Medical Policy Manual Surgery, Policy No. 178

Bronchial Thermoplasty

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IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Bronchial thermoplasty is a potential treatment option for patients with severe persistent asthma. It consists of radiofrequency energy delivered to the distal airways with the aim of decreasing smooth muscle mass believed to be associated with airway inflammation.

MEDICAL POLICY CRITERIA

Bronchial thermoplasty in considered **investigational** for all indications, including but not limited to the treatment of asthma.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

CROSS REFERENCES

None

BACKGROUND

Asthma, a chronic lung disease, affects approximately 9% of adults and 6% of children in the U.S.[1] Asthma symptoms include episodic shortness of breath that is generally associated with

other symptoms such as wheezing, coughing, and chest tightness. Objective clinical features include bronchial hyper-responsiveness and airway inflammation, and reversible airflow obstruction (at least 12% improvement in forced expiratory volume in one second [FEV1] post-bronchodilator, with a minimum of 200 mL improvement). However, there is substantial heterogeneity in the inflammatory features of patients who are diagnosed with asthma, and this biological diversity is responsible, at least in part, for the variable response to treatment in the asthma population.

Management of asthma consists of environmental control, patient education, management of comorbidities, and regular follow-up for all affected individuals, as well as a stepped approach to medication treatment. Guidelines from the National Heart, Lung and Blood Institute define six pharmacologic steps; step 1 for intermittent asthma, and steps 2 through 6 for persistent asthma.[2] The preferred daily medications are:

Step 1: short-acting beta-agonists as needed
Step 2: low-dose inhaled corticosteroids (ICS)
Step 3: ICS and long-acting beta-agonists (LABA) or medium-dose ICS
Step 4: medium-dose ICS and LABA
Step 5: high-dose ICS and LABA
Step 6: high-dose ICS and LABA, and oral corticosteroids

Despite this multidimensional approach, many patients continue to experience considerable morbidity. In addition to ongoing efforts to optimally implement standard approaches to asthma treatment, new therapies are being developed. One new therapy is bronchial thermoplasty, the controlled delivery of radiofrequency energy to heat tissues in the distal airways. Bronchial thermoplasty is based on the premise that patients with asthma have an increased amount of smooth muscle in the airway and that contraction of this smooth muscle is a major cause of airway constriction. The thermal energy delivered via bronchial thermoplasty aims to reduce the amount of smooth muscle and thereby decrease muscle-mediated bronchoconstriction with the ultimate goal of reducing asthma-related morbidity. Bronchial thermoplasty is intended as a supplemental treatment for patients with severe persistent asthma (i.e., steps 5 and 6 in the stepwise approach to care).

Bronchial thermoplasty procedures are performed on an outpatient basis and last approximately one hour each. During the procedure, a standard flexible bronchoscope is placed through the patient’s mouth or nose into the most distal targeted airway and a catheter is inserted into the working channel of the bronchoscope. After placement, the electrode array in the top of the catheter is expanded, and radiofrequency energy is delivered from a proprietary controller and used to heat tissue to 65°C, over a 5 mm area. The positioning of the catheter and application of thermal energy is repeated several times in contiguous areas along the accessible length of the airway. At the end of the treatment session, the catheter and bronchoscope are removed. A course of treatment consists of three separate procedures in different regions of the lung scheduled about three weeks apart.

REGULATORY STATUS

In April 2010, the Alair® Bronchial Thermoplasty System (Asthmatx, Inc, now part of Boston Scientific Corporation.) was approved by the US Food and Drug Administration (FDA) through the premarket approval process for use in adults with severe and persistent asthma whose symptoms are not adequately controlled with inhaled corticosteroids and LABAs.[3] Use of the treatment is contraindicated in patients with implantable devices and those with sensitivities to

lidocaine, atropine or benzodiazepines. It should also not be used while patients are experiencing an asthma exacerbation, active respiratory infection, bleeding disorder, or within two weeks of making changes in their corticosteroid regimen. The same area of the lung should not be treated more than once with bronchial thermoplasty. Food and Drug Administration product code: OOY.

EVIDENCE SUMMARY

In order to evaluate the efficacy and safety of bronchial thermoplasty (BT) in the treatment of asthma, evidence from randomized controlled trials (RCTs) comparing BT with either medications or sham BT is required. In light of the high placebo effect suggested in the AIR2 study summarized below, a sham control group is preferable in studies of BT, particularly for subjective outcomes such as quality of life.

SYSTEMATIC REVIEWS AND TECHNOLOGY ASSESSMENTS

A 2017 Comparative Effectiveness Review by D'Anci summarized the safety and effectiveness of bronchial thermoplasty in the management of asthma.[4] The literature was reviewed through April 2017, and 15 studies were included. Three RCTs with five-year, single-arm followup in BT-treated patients (n=432 for the RCTs) examined the impact of BT in addition to standard care (continued medical management) on patients with asthma. Studies were evaluated for risk of bias using the Cochrane Risk of Bias instrument, and the evidence was assessed according to the Evidence-based Practice Center program.

The strength of evidence (SOE) was assessed as low for the following results:

- BT and standard care improved asthma control (defined by the Asthma Control Questionnaire [ACQ] change from baseline to 12 months) and Asthma Quality of Life Questionnaire (AQLQ) scores more than standard care alone to a degree that was statistically significant but not clinically important.
- BT and standard care, compared with a sham bronchoscopic procedure and standard care, did not improve asthma control (defined as ACQ change from baseline to 12 months), hospitalizations for respiratory symptoms, use of rescue medications, pulmonary physiology measures, or AQLQ scores (in the intention-to-treat analysis).
- BT reduced severe exacerbations after the 12-week treatment period to a statistically but not clinically important degree.

Additionally, patients undergoing BT had fewer emergency department visits than those who had the sham bronchoscopic procedure (moderate SOE). In the RCTs comparing BT and standard care to standard care alone, evidence was insufficient to assess if BT reduced rates of severe exacerbations.

Following the 12-week treatment period in the RCT's, common adverse events included the following:

- Bronchial irritation
- chest discomfort
- cough
- discolored sputum

- dyspnea
- night awakenings
- wheezing

Hospitalizations were more common in patients who underwent BT than with either standard care alone or sham bronchoscopy during the 12-week treatment period. Upper respiratory tract infections, wheezing, dyspnea, lower respiratory tract infections, anxiety, and segmental atelectasis were also more common, but the events were too infrequent to achieve statistical significance. Severe adverse events (including post-procedure segmental atelectasis due to mucus plugging, hemoptysis, chest infections requiring hospitalization, and bronchial artery pseudoaneurysm) were also reported in six case reports and two small case series. Rates of respiratory-related hospitalizations were not significantly different between groups for up to five years of followup. No deaths were attributed to BT.

The reported concluded that overall, there is a paucity of evidence on BT. Effects of the treatment beyond five years is unknown, and patient selection criteria are uncertain.

Zhou (2016) published a meta-analysis evaluating the long-term efficacy and safety of bronchial thermoplasty as a treatment for moderate-to-severe persistent asthma.[5] The authors pooled data on long-term effects in bronchial thermoplasty-treated patients only and did not include data from comparison groups. In an analysis of 216 patients with five years of follow-up, there was no significant decline in spirometry-detected pre-bronchodilator FEV1 (percent predicted) compared with one year findings (weighted mean difference [WMD] 0.75, 95% CI -3.36 to 1.85, p=0.57, I^2=0%). Similarly, there was no significant decline in postbronchodilator FEV1 (WMD 0.62, 95% CI -3.32 to 2.08, p=0.65, I^2=0%). In terms of adverse events over time, the rates of respiratory adverse events, emergency department visits for adverse events and hospitalizations did not differ significantly after the one- and five-year follow-ups.

In 2015, a TEC Assessment was published on bronchial thermoplasty for treatment of inadequately controlled severe asthma.[6] The Assessment included the three published RCTs discussed and concluded that “the evidence is insufficient to determine whether potential improvements in some outcomes, but not others defining the net health outcome, outweigh the potential harms” and that the technology did not meet TEC criteria.

Wu (2011) conducted a systematic review and meta-analysis of the one-year data from the three RCTs currently published.[7] The RCTs were rated as good quality. Two of the RCTs included a medication control group; one included a sham procedure control group. The possible placebo effect that might impact quality-of-life reporting in the medication trials was not discussed in the article. The authors concluded that BT appears promising and well-tolerated, but additional long-term RCTs are needed for further evaluation of both efficacy and safety.

The meta-analysis of the pooled data reported the following findings:

Efficacy:

- The bronchial thermoplasty patients had a significantly greater mean improvement in asthma quality of life compared with the control groups (WMD 0.63, 95% CI 0.10 to 1.15, p=0.02).

- The bronchial thermoplasty patients had a significantly greater improvement in the morning peak expiratory flow (PEF) compared with the control groups (WMD 21.78, 95% CI 8.06 to 35.50, p=0.002).

Exacerbations:

- During the treatment period, there was a significantly higher risk of hospitalization with bronchial thermoplasty than control (risk ratio [RR] 3.78, 95% CI 1.39 to 10.24, p=0.009).
- In the post-treatment period (end of treatment to the 12-month follow-up visit), there was no significant difference between groups in the risk of hospitalization between groups (RR 1.15, 95% CI 0.47 to 2.79).

Adverse events:

During the treatment period (beginning on the day of the first treatment session and lasting six weeks after the last session):

- There were more respiratory adverse events in the bronchial thermoplasty groups (1,113 events in 257 patients) compared with the control groups (369 events in 164 patients) (p value not reported).
- There were no patient deaths and no permanent disability in any study participant.

The article listed the following factors that limited the interpretation and validity of the analysis of the pooled data:

- Heterogeneity of patient characteristics, study methodology, and treatment protocols between the studies
- All three trials provided medications to all patients; thus, the independent effects of bronchial thermotherapy cannot be determined
- Small sample size due to the meta-analysis having been limited to the three RCTs
- Lack of individual patient data and information for stratified analysis
- The included trials were underpowered to detect some other important outcomes such as FEV1, FEV1 percent predicted, exacerbations, rescue medication use, and longer term (greater than one year) efficacy and safety.

A 2014 Cochrane review of the three randomized BT trials showed no clinical or statistical difference in the asthma control scores [Asthma Quality of Life Questionnaire (AQLQ) or the Asthma Control Questionnaire (ACQ-which measures symptom control)].[8] Limitations of the analysis included a lack of sham intervention for the control groups and lack of blinding in two of three of these studies, raising questions regarding placebo effect, as seen in the high rate of response in the single sham group. (AIR2 trial: 64% experienced a clinically significant increase in the AQLQ). Two of the studies showed lower rates of exacerbation after 12 months with BT compared to medical treatment alone. BT patients had a greater risk of hospitalization for respiratory adverse events during the treatment period with an absolute increase from 2% to 8% (95% CI 3% to 23%) over the treatment period, suggesting six of every 100 participants treated with thermoplasty would require an additional hospitalization over the treatment period. The authors concluded additional data from clinical trials and registries was needed to “better understanding of the mechanisms of action of bronchial thermoplasty, as well as its effect in different asthma phenotypes or in patients with worse lung function.”

RANDOMIZED CONTROLLED TRIALS

Three RCTs evaluating the safety and efficacy of bronchial thermoplasty have been published and were included in the systematic reviews described above. All of the RCTs were supported by Asthmatx, the manufacturer of the Alair system. The initial follow-up period for all three studies was one year. Reports with longer term data have also recently been published. The following is a summary of the findings in the three RCTs.

Research in Severe Asthma (RISA) Trial

This study, published by Pavord (2007), was conducted at eight centers in the U.K., Brazil, and Canada, and was primarily intended to investigate the safety of BT.[9] Eligibility criteria included:

- age 18 or older; asthma diagnosis;
- uncontrolled symptoms despite treatment with high-dose inhaled corticosteroids (at least 750 µg fluticasone propionate per day or equivalent) and long-acting beta-agonists (LABAs) (at least 100 µg salmeterol per day or equivalent), with or without other medications including oral prednisone or leukotriene modifiers;
- FEV1 at least 50% of predicted;
- demonstrated airway hyper-responsiveness by challenge with methacholine or reversible bronchoconstriction during the prior 12 months;
- abstinence from smoking for at least one year, and a past smoking history of less than 10 pack-years.

After a two-week run-in period, 34 participants were randomly assigned to a control group (n=17) that received continued medical management alone or medical management plus treatment with the Alair Bronchial Thermoplasty System (n=17). The bronchial thermoplasty group received three procedures at least three weeks apart (weeks 0 to 6). During weeks 6 to 22 all participants remained on a stable dose of steroids, and then during weeks 22 to 36 an attempt was made to reduce the dose of oral corticosteroids (or inhaled corticosteroids for patients not taking the oral medication). Between weeks 36 to 52, patients took the reduced dose of steroids.

The primary outcomes of the study were the rate of adverse events and serious adverse events (defined as any event that was fatal, required prolonged hospitalization, caused substantial immediate risk of death, resulted in permanent impairment, or required intervention to prevent permanent impairment). A total of 32 of the 34 participants (94%) completed the study. A limitation of the study is the lack of a sham intervention and consequently, an inability to blind patients to treatment group. In addition, the study was limited in its ability to accurately evaluate safety by a small sample size.

One-Year Outcomes

Adverse events (primary outcome for this study): In the initial treatment period, four patients in the bronchial thermoplasty group experienced seven serious adverse events requiring hospitalization and none occurred in the control group. During the remainder of the study, three patients in the bronchial thermoplasty group experienced five serious adverse events, and one patient in the control group experienced four serious adverse events; all of these events required hospitalization. There were an additional five severe adverse events in two bronchial thermoplasty group patients and one event in a control group patient that were

medically treated without hospitalization (the authors did not report whether these were the same patients who were hospitalized). No overall statistical analysis was done that compared serious adverse events in the two groups.

Efficacy variables (secondary outcome for this study): The authors reported of the following efficacy variables at the end of the study at 52 weeks.

- Bronchial thermoplasty patients had a significantly greater improvement in beta-agonist use than control patients (decrease of 26 puffs vs. 6 puffs per week, respectively, $p<0.05$)
- There was no significant difference between groups in other efficacy variables including morning and evening peak expiratory flow (PEF), symptom scores, number of symptom-free days, improvement in FEV1 predicted, and several quality of life measures.

The small sample size resulted in limited power to detect differences in the efficacy outcomes.

Extended Study

Pavord (2013) published five-year safety data on 14 of the 17 (82%) patients assigned to bronchial thermoplasty in the RISA trial.[10] All 14 individuals completed the three year evaluation and 12 patients completed evaluations at four and five years. As described above, safety outcomes were the primary outcomes in the RISA study. In year one of the study, each asthma symptom was considered an adverse event and in subsequent years, multiple asthma symptoms were considered to be a single adverse event. Among those with follow-up data available, the number of patients with asthma adverse events in years two, three, four and five were five (36%), seven (50%), two (17%) and five (42%), respectively. In addition, during years two through five, there were a total of 11 respiratory-related hospitalizations in five patients. The number of patients with data available was too small to draw reliable conclusions about long-term safety and there were no long-term data available on patients in the control group.

Asthma Intervention Research (AIR) Trial

Cox (2007) published the original findings of the AIR trial, which was designed to evaluate symptom control and adverse events following bronchial thermoplasty. Patients were recruited from the same three countries as the RISA study plus Denmark.[11] The eligibility criteria included:

- age 18 to 65
- moderate to severe persistent asthma requiring daily therapy with inhaled corticosteroids (equivalent to at least 200 µg beclomethasone) and LABAs (at least 100 µg salmeterol or equivalent)
- FEV1 of 60%-85% predicted
- airway hyper-responsiveness
- stable asthma in the six weeks before enrollment
- no current respiratory infection
- no more than two lower respiratory infections requiring treatment in the past year
- worsening asthma control during a two-week baseline test period during which time LABA were withheld.

A total of 112 individuals met eligibility following the baseline test phase and were randomly assigned to receive medical management with inhaled corticosteroids and LABAs (n=56), or

the same medical management strategy plus bronchial thermoplasty three sessions approximately three weeks apart (n=56). After follow-up visits at three, six, and 12 months, there was a two-week period of abstinence from LABAs, during which data on exacerbations were collected. Between data collection periods, patients could use all maintenance therapies.

The primary outcome was the difference between groups in change in rate of mild exacerbations from the baseline two-week abstinence period. An exacerbation was defined as the occurrence on two consecutive days of a reduction in the morning peak expiratory flow of at least 20% below the average value (recorded during the week before the abstinence period), the need for more than three additional puffs of rescue medication compared to the week before the abstinence period, or nocturnal awakening caused by asthma symptoms. The study was powered to detect a difference between groups of eight mild exacerbations per person per year. Data were available at three months for 100 of 112 patients (89%) and at 12 months for 101 patients (90%); all patients were included in the safety analysis. A limitation of the study is the lack of a sham intervention and consequently, an inability to blind patients to treatment group.

One-Year Outcomes

Mild exacerbations: The mean number of mild exacerbations per person per week in the bronchial thermoplasty group was 0.35 (standard deviation [SD] 0.32) during the baseline test period, and 0.18 (SD 0.31) per person per week at 12 months (a decrease of 0.17 per person per week). In the control group, the mean number of mild exacerbations per person per week was 0.28 (SD 0.31) at baseline and 0.31 (SD 0.46) at 12 months (an increase of 0.03 per person per week). Compared to the control group, the bronchial thermoplasty group had a significantly greater reduction in mild exacerbations at the 12-month follow-up (p=0.003). Overall, the average number of exacerbations during the two-week data collection periods at three, six, and 12 months decreased in the bronchial thermoplasty group, a mean decrease of 0.16 (SD 0.37) per person per week but not in the control group, which had a mean increase of 0.04 (SD 0.29) mild exacerbations. This resulted in a mean difference of 0.2 mild exacerbations per week, or about 10 per year.

Severe exacerbations: In contrast, there was not a significant difference between the number of severe exacerbations at any time point, compared to baseline. However, the study may not have had sufficient statistical power for this outcome. At the 12-month follow-up, the mean number of severe exacerbations in the bronchial thermoplasty group was 0.01 (SD 0.08) per person per week compared to 0.07 (SD 0.18) at baseline. The number of severe exacerbations in the control group was 0.06 (SD 0.24) per person per week compared to 0.09 (SD 0.31) at baseline.

Adverse events: The rate of adverse events was higher in the bronchial thermoplasty group during the active treatment period, but the proportion of adverse events was similar in the two groups in the post-treatment period. Post-treatment, three individuals in the bronchial thermoplasty group required hospitalization and two patients in the control group required a total of three hospitalizations.

Five-Year Outcomes

Thomson (2011) published five-year safety data from the AIR trial.[12] All study participants who completed the one-year follow-up visit were invited to participate in the extension study; 45 of 52 (87%) in the bronchial thermoplasty group and 24 of 49 (49%) in the control group opted to

participate. Follow-up was done on an annual basis. Patients in the control group were followed for two additional years and patients in the bronchial thermoplasty group were followed for five years. Twenty-one of 24 (88%) patients in the control group and 42 of 45 (93%) in the bronchial thermoplasty group completed the final follow-up.

Although the primary purpose of the Thomson study was to examine long-term safety of the Alair device, some efficacy data was reported for two measures of lung function, post-bronchodilator FEV1 and forced vital capacity (FVC). The group comparisons of safety and efficacy in this follow-up trial was limited by the differential rate of follow-up between the two groups, with a lower percent of patients in the control group agreeing to participate in the follow-up study. In addition, as previously stated, data were collected on both treatment groups only during the first two years of this extension study; thereafter, no further data was obtained from the control group.

Exacerbations:

- FEV1 and FVC remained stable in both groups during years two and three and in the bronchial thermoplasty group in years four and five. Exact numbers were not reported, but post-bronchodilator FEV1 did not go below 80% of predicted in either group.
- In the first year (year two of the study), the rate of hospitalizations was 3 of 45 (7%) in the bronchial thermoplasty group; there were no hospitalizations in the control group (p=0.55). In year three, the rate of hospitalizations in the bronchial thermoplasty group was again 3 of 45 (7%) and 1 of 21 (5%) patients in the control group was hospitalized (p=1.00).
- Rates of emergency room visits in year two were three (7%) and three (12.5%) in the bronchial thermoplasty and control groups respectively (p=0.41) and in year three rates were three (5%) and three (5%), respectively (p=1.00). There was one hospitalization each year in the bronchial thermoplasty group in years four and five.

Adverse events: In the extension study, unlike the initial follow-up period, respiratory adverse events with multiple symptoms were recorded as a single adverse event. This could give a misleading impression of the total number of adverse events or relative number in the two groups.

- In years two and three, differences between groups for incidence of respiratory adverse events were not statistically significant. The incidence of respiratory adverse events during year two was 24 of 45 (53%) in the bronchial thermoplasty group and 13 of 24 (54%) in the control group. During year three, incidence was 24 of 43 (56%) in the bronchial thermoplasty group and 12 of 21 (57%) in the control group.
- In subsequent years, the incidence of respiratory adverse events in the bronchial thermoplasty group was similar to years two and three; rates were 23 of 43 (53%) in year four and 22 of 42 (52%) in year five.
- No instances of pneumothorax, intubation, mechanical ventilation, cardiac arrhythmias, or death were reported over the course of this extension study.
  These five-year safety data on a subset of the participants in the AIR trial do not suggest a high rate of delayed complications following bronchial thermoplasty.

Asthma Intervention Research 2 (AIR2) Trial

The AIR2 trial was a randomized, sham-controlled trial conducted at 30 sites in six countries including the U.S.; one- and two-year findings were published by Castro (2010, 2011).[13, 14]

Unlike the other two RCTs, the control condition was a sham intervention and the trial was double-blind; participants and outcome assessment was blinded, but the intervention team was unblinded. Eligibility criteria were similar to those in the AIR trial; key differences were that a higher initial dose of inhaled corticosteroids was required (equivalent to at least 1000 µg beclomethasone) and patients were required to have experienced at least two days of asthma symptoms during the four-week baseline period and have a baseline score on the Asthma Quality of Life Questionnaire (AQLQ) of no more than 6.25. (The possible range of the AQLQ score is 1 to 7, with a higher number representing a better quality of life.) Also different from the AIR trial: patients were not required to experience symptom worsening during a period of abstinence from LABAs. Patients were stable on their asthma medication and continued their medication regimen during the study.

The primary outcome was the difference between groups in the change from baseline in the AQLQ score, with scores from the 6-, 9-, and 12-month follow-ups averaged (integrated AQLQ score). A related outcome was the proportion of patients who achieved a change in their AQLQ score of 0.5 or greater, generally considered the minimally important difference for this scale. Bayesian analysis was used. The target posterior probability of superiority (PPS) of bronchial thermoplasty over sham was 95%, except for the primary AQLQ endpoint; there the target was 96.4% to adjust for two interim looks at the data.

A total of 297 individuals were randomly assigned, 196 to a bronchial thermoplasty group and 101 to a sham control group. The intervention for all participants consisted of three bronchoscopy procedures, performed three weeks apart. The sham intervention was identical to the active treatment, except that no radiofrequency energy was delivered. Nine participants withdrew consent before beginning treatment, and 288 underwent bronchoscopy and were included in the intention to treat (ITT) population. One hundred and eight-five participants in the treatment group and 97 in the sham control group underwent the second bronchoscopy, and the same numbers of individuals had the third bronchoscopy; it is not clear whether these were exactly the same patients.

One-Year Outcomes[13]

A total of 278 out of the 297 enrolled patients (94%) completed the 12-month visit, 181 in the treatment group and 97 in the sham control group. Primary outcomes in the ITT population were as follows:

- The mean change in the integrated AQLQ score, the primary effectiveness outcome, was 1.35 (SD 1.10) in the bronchial thermoplasty group and 1.16 (SD 1.23) in the sham control group. Using Bayesian analysis, the posterior probability of superiority (PPS) was 96%. This did not surpass the target PPS of 96.4%.
- The percentage of patients achieving an AQLQ score change of 0.5 or greater (i.e., at least the minimal important difference) was 79% in the bronchial thermoplasty group and 64% in the control group. The posterior probability of superiority at 99.6% surpassed the target probability for secondary outcomes of 95%.
- Additional analysis of data from the active treatment group suggests that responders (defined as a change in AQLQ score of at least 0.5) were more likely to have a lower baseline score than nonresponders (mean of 4.1 vs. 5.1, respectively).

Several secondary outcomes favored bronchial thermoplasty over the sham control group. These included:

- Reduction in the proportion of patients reporting asthma worsening during follow-up (27.3% vs. 42.9%, respectively, posterior probability of superiority 99.7%)
- Reduction in the number of emergency department visits (0.07 vs. 0.43 visits per person per year, respectively, PPS 99.9%).
- Reduction in severe exacerbations of 0.47 per person per year in the bronchial thermoplasty group compared to 0.70 per person per year in the control group (the PPS was 95.5%).
- There was no significant difference between groups in other secondary efficacy outcomes including morning peak expiratory flow, number of symptom-free days, symptom score, and rescue medication use.

Regarding safety outcomes, during the treatment phase, there was a higher rate of respiratory adverse events in the active treatment group (85% of participants; mean of 1.0 event per bronchoscopy) compared to the sham group (76% of participants, mean of 0.7 events per bronchoscopy).

- A total of 16 patients (8.4%) in the active treatment group required 19 hospitalizations for respiratory symptoms during the treatment phase compared to two patients (2%) in the sham group who required one hospitalization each.
- However, during the post-treatment period, 70% of patients in the bronchial thermoplasty group and 80% of patients in the sham group reported adverse respiratory events. During this phase of the study, five patients (2.6%) in the bronchial thermoplasty group had a total of six hospitalizations for respiratory symptoms, and four patients (4.1%) in the sham group had 12 hospitalizations (one patient had nine hospitalizations).

In the AIR2 study, the sham group had a relatively high rate of response, e.g., 64% experienced a clinically significant increase in the AQLQ. Blinding appeared to be initially successful and remained so for the sham group. After the first bronchoscopy, participants in both groups were unable to correctly guess their treatment group after the first bronchoscopy. During subsequent assessments, this continued among patients in the sham group, whereas in the bronchial thermoplasty group, a larger proportion guessed correctly.

The high rate of response in the sham group of the AIR2 suggests a large placebo effect with novel asthma treatments, particularly for subjective outcomes such as quality of life. This calls into question conclusions about efficacy in the earlier trials that did not have a sham control. In the AIR2 trial, bronchial thermoplasty provided benefit in terms of quality of life and some, but not all, secondary outcomes. However, it is unclear which patients are most likely to respond. Data from this trial suggest that those with more severe asthma may experience the greatest improvement.

Two-Year Outcomes[14]

This study reported on the subset of subjects in the BT group who experienced exacerbations, adverse events, and healthcare utilization in the second year of the AIR2 trial. Patients in the sham control group were not included in the extension study because it was felt to be unethical to require patients with severe asthma to refrain from alternative treatment options beyond the first year of the study. A total of 166 of 190 (87%) individuals randomized to the bronchial thermoplasty group completed the two-year evaluation. The primary outcome was the proportion of BT subjects experiencing severe exacerbations in year two compared to year

one. Other outcomes were severe exacerbation rates, proportions of subjects and rate of respiratory adverse events, emergency department visits and hospitalizations for respiratory symptoms, stability of pre- and post-bronchodilator FEV, and changes in maintenance asthma medications. No significant change was found in any of these measures. A limitation of this study included the lack of data from the sham control group and, thus, a non-inferiority model design was used.

Five-Year Outcomes[15]

Similar to the RISA trial, only BT treated patients (n=162 of 190, 85%) were followed up to five years. In a matched-pair analysis including the 162 study completers and the same group in previous years, the rate of severe exacerbations in years one, two, three, four and five were 30.9%, 23.5%, 34.0%, 36.4% and 21.6%, respectively. The proportion of individuals experiencing severe exacerbations in years two, three, four and five did not differ significantly from the number of exacerbations in year one. The proportion of patients who experienced asthma adverse events (at least two or more asthma symptoms occurring at the same time) were 28.7%, 27.9%, 29.6%, 31.4% and 24.7%, respectively. The proportion of patients with at least one hospitalization for respiratory adverse events these same years were 3.3%, 4.2%, 6.2%, 5.7% and 1.9%, respectively. In the 12 months before bronchial thermoplasty, the rate of hospitalization for respiratory symptoms in this group was 4.2%. Although several secondary outcomes favored BT therapy over sham, the primary study outcome was the change in AQLQ score from baseline; however, AQLQ scores were not reported as part of the five-year follow-up. This follow-up study is limited in that long-term data were not collected on patients randomized to the sham group, and therefore outcomes such as rate of exacerbations and hospitalizations, cannot be compared in patients who did and did not receive bronchial thermoplasty.

AIR, RISA, and AIR2

10-Year Outcomes

Chaudhuri (2021) reported 10-year safety and efficacy results for patients enrolled in the AIR, RISA, and AIR2 trials, including 136 (52%) patients who had received bronchial thermoplasty and 56 (33%) sham or control patients.[16] Eighteen patients in the sham/control group received bronchial thermoplasty after participation in the original trials. Median patient follow-up was 12.1 years post-treatment (range, 10.8 to 15.6 years). The primary study effectiveness endpoint was the durability of treatment effect, described as the proportion of participants with severe exacerbations during years one and five compared to the proportion of patients who experienced severe exacerbations in the 12 months preceding the 10+ year visit. No formal hypothesis testing was planned. Severe exacerbations were defined as a self-reported worsening of symptoms requiring the use of systemic corticosteroids or increased dose of systemic corticosteroids. The primary safety endpoint was the absence of clinically significant respiratory changes, including bronchiectasis or bronchial, as confirmed by CT imaging. In the year preceding the 10+ year visit, 34/136 (24%, 95% CI 18.0 to 33.1) patients treated with bronchial thermoplasty experienced severe exacerbations, which were similar to the year five (22%, 95% CI 14.8 to 29.6) and year one (24%, 95% CI 17.5 to 32.6) proportions. The number of severe exacerbations per patient were significantly higher compared to year five (p=0.044), but not significantly different compared to year one (p=0.43). In the year preceding the 10+ year visit, severe exacerbations were experienced in 14/38 (37%, 95% CI 21.8 to 54.0) sham or control patients compared to 12/38 (32% 95% CI, 17.5 to 48.7) in year one. There was no

change in the rate of severe exacerbations over time in the 24 sham participants from the AIR2 trial who had baseline, one-year, and 10-year data. Both treated and non-treated groups experienced a reduction in emergency department visits. Six (7%) AIR2 patients treated with bronchial thermoplasty developed new cases of asymptomatic bronchiectasis compared to 0 cases in the sham group at the 10-year visit. Improvements in AQLQ and ACQ scores were sustained in patients treated with bronchial thermoplasty. However, these scores were not reported for sham/control patients. Interpretation of study results is limited by recall bias and low enrollment of sham-treated patients. While bronchial thermoplasty is only recommended for use in patients with severe asthma, 26% of participants did not fulfill these criteria. Additionally, the long-term effects of treatment on clinically significant respiratory changes requires further elucidation.

Additional, smaller RCTs of BT have been published, but lack long-term follow-up.[17]

NON-RANDOMIZED STUDIES

Since the publication of the RCTs described above, several case series have been published describing outcomes in clinical practice,[18-23] which have generally had small sample sizes.[18-21]

Post-U.S. Food and Drug Administration Approval Clinical Trial Evaluating Bronchial Thermoplasty in Severe Persistent Asthma

Post-U.S. Food and Drug Administration Approval Clinical Trial Evaluating Bronchial Thermoplasty in Severe Persistent Asthma (PAS2) is an ongoing, open-label, nonrandomized trial of the Alair system, required for post premarket approval. Chupp (2017) compared three-year follow-up results from 190 patients in the AIR2 trial with a subgroup (n=190) from PAS2.[22] Of those enrolled, 168 patients from PAS2 reached three years of follow-up and were compared with 165 patients from AIR2 who also had three years of follow-up. The primary outcome was the incidence of severe exacerbation in each trial. In the 12 months before treatment, 74.2% of patients from PAS2 experienced severe exacerbations, which decreased significantly during the third year of follow-up to 39.9% ($p<0.001$). A similar reduction was observed in AIR2 patients, with the incidence of severe exacerbations decreasing 36.8%. Similar decreases in emergency department visits occurred in both groups when year three was compared with the 12 months before treatment (PAS2 55% reduction, AIR2 72.3% reduction, $p<0.001$); the incidence of hospitalization also decreased for both groups. In the first and second years after treatment, the incidence of hospitalization in PAS2 decreased to 14.4% and 12.7%, respectively; the incidence of emergency department visits decreased to 18.3% in the first year and 13.5% in the second year after treatment. Overall, patients from PAS2 showed improved results comparable to those observed in AIR2; however, there were a number of differences between the trials that limited conclusions. At baseline, patients enrolled in AIR2 had better asthma control than those in PAS2; PAS2 was restricted to North America, and different definitions of severe exacerbations were used in each trial.

The five-year follow-up results for the full PAS2 cohort are described in a study by Chupp (2022).[24] Of the 284 individuals enrolled in PAS2, 227 (81%) completed five years of follow up; 84% of individuals included were White, 9% Black or African heritage, 3% Hispanic or Latino, 1.4% Asian, 1% American Indian or Alaska native, and 1.6% from other racial or ethnic groups that were not described by investigators. Of note, a larger proportion of the 52 individuals who were not followed for five years experienced severe exacerbations (92.3% vs. 74.4%), emergency department visits (51.9% vs. 24.2%), and hospitalizations (30.8% vs.

12.8%) during the 12 months before bronchial thermoplasty compared with the 227 individuals followed for five years, indicating that those who dropped out of PAS2 may have had more serious disease and were not included in the analysis. By five years posttreatment, the proportion of individuals with severe exacerbations was significantly lower at 42.7%, compared with 77.8% in the 12 months prior to treatment ($p<0.001$). There was also a significant reduction in severe exacerbations from baseline (1.61 exacerbations/individual) to five years posttreatment (0.72 exacerbations/individual, $p<0.001$). Emergency department visits and hospitalizations were also significantly decreased by five years compared to 12 months prior to treatment, from a rate of 29.4% to 7.9% ($p<0.001$) and 16.1% to 4.8% ($p=0.0003$), respectively. At year five after bronchial thermoplasty, annual hospitalization rates fell from 0.22 hospitalizations per individual at baseline to 0.06 hospitalizations per individual ($p=0.0012$). Bronchial thermoplasty did not alter spirometric parameters as reported in previous studies but did reduce asthma maintenance medication use. The mean daily dose of inhaled corticosteroids (beclomethasone or equivalent) was reduced from 2,272 microg/d at baseline to 1,928 microg/d by year five. The number of individuals on maintenance oral corticosteroids decreased from 19.4% at baseline to 9.7% at five years. Clinical improvement was statistically significant across all subgroup analyses, regardless of baseline eosinophil and neutrophil counts. These results are limited by the lack of a comparator arm, increased drop-out rates of those with more severe asthma, lack of long term quality-of-life scores, and lack of response comparison between bronchial thermoplasty and standard of care medications.

Additional Studies

The BTGR is a prospective, open-label, multicenter study across 18 centers in Spain, Italy, Germany, the UK, the Netherlands, the Czech Republic, South Africa, and Australia that enrolls adults indicated for and treated with bronchial thermoplasty. Torrego (2021) reported on the two-year outcomes from the BTGR.[25] One hundred fifty-seven adults were included in the registry at two years. Racial and ethnic demographics of participants were not described. A comparison of the proportion of individuals experiencing asthma events during the 12 months prior to bronchial thermoplasty to the two-year follow-up showed a reduction in severe exacerbations requiring corticosteroids (90.3% vs. 56.1%, $p<0.0001$), emergency department visits (53.8% vs. 25.5%, $p<0.0001$), and hospitalizations (42.9% vs. 23.5%, $p=0.0019$). Asthma Control Questionnaire and AQLQ scores improved from 11.18 and 3.26 at baseline to 15.54 and 4.39 at two years, respectively ($p<0.0001$ for both). The registry results were limited by a lack of a comparator arm, a high attrition rate, with approximately one-third of individuals dropping out, and variation in investigator experience with bronchial thermoplasty between clinical sites.

d'Hooghe (2017) published results from the prospective imaging Unravelling Targets of Therapy in Bronchial Thermoplasty in Severe Asthma trial, which assessed 12 patients who underwent 36 bronchial thermoplasty procedures and had chest x-ray (n=34) or ultra-low-dose computed tomography (n=16).[26] The primary outcome was radiologic abnormalities following bronchial thermoplasty, and a large percentage of the cohort showed one of four abnormalities: peribronchial consolidations and ground glass opacities (94%), atelectasis (38%), partial bronchial occlusions (63%), or bronchial dilatations (19%). There was no clear association between abnormal x-ray results and asthma exacerbation (55% experienced both) compared with the incidence of asthma exacerbations in those who had normal radiologic images (roughly two of every three patients). Seventy-three percent of abnormal results resolved within six weeks, and 100% resolved six months postprocedure.

In addition, a rigorous U.K. registry study was published by Burn (2016), which focused on safety outcomes.[27] The study combined data from two sources, the U.K. Difficult Asthma Registry and the Hospital Episode Statistics warehouse, and included patients treated with bronchial thermoplasty in the U.K. between June 2011 and January 2015. Eighty-three patients were identified in the Difficult Asthma Registry and 85 in the Hospital Episode Statistics database. For 59 patients, data in the two databases could be matched. Most patients had a course of three bronchial thermoplasty treatment sessions. Data from the matched cohort were used to calculate event rates for four binary safety outcomes. Procedural complications were reported in 17 (11%) of 152 procedures in 13 (22%) patients; emergency readmissions within 30 days of the initial hospitalization were reported for 15 (11.8%) patients; and accident and emergency visits (i.e., emergency department) visits for any reason were reported for 13 (8.6%) patients. For the fourth binary outcome, postprocedure overnight stay, 70 (46.1%) of 152 procedures were followed by an overnight stay. In total, 20.4% of procedures in the matched cohort were associated with at least one of the four safety issues. The authors noted that the relatively high rate of safety events might be related to older patients with more severe disease being treated in clinical practice compared with patients included in clinical trials. A follow-up on this registry study was published in 2019 and reported a mean improvement in AQLQ from baseline of 0.75 (n=28, p=0.0003), and a reduction in hospital admissions per year (-1.0, n=26, p<0.0001).[28] There was no significant change in mean forced expiratory volume (FEV1) at 12 or 24 months. Because of the strong placebo effects noted in the controlled trials, interpretation of subjective quality of life measures is limited.

PRACTICE GUIDELINE SUMMARY

EUROPEAN RESPIRATORY SOCIETY AND THE AMERICAN THORACIC SOCIETY (ERS/ATS)

Evidence-based guidelines from ERS/ATS (2014) state that bronchial thermoplasty may be considered as a potential treatment for severe asthma patients but only in the context of an IRB approved registry or clinical study.[29] The committee indicated that, “This recommendation places a higher value on avoiding adverse effects and on increased use of resources, and on a lack of understanding of which patients may benefit, and a lower value on the uncertain improvement in symptoms and quality of life.” The authors remarked: “This is a strong recommendation, because of the very low confidence in the available estimates of effects of bronchial thermoplasty in patients with severe asthma.”

GLOBAL INITIATIVE FOR ASTHMA (GINA)

GINA is an international network of organizations and individuals with expertise in asthma. The group has been updating a report entitled Global Strategy for Asthma Management and Prevention annually since 2002, the most recent update was issued in 2023.[30] The organization recommends stepped care for treatment of asthma. Step 5 options for patients with uncontrolled symptoms and/or exacerbations include referral for phenotypic investigation and potential add-on treatment. Bronchial thermoplasty may be considered as an add-on treatment in adults with severe asthma that remains uncontrolled despite optimization of asthma therapy and referral to a severe asthma specialty center. GINA notes that bronchial thermoplasty should only be administered in the context of a systematic registry or a clinical study, as the evidence for efficacy and long-term safety is limited.

A guide for the diagnosis and management of difficult-to-treat and severe asthma was first published in 2019 and updated in 2023.[31] For patients whose asthma remains uncontrolled despite GINA step 4 or 5 treatment with no evidence of type 2 inflammation (i.e., medium- or high-dose inhaled corticosteroids and long-acting beta-agonists), treatment options include a trial of long-acting muscarinic agent (LAMA), low-dose azithromycin, interleukin-4 receptor antagonist (dupilumab), or anti-thymic stromal lymphoprotein (tezepelumab). Oral corticosteroids are considered as a last resort. Bronchial thermoplasty with registry enrollment may also be considered for patients who do not respond to type 2-targeted biologic therapy. The guidance notes that the evidence for the efficacy and long-term safety of bronchial thermoplasty is limited.

NATIONAL ASTHMA EDUCATION AND PREVENTION PROGRAM

In 2020, the National Asthma Education and Prevention Program Coordinating Committee (NAEPPCC) Expert Panel Working Group published focused updates to the National Heart, Lung, and Blood Institute's guidelines for the diagnosis and management of asthma.[32] This update was based on prior systematic reviews of the evidence published by the Agency for Healthcare Research and Quality.[4]

The following conditional recommendation based on low certainty evidence on the use of bronchial thermoplasty was issued:

- "In individuals ages 18 years and older with persistent asthma, the Expert Panel conditionally recommends against bronchial thermoplasty.
- Individuals ages 18 years and older with persistent asthma who place a low value on harms (short-term worsening symptoms and unknown long term side effects) and a high value on potential benefits (improvement in quality of life, a small reduction in exacerbations) might consider bronchial thermoplasty."

For patients who opt to choose this intervention via shared decision-making, the panel recommends that clinicians offer the procedure in the setting of a clinical trial or registry study to facilitate the collection of long-term outcomes.

AMERICAN COLLEGE OF CHEST PHYSICIANS (ACCP)

An ACCP statement (2014) on coverage and payment for bronchial thermoplasty for severe persistent asthma supports BT as a treatment option for patients with severe asthma.[33] However, this statement is based on clinical consensus; no systematic review or meta-analysis was performed from which to formulate this position.

SUMMARY

There is not enough research to show whether bronchial thermoplasty can improve long-term health outcomes in patients with severe asthma. In addition, there are no clinical guidelines based on research that specifically recommend this treatment. Therefore, bronchial thermoplasty is considered investigational as a treatment of asthma.

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CODES

Codes	Number	Description
CPT	31660	Bronchoscopy, rigid or flexible, including fluoroscopic guidance, when performed; with bronchial thermoplasty, 1 lobe
	31661	Bronchoscopy, rigid or flexible, including fluoroscopic guidance, when performed; with bronchial thermoplasty, 2 or more lobes
HCPCS	None	

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