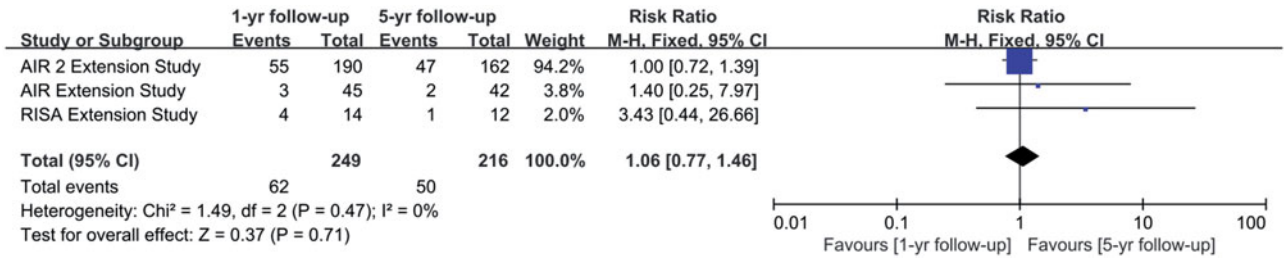


Figure 5. No statistically significant increase in the number of ER visits for adverse respiratory events (RR 1.06, 95% CI: 0.77–1.46, $p = 0.71$).

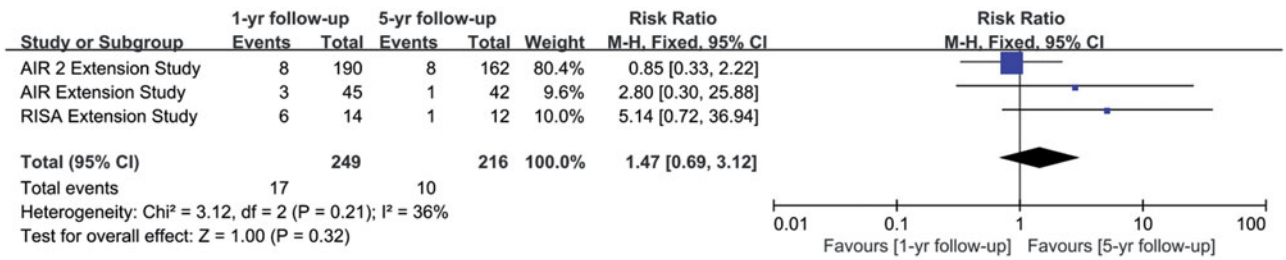


Figure 6. No statistically significant increase in the incidence of hospitalization for respiratory adverse events (V5 vs. V1, RR = 1.47, 95%CI: 0.69–3.12, $p = 0.32$).

based on a careful histological assessment [5]. Until now, the exact pathway that leads to loss of ASM is not well known, and therefore, further animal studies and clinical investigation should be designed to examine whether BT-induced ablation of ASM could become a two-edged sword during the period in the post-treatment course and to determine the precise mechanisms through which BT produces beneficial effects on asthmatic patients. [36,37].

Despite of all data supporting the usage of BT treatment, the frequency of respiratory adverse events should not be neglected during the early stage of BT intervention. The most common side effects were airway irritation, including worsening asthma symptoms (wheezing, chest discomfort, cough and chest pain), and upper respiratory tract infections. The majority of respiratory adverse events occurred within 1 day of the bronchoscopy and resolved within 7 days [8–11,14,24].

There are several limitations in this study. First of all, almost all studies included in this meta-analysis did not have a control group (sham group) for 5-year follow-up. As Pavord mentioned [12], the ethical consideration is the most important issue impeding researchers to acquire a matched long-term follow-up control group for BT treatment. Secondly, the findings from current studies are still based merely on clinical

Downloaded by [University of Liverpool] at 06:42 27 October 2015

manifestations and outcomes. Histological assessment after BT treatment could provide more evidence to support our findings. A study designed to investigate the long-term effect of BT treatment with pathological examination conducted at the same time would be very helpful in addressing this concern.

Conclusions

In summary, through a systematic search, review and analysis of the currently available literatures, we conclude that bronchial thermoplasty shows reasonable long-term safety and efficacy for moderate-to-severe asthmatic patients. A large scale clinical study should be performed for confirming the finding.

Declaration of interest

This study was supported by National Natural Science Foundation of China (81370130). The authors report no conflicts of interest.

Downloaded by [University of Liverpool] at 06:42 27 October 2015

References

1. Masoli M, Fabian D, Holt S, Beasley R. The global burden of asthma: executive summary of the GINA Dissemination Committee report. Allergy 2004;59:469–478.
2. Braman SS. The global burden of asthma. Chest 2006;130:4S–12S.
3. Moore W, Bleecker E, Curran-Everett D, Erzurum SC, Ameredes BT, Bacharier L, Calhoun WJ, et al. Characterization of the severe asthma phenotype by the National Heart, Lung, and Blood Institute's Severe Asthma Research Program. J Allergy Clin Immunol 2007;119:405–413.
4. Chipps BE, Zeiger RS, Dorenbaum A, Borish L, Wenzel SE, Miller DP, Hayden ML, et al. The TENOR Study Group. Assessment of asthma control and asthma exacerbations in the epidemiology and natural history of asthma: outcomes and treatment regimens (TENOR) observational cohort. Curr Respir Care Rep 2012;1: 259–269.
5. Cox G, Miller J, Mitzner W, Leff AR. Radiofrequency ablation of airway smooth muscle for sustained treatment of asthma: preliminary investigation. Eur Respir J 2004;24:659–663.
6. Danek CJ, Lombard CM, Dungworth DL, Cox G, Miller JD, Biggs MJ, Keast TM, et al. Reduction in airway hyperresponsiveness to methacholine by the application of RF energy in dogs. J Appl Physiol 2004;97:1946–1953.
7. Cox G, Miller J, McWilliams A, FitzGerald JM, Lam S. Bronchial thermoplasty for asthma. Am J Respir Crit Care Med 2006;173: 965–969.
8. Rubin AS, Cardoso PF. Bronchial thermoplasty report on the first endoscopic treatment for asthma in Latin America. J Bras Pneumol 2008;34:59–62.
9. Castro M, Rubin A, Laviolette M, Fiterman J, Lima MA, Shah PL, Fiss E, et al. Effectiveness and safety of bronchial thermoplasty in the treatment of severe asthma: a multicenter, randomized, double-blind, sham-controlled clinical trial. Am J Respir Crit Care Med 2010;181:116–124.
10. Wechsler ME, Laviolette M, Rubin AS, Fiterman J, Lapa e Silva JR, Shah PL, Fiss E, et al. Asthma Intervention Research 2 Trial Study Group. Bronchial thermoplasty: long-term safety and effectiveness in patients with severe persistent asthma. J Allergy Clin Immunol 2013;132:1295–1302.
11. Thomson NC, Rubin AS, Niven RM, Corris PA, Siersted HC, Olivenstein R, Pavord ID, et al. AIR Trial Study Group. Long-term (5 year) safety of bronchial thermoplasty: Asthma Intervention Research (AIR) trial. BMC Pulm Med 2011;11:8.
12. Pavord ID, Thomson NC, Rubin AS, Niven RM, Corris PA, Chuang KF, Cox G, et al. Research in Severe Asthma Trial Study Group. Safety of bronchial thermoplasty in patients with severe refractory asthma. Ann Allergy Asthma Immunol 2013;111:402–407.
13. Higgins JPT, Green S. Cochrane handbook for systematic reviews of interventions 4.2.6. In The Cochrane Library, 2006, Issue 4. Chichester: John Wiley; 2006 (updated September 2006).
14. Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention: updated 2012. Available from: http://www.ginaasthma.org/documents/5/documents_variants/37 [last accessed 20 Apr 2014].
15. Cox G, Thomson NC, Rubin AS, Niven RM, Corris PA, Siersted HC, Olivenstein R, et al. Asthma control during the year after bronchial thermoplasty. N Engl J Med. 2007;356: 1327–1337.
16. Mayse ML, Laviolette M, Rubin AS, Lampron N, Simoff M, Duhamel D, Musani AI, et al. Clinical pearls for bronchial thermoplasty. J Bronchol Interv Pulmonol 2007;14:115–123.
17. Jüni P, Altman DG, Egger M. Systematic reviews in health care: assessing the quality of controlled clinical trials. BMJ 2001;323: 42–46.
18. Guyatt GH, Sackett DL, Cook DJ. Users' guides to the medical literature. II. How to use an article about therapy or prevention. A. Are the results of the study valid? Evidence-Based Medicine Working Group. JAMA 1993;270:2598–2601.
19. Guyatt GH, Sackett DL, Cook DJ. Users' guides to the medical literature. II. How to use an article about therapy or prevention. B. What were the results and will they help me in caring for my patients? Evidence-Based Medicine Working Group. JAMA 1994; 271:59–63.
20. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJM, Gavaghan DJ, McQuay HJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996;17:1–12.
21. Moher D, Pham B, Jones A, Cook DJ, Jadad AR, Moher M, Tugwell P, Klassen TP. Does quality of reports of randomized trials affect estimates of intervention efficacy reported in meta-analyses? Lancet 1998;352:609–613.
22. Higgins JP, Thompson SG, Deeks JJ, Higgins JP, Thompson SG, Deek JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–560.
23. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–188.
24. vanHouwelingen HC, Arends LR, Stijnen T. Advanced methods in meta-analysis: multivariate approach and meta-regression. Stat Med 2002;21:589–624.
25. Pavord ID, Cox G, Thomson NC, Rubin AS, Corris PA, Niven RM, Chuang KF, Laviolette M. Safety and efficacy of bronchial thermoplasty in symptomatic, severe asthma. Am J Respir Crit Care Med 2007;176:1185–1191.
26. Cox G, Miller J, Goodwin S, Fitzgerald JM, Hui L, Lam S. Long-term follow-up of bronchial thermoplasty for asthma: safety results at 5 years. Am J Respir Crit Care Med 2008;177:A567.
27. Wu Q, Xing Y, Zhou X, Wang D. Meta-analysis of the efficacy and safety of bronchial thermoplasty in patients with moderate-to-severe persistent asthma. J Int Med Res 2011;39:10–22.
28. Bai TR, Vonk JM, Postma DS, Boezen HM. Severe exacerbations predict excess lung function decline in asthma. Eur Respir J 2007; 30:452–456.
29. O'Bayrne PM, Pedersen S, Lamm CJ, Tan WC, Busse WW. START Investigators Group. Severe exacerbations and decline in lung function in asthma. Am J Respir Crit Care Med 2009;179: 19–24.
30. Lange P, Parner J, Vestbo J, Schnohr P, Jensen G. A 15-year follow-up study of ventilatory function in adults with asthma. N Engl J Med 1998;339:1194–1200.
31. James AL, Palmer LJ, Kicic E, Maxwell PS, Lagan SE, Ryan GF, Musk AW. Decline in lung function in the Busselton Health Study: the effects of asthma and cigarette smoking. Am J Respir Crit Care Med 2005;171:109–114.
32. Castro M, Rubin A, Laviolette M, Hanania NA, Armstrong B, Cox G. Persistence of effectiveness of bronchial thermoplasty in patients with severe asthma. Ann Allergy Asthma Immunol 2011;107: 65–70.
33. Cox G, Laviolette M, Rubin A, Thomson N. AIR and RISA study group. Long term safety of bronchial thermoplasty (BT): 3 year data from multiple studies. Am J Respir Crit Care Med 2009;179: A2780.

34. Solway J, Irvin CG. Airway smooth muscle as a target for asthma therapy. N Engl J Med 2007;356:1367–1369.
35. Tshumperlin DJ, Dai G, Maly IV, Kikuchi T, Laiho LH, Mcvittie AK, Haley KJ, et al. Mechanotransduction through growth-factor shedding into the extracellular space. Nature 2004;429: 83–86.
36. Drazen JM. Asthma and the Human Genome Project: summary of the 45th annual Thomas L. Petty Aspen Lung Conference. Chest 2003;123:447S–449S.
37. Janssen LJ. Airway smooth muscle as a target in asthma and the beneficial effects of bronchial thermoplasty. J Allergy (Cairo) 2012; 2012:593784.

Downloaded by [University of Liverpool] at 06:42 27 October 2015