Anthem

Medical Policy

Subject: Bronchial Thermoplasty
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Description/Scope

This document addresses the use of bronchial thermoplasty as a treatment option for adults whose severe persistent asthma is not well-controlled with inhaled corticosteroids and long-acting beta-agonists.

Note: Please see the following documents for additional information related to the treatment of asthma:

- CG-REHAB-03 Pulmonary Rehabilitation

Position Statement

Investigational and Not Medically Necessary:

Bronchial thermoplasty is considered **investigational and not medically necessary** for the treatment of asthma and all other conditions.

Rationale

Bronchial thermoplasty for the treatment of severe persistent asthma in adults was evaluated in three randomized controlled trials (RCTs) supported by the manufacturer of the Alair® Bronchial Thermoplasty System (Boston Scientific Corporation, Natick, MA [Asthmatx, Inc., Sunnyvale, CA]). The system received U.S. Food and Drug Administration (FDA) premarket approval (PMA) in April 2010 for use in adults with severe and persistent asthma whose symptoms are not adequately controlled with inhaled corticosteroids (ICSs) and long-acting beta-antagonists (LABAs).

Research in Severe Asthma (RISA) Trial

Pavord and colleagues (2007) evaluated bronchial thermoplasty in adults (18 years of age or older) with symptomatic, severe asthma in a multicenter study conducted at eight centers in the United Kingdom, Brazil, and Canada. Individuals eligible for participation included those with uncontrolled asthma symptoms despite treatment with high-dose ICSs (at least 750 µg fluticasone propionate per day or equivalent) and LABAs (at least 100 µg salmeterol per day or equivalent), with or without other medications (including oral prednisone, leukotriene modifiers, or theophylline); prebronchodilator forced expiratory volume in 1 second (FEV_1) ≥ 50% of predicted; demonstrated airway hyperresponsiveness by challenge with methacholine or reversible bronchoconstriction during the prior 12 months; uncontrolled symptoms despite taking maintenance medication; abstinence from smoking for 1 year or greater; and past history of smoking < 10 packs of cigarettes per year. After a 2-week run-in period, subjects were randomized 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 3 weeks apart (Weeks 0 to 6). During the 16-week phase (Weeks 6 to 22), all subjects remained on a stable dose of steroids followed by a 14-week steroid wean phase (Weeks 22 to 36) when an attempt was made to reduce the dose of oral corticosteroids (or ICSs for subjects not taking the oral medication). Between Weeks 36 to 52, subjects took the reduced dose of steroids.

The primary outcomes of the study measured the rate of adverse events and serious adverse events, the latter defined as any event that was fatal, required hospitalization or prolonged hospitalization, caused substantial immediate risk of death, resulted in permanent or significant disability/incapacity, or required intervention to prevent permanent impairment. A total of 32 of the 34 subjects (94%) completed the study. During the initial treatment period, 4 subjects in the bronchial thermoplasty group experienced seven serious adverse events requiring hospitalization; none occurred in the control group. In the bronchial thermoplasty group, 2 subjects had five severe respiratory adverse events and 2 subjects in the control group had two severe respiratory adverse events that were medically treated and did not result in hospitalization. In the post-treatment period, 3 subjects in the bronchial thermoplasty group experienced five serious adverse events and 1 subject in the control group experienced four serious adverse events; all of these events required hospitalization. The investigators noted this difference was not statistically significant (p=0.32). The investigators also reported a number of efficacy variables as secondary outcomes. At the end of the study (Week 52), bronchial thermoplasty subjects had a significantly greater improvement in beta-agonist use than control subjects (decrease of 26 puffs vs. 6 puffs per week, p<0.05). There were no significant differences between groups in other efficacy variables including morning and evening peak expiratory flow (PEF), symptom scores, number of symptom-free days, improvement in FEV_1 predicted and several quality of life measures. Limitations of the study include its small sample size and lack of a sham treatment group.

Asthma Intervention Research (AIR) Trial

Cox and colleagues (2007) also compared medical management alone to medical management plus bronchial thermoplasty and did not include a sham control group or blinding of subjects. The study included adults age 18 to 65 years old with moderate or severe persistent asthma who required daily therapy with ICSs to maintain reasonable asthma control (equivalent to a dose of 200 µg or more of beclomethasone) and LABAs (at a dose of 100 µg or more of salmeterol or the equivalent). In addition, participants were required to have an FEV_1 of 60% to 85% of the predicted value; airway hyperresponsiveness and stable asthma in the 6 weeks before enrollment; no current respiratory infection; and not more than two lower respiratory infections requiring treatment in the past year. An additional criterion was worsening asthma control during a 2-week baseline test period during which time LABAs were withheld. A total of 112 individuals met eligibility following the baseline test phase and were randomized to receive medical management with ICSs and LABAs (n=56) or the same medical management strategy plus bronchial thermoplasty (3 sessions approximately 3 weeks apart, n=56). After follow-up visits at 3, 6, and 12 months, there was a 2-week period of abstinence from LABAs, during which time data on exacerbations were collected. Between data collection periods, subjects could use all maintenance therapies. The primary outcome was the difference between the 2 groups in the change in the rate of mild exacerbations between the baseline and the 2-week abstinence period. An exacerbation was defined as the occurrence on 2 consecutive days of a reduction in the morning PEF 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 subject per year. Data was available at 3 months for 100 of 112 subjects (89%) and at 12 months for 101 subjects (90%). All subjects were included in the safety analysis.

The mean rate of mild exacerbations, as compared with baseline, was reduced in the bronchial thermoplasty group but was unchanged in the control group (change in frequency per subject per week, -0.16 ± 0.37 vs. 0.04 ± 0.29, p=0.005). At 12 months, there were significantly greater improvements in the bronchial thermoplasty group than in the control group in the morning PEF (39.3 ± 48.7 vs. 8.5 ± 44.2 liters per minute).

Changes in secondary outcomes included airflow, airway hyperresponsiveness, asthma symptoms, the number of symptom-free days, use of rescue medication, and scores on the Asthma Quality of Life Questionnaire (AQLQ) and the Asthma Control Questionnaire (ACQ) in subjects receiving usual care at 3 months and when LABAs were withdrawn at 3, 6, and 12 months. At 12 months, values for airway responsiveness and FEV_1 did not differ significantly between the two groups. There were significantly greater improvements in the bronchial thermoplasty group than in the control group in scores on the AQLQ (1.3 ± 1.0 vs. 0.6 ± 1.1) and ACQ (reduction, 1.2 ± 1.0 vs. 0.5 ± 1.0), the percentage of symptom-free days (40.6 ± 39.7 vs. 17.0 ± 37.9), and symptom scores (reduction, 1.9 ± 2.1 vs. 0.7 ± 2.5). In addition, the bronchial thermoplasty group required fewer puffs of rescue medication.

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, 3 subjects in the bronchial thermoplasty group required hospitalization and 2 subjects in the control group required a total of three hospitalizations.

Asthma Intervention Research 2 (AIR2) Trial

Castro and colleagues (2010) conducted a randomized, double-blind, sham-controlled trial at 30 sites in 6 countries including the United States. Eligibility criteria in the AIR2 trial were similar to those in the AIR trial; key differences were that a higher initial dose of ICSs was required (equivalent to at least 1000 µg beclomethasone) and subjects were required to have experienced at least 2 days of asthma symptoms during the 4-week baseline period and have a baseline score on the AQLQ of no more than 6.25 (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, subjects were not required to experience worsening symptoms during a period of abstinence from LABAs. Subjects were on stable maintenance asthma medications for at least 4 weeks before entry 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 subjects who achieved a change in their AQLQ score of 0.5 or greater, generally considered the minimally important difference for this scale. All endpoints were analyzed using Bayesian statistics. The target posterior probability of superiority (PPS) of bronchial thermoplasty over sham was 95%, except for the primary AQLQ endpoint, where in that instance, the target was 96.4% to adjust for two interim reviews of the data.

A total of 297 individuals were randomized, 196 to a bronchial thermoplasty group and 101 to a sham control group. The intervention for all subjects consisted of three bronchoscopy procedures, performed 3 weeks apart. Subjects and outcome assessment were blinded, but the intervention team was unblinded. The sham intervention was identical to the active treatment except that no radiofrequency energy was delivered. A total of 9 subjects withdrew consent before beginning treatment and 288 subjects underwent bronchoscopy and were included in the intention-to-treat (ITT) population. A total of 185 subjects in the treatment group and 97 subjects in the sham control group attended the second bronchoscopy and the same numbers of subjects had the third bronchoscopy (it is not clear whether these were exactly the same subjects). A total of 278 out of the 297 enrolled subjects (94%) completed the 12-month visit, 181 subjects in the treatment group and 97 subjects in the sham control group.

In the ITT population, the mean change in the integrated AQLQ score (the primary effectiveness outcome) was 1.35 (standard deviation [sd]=1.10) in the bronchial thermoplasty group and 1.16 (sd=1.23) in the sham control group. Using Bayesian analysis, the PPS was 96% which did not surpass the target PPS of 96.4%. However, in the ITT population, the percentage of subjects achieving an AQLQ score change of 0.5 or greater (the minimally important difference) was 79% in the bronchial thermoplasty group and 64% in the control group. The PPS of 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 non-responders (mean of 4.1 compared to 5.1, respectively). Several secondary outcomes favored bronchial thermoplasty over the sham control group. These include a reduction in the proportion of subjects reporting asthma worsening during follow-up (27.3% compared to 42.9%, respectively; PPS, 99.7%) and a reduction in the number of emergency room visits (0.07 compared to 0.43 visits per subject per year, respectively; PPS, 99.9%). Moreover, there was a reduction in severe exacerbations of 0.47 per subject per year in the bronchial thermoplasty group compared to 0.70 per subject per year in the control group (PPS, 95.5%). There was no significant difference between groups in other secondary efficacy outcomes including morning PEF, number of symptom-free days, symptom score and rescue medication use.

Safety outcomes reported during the treatment phase included a higher rate of respiratory adverse events in the active treatment group (85% of subjects, mean of 1 event per bronchoscopy) compared to the sham group (76% of subjects, mean of 0.7 events per bronchoscopy). A total of 16 subjects (8.4%) in the active treatment group required 19 hospitalizations for respiratory symptoms during the treatment phase compared to 2 subjects (2%) in the sham group who required 1 hospitalization each. However, during the post-treatment period, 70% of subjects in the bronchial thermoplasty group and 80% of subjects in the sham group reported adverse respiratory events. During this phase of the study, 5 subjects (2.6%) in the bronchial thermoplasty group had a total of 6 hospitalizations for respiratory symptoms and 4 subjects (4.1%) in the sham group had 12 hospitalizations (1 subject had 9 hospitalizations). In the AIR2 study, the sham group had a relatively high rate of response, in that 69% 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, subjects in both groups were unable to correctly guess their treatment group. During subsequent assessments, this continued among subjects in the sham group, whereas in the bronchial thermoplasty group, a larger proportion guessed correctly.

Long-term Follow-up of RCT Treatment Groups

Thomson and colleagues (2011) described safety and effectiveness outcomes up to 5 years after bronchial thermoplasty from a subset of AIR trial participants with moderate to severe asthma. Participants were assessed for adverse events and spirometric stability. The authors concluded there was no evidence of clinical complications (based on adverse event reporting) and maintenance of stable lung function (no deterioration of FVC and FEV_1). However, the study had significant methodological limitations. The subset of participants followed were self-selected volunteers and represented only a small number of the actual treatment group. Thus, it is not possible to conclude that bronchial thermoplasty demonstrates long-term safety; rather, it is appropriate to conclude that, in this small cohort, there was no increase in adverse events. It is also unclear whether the bronchial thermoplasty had any lasting effect or whether a single bronchial thermoplasty treatment would be effective for such an extended period of time. The method of collecting adverse events was unconventional. The authors used one method of collecting and reporting adverse events for the first year and a different method for subsequent years. In addition, controls were only followed for 3 years and in the active treatment group, there were a number of individuals lost to follow-up. After Year 1, adverse events were based in part on subject recollection, and were

therefore subject to recall bias. Last, the data was limited to records available at the authors' institutions; there was a lack of data collection from other facilities including emergency department visits and hospitalizations.

Pavord and colleagues (2013) evaluated 5-year safety data on 14 of the 17 (82%) subjects randomized to the bronchial thermoplasty group in the RISA study. All 14 subjects completed the 3-year evaluation and 12 participants completed evaluations at 4 and 5 years. In Year 1 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. For those with available follow-up data, 5 (36%), 7 (50%), 2 (17%) and 5 (42%) subjects experienced asthma adverse events in Years 2, 3, 4 and 5, respectively. A total of 11 respiratory-related hospitalizations in 5 subjects were reported during Years 2 to 5 after bronchial thermoplasty. Measures of lung function showed no deterioration for 5 years. The number of subjects with data available was too small to draw meaningful conclusions concerning the long-term safety of bronchial thermoplasty. In addition, no long-term data were available on subjects in the control group.

Durability of bronchial thermoplasty among treated individuals in the AIR2 trial was reported by Castro and colleagues (2011) (2 years) and Wechsler and colleagues (5 years). The Castro study included follow-up on 181 individuals at Year 1 and 166 individuals at Year 2. The authors found that the percentage of bronchial thermoplasty subjects experiencing severe exacerbations, defined as those requiring treatment with oral or intravenous corticosteroid, or a doubling of the baseline inhaled corticosteroid dose for at least 3 days, or any temporary increase in the dosage of oral corticosteroids for a subject taking maintenance oral corticosteroids at entry into the AIR2 trial, were comparable between Years 1 and 2, at 30.9% and 23.0%, respectively. The percentage of subjects reporting emergency department visits was 5% (9 subjects) at Year 1 and 6.6% (11 subjects) at Year 2. The percentage of subjects reporting respiratory-related hospitalizations was comparable for subjects at Year 1 and Year 2 in the posttreatment group at 3.3% (n=6) and 4.2% (n=7), respectively. Methodological limitations of this study include lack of a comparable sham-controlled group beyond Year 1, as subjects in the sham-control group in the AIR2 trial exited from the study at 1 year post bronchial thermoplasty. In addition, 15 of the 166 subjects (9.0%) did not complete the Year 2 evaluation. Finally, adverse event reporting for bronchial thermoplasty-treated individuals was subject to recall bias as data were collected from quarterly telephone calls and during an annual in-office evaluation.

Wechsler and colleagues (2013) reported 5-year safety and effectiveness data on 162 (85.3%) of 190 bronchial thermoplasty-treated subjects from the AIR2 study. Matched-pairs analysis comparing the 162 subjects completing the Year 5 evaluations with the same group in previous years showed a similar proportion of subjects having a severe exacerbation in Years 1, 2, 3, 4 and 5, that is, 30.9%, 23.5%, 34.0%, 36.4% and 21.6%, respectively. The proportion of subjects experiencing severe exacerbations in Years 2, 3, 4 and 5 did not differ significantly from the number of exacerbations in Year 1. The proportion of subjects who experienced any asthma adverse events (multiple symptoms) were 28.7%, 27.9%, 29.6%, 31.4% and 24.7%, respectively. In the 12 months before bronchial thermoplasty, the rate of hospitalization for respiratory symptoms in this group was 4.2%. Limitations of this study include lack of follow-up data collected on subjects randomized to the sham group beyond 1 year; therefore, outcomes such as rate of exacerbations and hospitalizations cannot be compared in subjects who did and did not receive bronchial thermoplasty.

Chaudhuri and colleagues (2021) reported on individuals previously enrolled in the RISA, AIR and AIR2 trials who had at least 10 years of follow-up since treatment; the follow-up study is known as BT10+. A total of 136 of the 260 (52%) individuals treated with bronchial thermoplasty in the three trials were enrolled. In addition, the BT10+ included 56 individuals from the trials' control groups, of whom 18 were later treated with bronchial thermoplasty and 38 did not receive bronchial thermoplasty. The primary effectiveness outcome of the BT10+ study was the durability of bronchial thermoplasty determined by number of severe exacerbations. In the 12 months before the BT10+ 10-year visit, 34 of 136 (25%) individuals who had been treated with bronchial thermoplasty experienced at least 1 severe exacerbation. The rate of severe exacerbations was similar to those experienced by bronchial thermoplasty participants during the first year after treatment (33 of 135 participants, 24%) and during the fifth year after treatment (28 of 130 participants, 22%). Among the 38 individuals who were not treated with bronchial thermoplasty, the number of severe exacerbations in Year 1 and Year 10 was 12 (32%) and 14 (37%), respectively.

For the outcome of hospital emergency department visits, during the 12 months prior to treatment with bronchial thermoplasty, 33 (24%) of 136 individuals had an emergency department visit due to asthma symptoms. Visits remained lower following bronchial thermoplasty treatment. During the first, fifth and tenth year after bronchial thermoplasty treatment, the proportion of participants who required an emergency department visit due to asthma symptoms was 6 (4%), 9 (7%) and 14 (10%) of 136, respectively. Among the 38 individuals who were not treated with bronchial thermoplasty, the proportion who visited an emergency department due to asthma symptoms was 7 (18%) before receiving the study intervention, 2 (5%) during the first year after the intervention and 3 (8%) during the tenth year. Limitations of the BT10+ study include that it enrolled individuals from previously published trials (RISA, AIR And AIR2) and does not represent a new study population. Moreover, only about half of individuals who participated in the bronchial treatment groups of the RISA, AIR and AIR2 trials were included in the analysis which can introduce selection bias. Furthermore, the study included a relatively small number of individuals who received a control intervention; most control participants in the original trials were not included. These methodological limitations reduce the ability to have confidence that the study findings reflect a true clinically meaningful improvement in long-term outcomes after bronchial thermoplasty.

Observational Studies

Chupp and colleagues (2017) reported on 3-year outcomes of bronchial thermoplasty in individuals from two prospective multicenter studies. The authors compared "real-world" clinical outcome data from the post-market PAS2 (Post-FDA Approval Clinical Trial Evaluating Bronchial Thermoplasty in Severe Persistent Asthma) study with data from the AIR2 trial (Castro, 2010, described above). Based on a modified version of the European Respiratory Society/American Thoracic Society guideline definition for severe asthma, 94.7% and 82.1% of participants analyzed were severe asthmatics in the PAS2 study and AIR2 trial, respectively (p=0.0001). A total of 279 participants were treated with bronchial thermoplasty in the PAS2 study; the first 190 PAS2 participants were compared with the 190 bronchial thermoplasty-treated participants in the AIR2 trial. The PAS2 participants were older (mean age, 45.9 vs. 40.7 years; p<0.0001), more obese, and took higher doses of inhaled corticosteroids (mean dose, 2301 vs. 1961 $\mu g/day^{-1}$; p<0.0001) than the AIR2 participants. More PAS2 participants experienced severe exacerbations (74% vs. 52%) and hospitalizations (15.3% vs. 4.2%) in the 12 months prior to bronchial thermoplasty. At year 3 after bronchial thermoplasty, the percentage of PAS2 participants with severe exacerbations, emergency department visits and hospitalizations significantly decreased by 45%, 55% and 40%, respectively, which is comparable to outcomes of the AIR2 trial. Limitations of this analysis include the potential for bias and confounding factors (outside the measured baseline demographics and clinical characteristics) when comparing a prospective nonrandomized clinical study (PAS2) to results from the AIR2 RCT. The authors state that further subgroup analysis is needed to help identify which individuals with asthma are most likely to benefit from bronchial thermoplasty in the "real-world."

In 2022, Chupp and colleagues reported 5-year results of the full cohort of 284 individuals in the PAS2 study. In this cohort, 77.8% of individuals experienced at least one severe asthma exacerbation in the year prior to bronchial thermoplasty treatment, which decreased to 44.2% of participants after 4 years and 42.7% after 5 years. The proportion of individuals with emergency department visits decreased from 29.4% of participants in the year prior to treatment to 11.7% after 4 years and 7.9% after 5 years. For hospitalizations, 16.1% of participants were hospitalized in the year prior to treatment, compared with 3.3% after 4 years and 4.8% after 5 years. The analysis did not compare outcomes of individuals in the PAS2 study with a control group of individuals who received a placebo or treatment other than bronchial thermoplasty.

Burn and colleagues (2017) published data from a United Kingdom registry study and found that 20% of 418 bronchial thermoplasty procedures in 168 persons were associated with at least one safety event, such as procedural complications, post-procedure overnight inpatient stays, emergency department visits, and 30-day emergency respiratory readmissions. Individuals treated with bronchial thermoplasty in routine clinical practice were on average, older, and had worse baseline lung function and asthma quality of life compared with published clinical trial data, which reported lower hospitalization rates post-bronchial thermoplasty procedures. In 2019, Burn and colleagues published additional data on records added since their previous report. A total of 19% of 370 procedures and 44.5% of 128 individuals were affected by a safety event. The most common adverse events were asthma-related symptoms (e.g., decrease in FEV1, shortness of breath, etc.) in 19 individuals and procedure-related events (e.g. bronchospasm, dry cough) in 16 individuals.

Pretolani and colleagues (2017) conducted an uncontrolled study examining the effect of bronchial thermoplasty on bronchial structures and explored the association with clinical outcomes in 15 individuals who met the American Thoracic Society/European Respiratory Society criteria for severe, refractory asthma. Participants underwent three sessions of bronchial thermoplasty separated by 1-month intervals. The pre-specified primary outcome was a reduction in airway smooth muscle (ASM) surface area at 3 months. At 3 months after bronchial thermoplasty, ASM correlated significantly with Asthma Control Test (ACT) scores (p=0.003) and numbers of severe exacerbations (p<0.001), emergency department visits (p=0.003), and hospitalizations for asthma (p=0.03). At 12 months, 8 of 10 (80%) participants still required regular oral corticosteroids with a mean daily dose of oral prednisone significantly lower compared with that administered at study onset (13.8 vs. 31.5 mg/d, 12 months after compared with before bronchial thermoplasty; p=0.002). In addition, at 12 months after bronchial thermoplasty, 4 of 15 (27%) participants continued to experience symptoms of uncontrolled asthma (e.g., mean ACT score of 7.8). Clinical outcomes after bronchial thermoplasty were inconsistent in over one-fourth of participants; additional study is needed to determine which individuals with severe asthma may respond to bronchial thermoplasty, and what the relationship is to both long-term clinical and histopathologic corrections of benefit to treatment with the procedure.

Torrego (2021) reported on 157 individuals who participated in the prospective observational Bronchial Thermoplasty Global Registry (BTGR). The primary endpoint of the study was the proportion of participants who experienced severe asthma exacerbations after bronchial thermoplasty treatment; this was compared with the proportion of participants with severe exacerbations in the year prior to treatment. In the year prior to treatment 140 of 155 (90.3%) participants experienced a severe asthma exacerbation requiring treatment with systemic corticosteroids. At 2 years after bronchial thermoplasty treatment, 55 of the 98 (56.1%) individuals for whom data were available experienced severe exacerbations; this represented a 38% relative reduction in the proportion of individuals with severe exacerbations. A total of 71 of 157 (45.2%) individuals reported procedure-related respiratory adverse events and 44 of 157 (28.0%) individuals experienced severe adverse events. During year 2 after bronchial thermoplasty, 51 of 98 (62.2%) reported respiratory adverse events and 19 of 98 (19.4%) experienced serious adverse events; none of the year 2 events was considered to be related to the bronchial thermoplasty procedure. A limitation of this study is that it did not include a control group of individuals who did not receive active bronchial thermoplasty treatment.

Systematic Reviews

Several systematic reviews have evaluated published literature on bronchial thermoplasty (D'Anci, 2017; Niven, 2018; Zhou, 2016). D'Anci and colleagues (2017) published a comparative effectiveness review for the Agency for Healthcare Research and Quality (AHRQ). The authors systematically reviewed 15 studies on bronchial thermoplasty, including 3 RCTs (RISA, AIR, AIR2) (n=432) with 5-year single-arm follow-up in bronchial thermoplasty-treated individuals. Both bronchial thermoplasty and standard care improved asthma control (defined by the ACQ change from baseline to 12 months) and AQLQ scores more than standard care alone (statistically significant, but not clinically important) (low strength of evidence). However, bronchial thermoplasty 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 (ITT analysis) (low strength of evidence).

In the RCTs comparing bronchial thermoplasty and standard care to standard care alone (RISA, AIR trials), evidence was insufficient to assess if bronchial thermoplasty reduced rates of severe exacerbations. The most common adverse events following bronchial thermoplasty during the 12-week treatment period in the RCTs included bronchial irritation, chest discomfort, cough, discolored sputum, dyspnea, night awakenings, and wheezing. The rate of hospitalizations was higher in participants undergoing bronchial thermoplasty than with either standard care alone or sham bronchoscopy during the 12-week treatment period, as were upper respiratory tract infections, wheezing, dyspnea, lower respiratory tract infections, anxiety, and segmental atelectasis; however, events were too infrequent to achieve statistical significance. In six case reports and two small case series, severe adverse events were reported, including post-procedure segmental atelectasis due to mucus plugging, hemoptysis, chest infections requiring hospitalization, and bronchial artery pseudoaneurysm. Rates of respiratory-related hospitalizations were not significantly different between groups following the 12-week treatment period and up to 5 years of follow-up. There were no deaths attributed to the bronchial thermoplasty procedure. The authors concluded that "uncertainty remains about appropriate patient selection criteria and the effects of the treatment beyond 5 years."

Niven and colleagues (2018) performed an indirect comparison of bronchial thermoplasty to omalizumab in the treatment of individuals with uncontrolled severe asthma. A systematic review of the literature identified relevant RCTs comparing the sham-controlled AIR2 trial to two placebo-controlled trials of omalizumab (INNOVATE and EXTRA). The indirect comparison of bronchial thermoplasty in the post-treatment period to ongoing treatment with omalizumab showed no significant differences in the rate ratios (RRs) for severe exacerbations (bronchial thermoplasty vs. omalizumab, RR equal to 0.91 [95% confidence interval (CI), 0.64, 1.30]; p=0.62) or hospitalizations (RR equal to 0.57 [95% CI, 0.17, 1.86]; p=0.53); however, emergency department visits were significantly reduced by 75% with bronchial thermoplasty (RR equal to 0.25 [95% CI, 0.07, 0.91]; p=0.04). The proportion of participants with clinically meaningful response on the AQLQ were comparable (RR equal to 1.06 [95% CI, 0.86, 1.34]; p=0.59). The RR for exacerbations statistically favored omalizumab over the total study period in AIR2 (RR equal to 1.50 [95% CI, 1.11, 2.02]; p=0.009), which likely reflected a transient increase in events during the bronchial thermoplasty periprocedural period. The authors suggest, however, this analysis should be interpreted with caution considering the heterogeneity between study populations in the evaluated trials.

Summary

To date, three industry-sponsored RCTs on bronchial thermoplasty have been published in the peer-reviewed medical literature and systematic reviews have evaluated these RCTs as well as uncontrolled studies. The largest RCT with the most rigorous methodology was the AIR2 trial, the only published double-blind, sham-controlled trial with sites in the United States. Over 1 year, bronchial thermoplasty was not found to be superior to sham treatment on the investigator-designated primary efficacy outcome, a mean change in quality of life score, but was found to be superior on a related outcome, an improvement in quality of life of at least 0.5 points on the AQLQ scale. The high rate of response in the sham group of the AIR2 suggests a large placebo effect, particularly for subjective outcomes such as quality of life which 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. Therefore, it is unclear which individuals are most likely to respond to bronchial thermoplasty. Data from the AIR2 trial suggests that those with more severe asthma may experience the greatest improvement. In the AIR and RISA trials, improvements were reported in quality of life for the bronchial thermoplasty group. However, given the lack of benefit in the AIR2 trial, it is possible that the differences in quality of life for these other trials were due to placebo effect.

Three-year comparative data from the AIR trial reporting rates of hospitalizations and respiratory adverse events did not differ significantly in the groups that received bronchial thermoplasty versus medication in Years 2 and 3. Data up to 5 years in the bronchial thermoplasty group did not suggest delayed complications. For the sham-controlled AIR2 trial, 2-year follow-up data are available for the bronchial thermoplasty group. In Year 2, subjects did not experience an increase in severe exacerbations or asthma adverse events compared to Year 1. Ten-year follow-up data were reported in the BT10+ study for about half of the participants in the AIR, RISA and AIR2 trials. The rate of severe exacerbations in the most recent year was significantly lower in the bronchial thermoplasty recipients than for the small group of reported controls. However, the large amount of missing data limits our ability to draw conclusions from these follow-up data.

Adverse events reported from the three trials suggest that bronchial thermoplasty is associated with a relatively high rate of adverse events including hospitalizations during the treatment period, but not in the post-treatment period. Safety data up to 10 years have been reported for a proportion of individuals enrolled in the three RCTs. Among those treated with bronchial thermoplasty, the rate of hospitalizations due to asthma during Year 1, Year 5 and Year 10 remained lower than the rate before bronchial thermoplasty.

The uncertain degree of benefit of bronchial thermoplasty beyond the placebo effect and the presence of substantial adverse events limits the ability to have confidence that bronchial thermoplasty improves the net health outcome compared with the best available alternative therapy. In addition, it is not possible to determine which individuals receive the most benefit as there are a lack of data on selection factors for appropriate candidates for bronchial thermoplasty.

Additional Considerations

The Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA, 2022) has published the following recommendation concerning bronchial thermoplasty:

> Add-on treatment with bronchial thermoplasty: may be considered for some adult patients with severe asthma (Evidence B). Evidence is limited and in selected patients... The long term effects compared with control patients, including in lung function, are not known.

In 2020, the National Asthma Education and Prevention Program (NAEPP) published a focused update of their 2007 asthma guidelines. The following recommendations were included regarding use of bronchial thermoplasty:

> 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.

The American College of Chest Physicians (CHEST™, 2014) issued a position statement for bronchial thermoplasty that stated:

> Based on the strength of the clinical evidence, bronchial thermoplasty offers an important treatment option for adult patients with severe asthma who continue to be symptomatic despite maximal medical treatment and, therefore should not be considered experimental. Randomized controlled clinical trials of bronchial thermoplasty for severe asthma have shown a reduction in the rate of severe exacerbations, emergency department visits, and days lost from school or work.

The position statement references the 5-year follow-up data from the AIR2 study (Wechsler, 2013), stating the reported outcomes further demonstrate the “safety, effectiveness, and durability” of bronchial thermoplasty.

A joint task force of the European Respiratory Society/American Thoracic Society (Chung, 2014) published guidelines on the definition, evaluation and treatment of severe asthma, stating:

> We recommend that bronchial thermoplasty is performed in adults with severe asthma only in the context of an Institutional Review Board approved independent systematic registry of a clinical study…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. Both potential benefits and harms may be large and the long-term consequences of this new approach to asthma therapy utilizing an invasive physical intervention are unknown. Specifically designed studies are needed to define its effects on relevant objective primary outcomes such as exacerbation rates, and on long-term effect on lung function.

Background/Overview

Description, Prevalence, and Pharmacologic Treatment of Asthma

According to the Centers for Disease Control and Prevention (CDC, 2022), asthma affected approximately 8.4% of adults and 5.8% of children in the United States in 2020. Asthma is a common chronic disorder of the airways that is complex and characterized by variable and recurring symptoms, airflow obstruction, bronchial hyperresponsiveness, and an underlying inflammation. The airway hyperresponsiveness is reversible either spontaneously or through therapy. Symptoms include wheezing, cough, and dyspnea, which can vary widely in severity and duration, although a typical attack does not last for more than several hours. The onset of asthma for most individuals begins early in life with the pattern of disease persistence determined by early, recognizable risk factors including atopic disease, recurrent wheezing, and a parental history of asthma (Akinbami, 2012). In some individuals, persistent changes in airway structure occur, including sub-basement fibrosis, mucus hypersecretion, injury to epithelial cells, and smooth muscle hypertrophy (NAEPP, 2007). Attacks can be triggered by a number of factors, including allergic triggers, smoke and pollution, cold air, colds and other respiratory infections, exercise, and strong emotions.

Guidelines from the National Heart, Lung and Blood Institute (NHLBI) (National Institutes of Health [NIH]) define 6 pharmacologic steps for treatment of intermittent asthma (Step 1), and persistent asthma (Steps 2-6):

> Step 1: Short-acting beta-agonists (such as albuterol) as needed;
> Step 2: Low-dose ICS;
> Step 3: ICS and LABA or medium-dose ICS;
> Step 4: Medium dose ICS and LABA;
> Step 5: High-dose ICS and LABA; and
> Step 6: High dose ICS and LABA, and oral corticosteroids.

In 2007, the NAEPP issued a document titled *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma*. According to the NAEPP guideline, the classification of asthma severity for severe persistent and moderate persistent asthma for individuals who are not currently taking long-term control medications is based on the following:

- Symptoms throughout the day
- Extremely limited normal activity
- Nocturnal symptoms are frequent (often seven times/week)
- FEV_1 or PEF less than 60% predicted
- Daily use of inhaled, short-acting, beta2-agonist for symptom control (can be several times/day)
- FEV_1/FVC (forced vital capacity) is reduced greater than 5%, or
- Exacerbations requiring oral systemic corticosteroid use greater than two times per year.

Description of Bronchial Thermoplasty

Bronchial thermoplasty uses radiofrequency energy to treat severe and persistent asthma in certain adults. The Alair System is a tool used to perform bronchial thermoplasty; according to the FDA, the procedure is indicated for the treatment of severe persistent asthma in individuals 18 years of age and older whose asthma is not well controlled with ICSs and LABAs. The device is composed of a catheter with an electrode tip that delivers a form of electromagnetic energy (radiofrequency energy) directly to the airways, resulting in a prolonged reduction in airway smooth muscle (ASM) mass. A controller unit generates and controls the energy. The treatment is performed in the outpatient setting (as a minimally invasive procedure) during a series of bronchoscopy procedures scheduled at least 3 weeks apart. The catheter is inserted through a bronchoscope with the individual under conscious sedation. The catheter is first positioned in the most distal targeted airway and the electrode array is extended. Once the array basket is in contact with the airway wall, radiofrequency energy is delivered through the catheter to heat tissue to 65° centigrade over the 5 millimeter area of exposed (uninsulated) electrode wire. Complete treatment of any given airway requires delivery of radiofrequency energy along the entire accessible length of the airway, so the catheter must be repositioned and the electrode redeployed several times. The procedure takes approximately 1 hour to complete. Use of the treatment is contraindicated in individuals with implantable devices and those with sensitivities to lidocaine, atropine or benzodiazepines. It should also not be used while individuals are experiencing an asthma exacerbation, active respiratory infection, bleeding disorder, or within 2 weeks of making changes in their corticosteroid regimen. The same area of the lung should not be treated more than once with bronchial thermoplasty.

Definitions

Asthma Quality of Life Questionnaire (AQLQ): A 32-item disease-specific questionnaire used to reflect areas of function important to adults with asthma; available in both interviewer- and self-administered forms. The 4 domains measured by the AQLQ include activity limitations, emotional function, exposure to environmental stimuli, and symptoms.

Dyspnea: Shortness of breath; subjective difficulty or distress in breathing.

Forced expiratory volume in 1 second (FEV_1): A measure of airway obstruction determined using spirometry; individual FEV_1 values are compared to predicted values based on age, height, sex and race.

Hyperresponsiveness: Also referred to as the early phase of asthma, when the airways of the lungs get smaller when exposed to certain allergens or environmental triggers, making it more difficult to breathe.

Inflammatory response: Also referred to as the late phase of asthma. Swelling and irritation of the lining of the lung that can cause bronchoconstriction and increased mucus that leads to asthma symptoms.

Inhaled corticosteroid(s) (ICS or ICSs): A class of medications also referred to as inhaled steroids; used for the treatment of asthma and chronic obstructive pulmonary disease (COPD). A potent anti-inflammatory medication that improves asthma control more effectively than any other agent used as a single treatment; helps to prevent chronic asthma symptoms such as wheezing, chest tightness, shortness of breath, and chronic cough.

Long-acting beta-agonist(s) (LABA or LABAs): Also referred to as long-acting $beta_2$-adrenergic agonists. A type of bronchodilator whose effects last for 12 hours or more when used as adjunctive treatment for the prevention of asthma symptoms such as wheezing, chest tightness, shortness of breath, and cough; improves asthma symptoms by increasing airflow through the lungs.

Peak expiratory flow (PEF): Often described as a percent of personal best measurement; personal best PEF is the highest PEF value attained after 2 to 3 weeks of testing when asthma is in good control.

Radiofrequency (RF) energy: Energy that travels as radio waves; electrical energy used in medical procedures for sculpting, shrinking or removing soft-tissue.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services are Investigational and Not Medically Necessary:
When the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

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

ICD-10 Diagnosis

	All diagnoses

When services are also Investigational and Not Medically Necessary:

ICD-10 Procedure

0B538ZZ	Destruction of right main bronchus, via natural or artificial opening endoscopic
0B548ZZ	Destruction of right upper lobe bronchus, via natural or artificial opening endoscopic
0B558ZZ	Destruction of right middle lobe bronchus, via natural or artificial opening endoscopic
0B568ZZ	Destruction of right lower lobe bronchus, via natural or artificial opening endoscopic
0B578ZZ	Destruction of left main bronchus, via natural or artificial opening endoscopic
0B588ZZ	Destruction of left upper lobe bronchus, via natural or artificial opening endoscopic
0B598ZZ	Destruction of lingula bronchus, via natural or artificial opening endoscopic
0B5B8ZZ	Destruction of left lower lobe bronchus, via natural or artificial opening endoscopic

ICD-10 Diagnosis

J45.20-J45.998	Asthma

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Index

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Document History

Status	Date	Action
Reviewed	05/11/2023	Medical Policy & Technology Assessment Committee (MPTAC) review. Updated Rationale, Background/Overview, References and Websites for Additional Information sections.
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