REVIEW

Bronchial Thermoplasty in Asthma: Scrutinizing the Current Evidence

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Abstract

Objectives: Severe asthma accounts for 5-10% of all asthma cases and half of asthma-related costs in developed countries. Targeting smooth muscle hypertrophy and hyperplasia using bronchial thermoplasty (BT) represents a novel therapeutic approach to this disease. This review aims to critically examine and appraise the methodology and interpretation of individual clinical trials concerning the use of BT in severe asthma. It is not intended to be a systematic review or a meta-analysis. Methods: PubMed, Ovid MEDLINE, Ovid EMBASE, Google Scholar, and Scopus were searched until August, 31st 2015 for published clinical trials concerning the use of BT in asthma patients. Search titles included BT, severe asthma, BT in asthma, BT and severe asthma and effectiveness and safety of BT in asthma. Results: One published non-randomized, three randomized and three extension trials were identified. The methodology and results of each individual trial were subjected to careful examination and appraisal. A good safety profile of BT as a novel therapeutic approach of severe asthma has been confirmed in multiple clinical trials. However, there are still unanswered questions and concerns regarding the effectiveness of this procedure in severe asthma. The evidence concerning this effectiveness needs to be augmented by further well-designed sham controlled trials. Conclusion: Well-designed controlled trials using hard outcome measures such as asthma control, lung function and ability to withdraw/reduce steroid are desperately needed to confirm the effectiveness of BT in severe asthma cases. Consideration of asthma phenotypes when conducting such trials would be rewarding.

Key words: Bronchial thermoplasty, Asthma, Airway, Smooth muscle

Introduction

Severe asthma is defined as asthma that requires treatment with high dose inhaled corticosteroids (ICSs) plus a second

controller (and/or systemic corticosteroids) to prevent it from becoming uncontrolled or which remains uncontrolled despite this therapy (1,2). Growing evidence suggests that severe asthma is a heterogeneous group of diseases that encompasses different phenotypes and endotypes (3). Severe asthma accounts for 5-10% of all asthma cases and is responsible for almost half of asthma-related direct costs in the United States (4). Airway inflammation (involving multiple cells) is the fundamental process in the pathogenesis of asthma. In addition to airway inflammation, changes in the airway smooth muscles contribute significantly to the pathogenesis of this disease. These changes include hypertrophy and hyperplasia with subsequent spread of the muscles up and down in the airways. Smooth muscle hypertrophy, formation of new matrix proteins such as collagen fibers and the proliferation of microvessels are responsible for airway thickness in chronic asthma (5-7). BT is a bronchoscopic procedure that is usually performed under conscious sedation in the outpatient setting. It delivers a tightly controlled radio-frequency thermal energy to the airway wall via a special catheter electrode aiming at reducing the amount of airway smooth muscle and therefore decreasing broncho-constriction and frequency and severity of asthma symptoms. Radio-frequency energy is systematically applied to the majority of airways between 3 and 10 mm in diameter throughout the tracheo-bronchial tree. Continuous feedback is used during energy delivery to tightly control the degree of tissue heating and achieve decrease in airway smooth muscle mass without airway perforation or stenosis (8). The theory behind the use of BT in asthma was derived from an animal model. In 2003, Danek et al. (9) examined the hypothesis that reductions in airway smooth muscle caused by radio-frequency energy would correlate inversely to the magnitude of airway hyper-responsiveness (AWH) to local methacholine challenge. They delivered three energy levels (55, 65 and 75 ^{0}C) each to the airways of anesthetized dogs. Reduction in airway smooth muscle as well as AWH to methacholine challenge that persisted for up to 3 years was observed in the treated airways (9). In 2010, the Food and Drug Administration (FDA) of the Department of Health and Human Resources in the United States approved the Alair BT System for use in adult patients (18 years or above) with severe persistent asthma after release of AIR2 trial results (10,11).

Methodology

A literature search for clinical trials concerning the use of BT in asthma patients until August, 31st 2015 was performed. PubMed, Ovid MEDLINE, Ovid EMBASE, Google Scholar, and Scopus were searched using various key words such as BT, severe asthma, BT in asthma, BT and severe asthma and effectiveness and safety of BT in asthma. The methodology and results of each individual trial were subjected to careful examination and appraisal.

Results

Seven published clinical trials (One non-randomized, three randomized and three extension) were identified. The methodology and results of each individual trial were subjected to careful examination and appraisal.

The first clinical trial

This was a two-site non-randomized prospective, open-label study conducted between October 2000 and June 2002 (12). The study objectives were to examine the safety and impact of BT on lung function and AWH. Follow up period was for 2 years and assessments were conducted at 12 weeks, 12 months and 2 years after treatment. Sixteen patients with mild to moderate asthma were enrolled. Baseline and 12-week post-treatment measurements of spirometry, methacholine challenge, daily peak flow (PEF) readings, symptoms, and medication usage were recorded. Aside from being the first trial conducted on BT in asthma, the importance of this study is related to safety of BT in asthmatic patients. The study demonstrated that BT was well tolerated with transient side effects that were similar to what commonly observed after bronchoscopy. Nevertheless, important limitations of this study include, in addition to being of small size, the open-label and non-randomized nature. The study also did not show any significant improvement in lung function. Although symptoms related to asthma were recorded, effects of BT on asthma control and asthma related quality of life were not among the outcomes of this study. The improvement in the morning and evening PEF readings recorded at 12 weeks post procedure (compared to the baseline) in this study should be interpreted with caution. There were no readings recorded beyond the twelfth week post procedure. In addition, 10 of the 16 subjects experienced no change in the morning PEF outside of baseline variability and 6 of the 16 subjects experienced transient decrease in morning PEF in the days after treatment. The authors also reported medication adjustments for some study subjects after the procedure but their effects on PEF readings were not examined. Similarly, the investigators reported an increase in the mean percentage of symptom-free days between baseline (50%) and 12 weeks after treatment (73%) but no data on asthma control and asthma quality of life testing.

Despite the increase in PEF and symptom-free days reported after BT, there was no significant change in the use of rescue medications. It would be interesting if the investigators measured the effect of BT on PEF and symptoms beyond 12 weeks as they did with AWH. In conclusion, being a feasibility study, this trial has demonstrated clearly that BT is a well-tolerated procedure. Neither the power nor the measured outcomes were sufficient to provide reliable information about BT effectiveness in asthma.

Asthma control during the year after bronchial thermoplasty trial (AIR)

This was the first multi-center randomized controlled trial to examine the efficacy of BT in patients with moderate and severe asthma (13). Subjects with moderate or severe persistent asthma (defined according to Global Initiative of Asthma (GINA) guidelines) (14) who were requiring daily ICSs (beclomethasone ≥ 200 μg or equivalent) and long acting B2 agonist (LABA) (salmeterol ≥ 100 μg or equivalent) to maintain reasonable asthma control were included in the study. The worsening of asthma control after withdrawal of LABA for a 2-week period was another inclusion criterion. The primary outcome of this trial was the difference between the two groups regarding the change in the rate of mild exacerbations from the baseline. Other outcomes included AWH, asthma symptoms, the number of symptom-free days, use of rescue medication and scores on the Asthma Quality of Life Questionnaire (AQLQ) and ACQ. Outcome measures were assessed at 6 weeks, 3 months, 6 months and 12 months. There was significant difference between the mean number of mild exacerbations between the BT and control groups (in favor of BT) at 12 months. In addition, the average number of exacerbations during the 2-week periods at 3 6, and 12 months when subjects in the two groups were treated with ICSs alone was reduced in the BT group but did not change significantly in the control group (10 fewer mild exacerbations per subject per year in the BT group). The investigators also found significant improvements in the morning PEF, scores on AQLQ and ACQ and percentage of symptom-free days in favor of the BT group at 12 months. The strength of this study comes from being the first randomized, multi-center trial on BT in asthma. Furthermore, it was the first to demonstrate a degree of effectiveness of BT in asthma. Important limitations of this study include the non-blinded design and a number of unexpected findings. One of these unexpected findings is that the improvements in AQLQ and ACQ in the BT-treated subjects were not reflected on the ability of these subjects to tolerate LABA withdrawal (15). Other findings include the lack of effect of BT on FEV1, and the inconsistency in the difference in rescue medication use between the two groups at different follow up points (despite the reduction in the symptom score in favor of BT). Another inconsistency in the results of this study is related to the primary end point (the rate of exacerbations). While the difference in mild exacerbations between the two groups was observed at 3 and 12 months of follow up, it was not significant at 6 months and there was no significant difference in the rate of severe exacerbations at any time point. It is unclear why difference in the rate of "mild" exacerbations was specifically selected as the primary end point rather than the difference in the rate of exacerbations in general (both mild and severe). This is a very soft primary end point in a trial like this. Another important limitation of this study is the short periods of time over which the primary and secondary outcomes were assessed. The 2-week periods of abstinence from LABA at 3, 6 and 12 months of follow up used to calculate events of exacerbations, asthma control or quality of life are probably short and may not reflect the true incidence of these outcomes in the study groups. It is also important to note that there were variations among the study centers in the size of the treatment effect and the number of adverse events (13). Overall, more adverse events were seen in the BT group as compared to the control group particularly in the first week after the procedure resulting in more hospitalizations for asthma exacerbations (13).

The AIR Extension Study

A five-year extension study conducted on 45 BT-treated and 24 control subjects (who were enrolled in the AIR trial) was published in 2011(16). Although one patient in the BT group developed lung abscess that required surgical intervention, the rate of the adverse events remained stable in years 2 to 5 following BT. In addition, the respiratory adverse event rate between the BT and control group was not significantly different during the year 2 and 3. There was statistically insignificant increase in hospitalization rate for respiratory events in the BT group and the number of emergency department visits remained comparable. However, despite stabilization of PFT and improvement in methacholine challenge test from the baseline in the BT group, the reduction in ICS dose was not significantly different between the BT group and the control group at 2 and 3 years ($p = 0.93$ and 0.92 respectively). The main conclusion that can be derived from this study is the good safety profile of BT in asthma subjects over 5 year period. In contrast to other extension studies performed on BT in

asthma, an additional and important point of strength in this study is the availability of the control group to compare with during the extension period (16). This is an extremely important point when examining efficacy rather than safety measures during the extension period.

Research in Severe Asthma Trial (RISA)

This was a randomized controlled but non-blinded trial conducted at eight investigational centers between April 2004 and February 2006 (17). The primary objective of this study was to determine the safety of BT in subjects with symptomatic severe asthma. Secondary objectives were the effects of BT on ACQ, AQLQ, PEF, FEV1 and the change in oral steroid, ICS and rescue medication requirements. Thirty two Adults with symptomatic asthma despite treatment with ICS (fluticasone ≥ 750 μg/day or equivalent) and a LABA (salmeterol ≥ 100 μg/day or equivalent) plus other medications such as oral prednisolone (30 mg or less) were randomized to a BT or a control group. After treatment, subjects entered a 16-week steroid stable phase (weeks 6–22), a 14-week steroid wean phase (weeks 22–36), and a 16-week reduced steroid phase (weeks 36–52) (17). BT resulted in statistically significant worsening of asthma symptoms and more hospitalizations for respiratory symptoms, particularly during the first week of treatment. Significant improvement from baseline in the stable steroid phase (at 22 weeks) was observed in pre-bronchodilator FEV1, AQLQ scores and rescue medication use (the latter persisted till 52 weeks). There was no significant difference between the two groups during this phase with regard to post-bronchodilator FEV1, PEF, symptom-free days, symptom scores or methacholine PC20. At 52 weeks post-treatment (reduced steroid phase), there was no difference between the two groups with regard to FEV1, PEF, AQLQ or other end points apart from the use of rescue medications. The difference between the two groups with regard to the ACQ scores in the RISA trial should be interpreted with a great caution as the BT group has significantly higher ACQ scores than the control group at the baseline (2.83±1.02 vs. 2.23±0.75). This has been addressed by the investigators in a post-hoc analysis which revealed that the baseline value did have a statistically significant relationship to ACQ at 22 weeks, resulting in a loss of statistical significance for ACQ measure (17). In addition, there was no statistically significant difference between the two groups with regard to the change in corticosteroid requirements. The non-blinded nature, the small sample size and the high potential for placebo effect are also important limitations of the RISA trial (17).

The RISA Extension Study

This was a 5-year extension safety study of 14 subjects who were enrolled in the BT arm of the RISA trial (18). Fourteen subjects completed follow-up evaluations at 3 years and 12 completed follow-up evaluations at 4 years. The small sample size and the lack of control group for comparison do not allow much expectation from this study other than those related to safety of BT in asthma.

The AIR2 trial

This study was the first randomized double-blind sham-controlled trial on BT in asthma. It was conducted between October 2005 and July 2008 at thirty investigational sites in six countries (11). The objective of this trial was to evaluate the effectiveness and safety of BT as compared to a sham procedure in subjects with severe asthma who remained symptomatic despite treatment with high dose ICSs (beclomethasone 1000 μg/d or equivalent) and LABA (salmeterol ≥100 μg /d or equivalent). Inclusion criteria included subjects on stable maintenance asthma treatment for at least 4 weeks before entry, baseline AQLQ score 6.25 or lower, pre-bronchodilator FEV1 more than or equal 60% of predicted, evidence of AWH, at least 2 days of asthma symptoms during the 4 week baseline period and being a non-smoker for at least 1 year. The primary outcome was the difference between the study groups in the change of AQLQ score from the baseline to the average of the 6, 9, and 12-month scores. The proportion of subjects within each group that achieved an AQLQ score change of 0.5 or greater was analyzed. Secondary outcomes included changes in AQLQ (absolute and individual domains), ACQ scores, and percentage of symptom-free days, symptom scores, morning PEF, rescue medication use, and FEV1. Additional outcomes included the number of severe asthma exacerbations (those requiring systemic corticosteroids or doubling the ICS dose), the percentage of subjects experiencing severe exacerbations, respiratory related unscheduled physician office visits, emergency department visits, hospitalizations, and days missed from work/school or other activities due to asthma. Follow up assessments were done at 3, 6, 9, and 12 months post-treatment (11). The 288 subjects with severe asthma who fulfilled the inclusion criteria were randomized in a 2:1 fashion (190 to BT and 98 to sham procedure). Neither the subjects nor the assessors were aware of the individual treatment assignment. In the statistical calculations the investigators used the "posterior probability of superiority" (PPS) of BT over sham to quantify the strength of evidence. A target PPS of 95% was used to

assess the difference in the outcomes between the 2 study groups except for the primary AQLQ endpoint, where the target PPS was 96.4% (11). The investigators reported that the improvement from the baseline in the integrated AQLQ score (the primary end point) was superior in the BT group compared with sham (BT, 1.35±1.10, sham, 1.16±1.23 with PPS of 99.6%) and the BT group experienced fewer severe exacerbations, emergency department visits, days missed from work/school compared with the sham group (PPS, 99.5, 99.9, and 99.3% respectively) with a 32% reduction in the rate of severe exacerbations in the BT group in the post treatment period. There was no statistically significant difference in the other secondary end points such as morning PEF, symptom-free days, symptoms score, ACQ, and rescue medication use. Aside from being the largest, first sham-controlled, multi-center and randomized landmark study conducted on BT in asthma, the AIR2 trial results represent a major turning point in the thinking of many respiratory physicians with regard to the role of BT in severe asthma cases. Nevertheless, there are important critique points concerning the findings of this landmark trial. The first is related to the difference between the two groups in the primary end point (the improvement in the AQLQ score from the baseline in the two groups). In their statistical analysis, the investigators stated that the target PPS of superiority of BT over sham for the primary end point (AQLQ) was 96.4%. However, the achieved one using the Intention-To-Treat Analysis (ITT) was only 96% which suggests no statistical difference between the two groups (11,19). Another important limitation is regarding which domain of the AQLQ showed the difference. A statistically significant difference was reached only for the emotional function domain of the AQLQ. This domain contains 5 subjective questions addressing patient fear and concerns about asthma (20). None of the other 3 domains (symptoms, activity limitations or environmental stimuli) showed a statistically significant difference. There is a concern that the improvement of the emotional domain was partly due to the fact that a larger proportion of subjects in the BT group than in the sham group could accurately guess their treatment assignment after the first bronchoscopy (11). Selecting soft end points such as the AQLQ in subjects who could largely guessed their treatment assignment in this landmark study has been addressed by other experts (21). Another important limitation of the AIR2 trial is related to the findings of reduced rate of asthma exacerbations, the number of emergency department visits and time lost from work/school. The two treatment groups were not matched in their baseline characteristics for these parameters. Thus, there is a concern that more patients who were "frequent-exacerbators" or frequent "emergency department visitors" included in the BT group resulting in a significant difference in these outcomes (in favor of BT). Although some experts have raised concerns that the analysis of these outcomes was unplanned in the early course of the trial (19,22), one would assume that the FDA would be aware of such protocol or end points changes if they happened.

Discussion

BT represents a novel invasive and expensive therapeutic approach to severe asthma and hence worth adequate evidence to support its safety and effectiveness in this disease with huge economic and clinical burden. The current available evidence is very reassuring with regard to the short and long-term safety of the procedure. The side-effects probably do not differ from the conventional bronchoscopy. Nevertheless, there is currently only one sham-controlled clinical trial that revealed effectiveness in asthma with regard to certain end points. Although BT is being increasingly used in developed (and cautiously in few developing) countries after FDA approval in 2010, there is still a number of concerns and questions regarding the effectiveness of this procedure that remained unanswered. Some of these concerns include:

Inconsistency of results, single source of evidence and use of soft outcomes among some BT trials

A careful examination of the various clinical trials concerning the efficacy of BT in asthma reveals some degree of inconsistency between the results of these trials. While the AIR2 trial (11) did not show any statistically significant difference in certain end points such as morning PEF, symptom-free days, symptom score, ACQ, and rescue medication use, the AIR (13) trial revealed significant improvements in the morning PEF, ACQ scores and percentage of symptom-free days in the BT group while no difference between the two groups in the ability to withdraw LABA. Similarly, the number of symptom-free days was significantly better in the BT group in the AIR trial (13) but did not differ in the AIR2 and RISA trials (11,17). Furthermore, it has been observed that soft primary outcomes, such as the rate of mild exacerbations in the AIR trial and the AQLQ in the AIR2 trial were used (21). It would also be reaffirming if the evidence of effectiveness in future BT trials comes from different study groups rather than a single group of investigators

Misleading comparisons (comparisons within the group against baseline)

When the study contains a control group, the comparison of interest is whether the treatment group has better or worse outcomes than the control group. The aim of randomization is to ensure that the two groups are comparable in every respect except the intervention. Rather than comparing the randomized groups directly, some researches look within the groups at the change of outcome measure from baseline (or different time intervals) to the final measurement at the end of the trial. They then perform a test of null hypothesis that the mean difference is zero, separately in each randomized group. They may then report that in one group the difference is significant but not in the other group and conclude that this is evidence that groups, and hence treatments are different. This is well-known statistically to be very misleading as the improvement in the treatment group may be attributable to spontaneous resolution of symptoms, other interventions, the placebo effect or combination of these (23,24). The extension study of the AIR2 (25) is an example of such comparisons. While the study clearly confirmed the long-term safety of BT in asthma, a conclusion regarding the effectiveness of the BT over a 5-year follow up period was derived from comparing various parameters (such as the difference in AQLQ and ACQ scores, hospitalization rate and number of symptom-free days) within the BT group at different point intervals (from the baseline) in the absence of comparison with the sham group. In contrast, the AIR extension study involved the control group in its long-term follow up (16).

The million-dollar question: Can I step down my patient's treatment after BT?

The definition of severe asthma entitles the requirement of high dose ICSs plus a second controller (and/or systemic corticosteroids) to maintain adequate asthma control (1,2). It was anticipated from BT trials to provide a positive answer to the one million-dollar question; can I step down severe asthma treatment or reduce ICS requirement of my patient after BT? (26,27). Unfortunately, the answer to this question from the currently available evidence is probably "NO". In the AIR trial (13), there was no significant difference between the BT and the control group in their ability to tolerate LABA withdrawal. Similarly, in the RISA trial (17) there was no significant change in corticosteroid requirement between the BT and control group. In the AIR2 trial, this question was not specifically addressed. However, the absence of significant changes in the total symptom score, percentage of symptom-free days and rescue medication use between the BT and control group would have eventually resulted in a negative outcome with regard to ability of the subjects in the BT group to step down their asthma medications (11). As mentioned earlier, the results of the extension study (25) carried out by AIR2 study group that revealed a 17% reduction in the average ICS dose at 5 years in the BT group subjects should be interpreted with caution as this comparison was within the BT group in absence of comparison with the control group as discussed above.

Which asthma phenotype(s) may benefit from BT?

Severe asthma is a heterogeneous group of disease phenotypes rather than a single disease. This heterogeneity has been identified as one of the reasons for the poor response to medication in severe asthma. Over the past decade, there has been a lot of emphasis on categorization and characterization of asthma phenotypes for specific treatment consideration (3,28). Based on the current evidence concerning the role of BT in severe asthma, it is uncertain which asthma phenotype(s) would benefit from this type of therapy.

Conclusions

A good safety profile of BT as a novel therapeutic approach to severe asthma has been confirmed in multiple clinical trials. Nevertheless, there are still unanswered questions and concerns regarding the effectiveness of this procedure in severe asthma. The evidence concerning this effectiveness needs to be augmented by further well-designed sham controlled trials that use hard outcome measures such as asthma control, lung function and ability to withdraw/reduce steroid. It would be interesting if such trials consider asthma phenotype characterization to ascertain which phenotype(s) benefit from this new therapy. Until results of such trials are available, we recommend that institutions currently using this novel therapy to incorporate it in a dedicated severe asthma service program that uses a systematic stepwise assessment and approach (29).

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