Bronchial Thermoplasty for Asthma (Alair®)

Policy # 00266
Original Effective Date: 07/21/2010
Current Effective Date: 09/19/2018

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers bronchial thermoplasty for the treatment of asthma to be **investigational.***

Background/Overview

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.

Asthma

Asthma, a chronic lung disease, affects approximately 8% of adults and 9.5% of children in the U.S. and, in 2012, accounted for approximately 440,000 hospitalizations and 3,400 deaths. 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 1 second [FEV-1] 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

Management of asthma consists of environmental control, patient education, management of co-morbidities, 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 (NHLBI) define 6 pharmacologic steps: step 1 for intermittent asthma and steps 2-6 for persistent asthma. The preferred daily medications: 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; and, 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 recently developed 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 (ie, steps 5 and 6 in the stepwise approach to care).

Bronchial thermoplasty procedures are performed on an outpatient basis, and each session lasts approximately 1 hour. 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 degrees Centigrade 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 3 separate procedures in different regions of the lung scheduled about 3 weeks apart.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

In April 2010, the Alair®‡ Bronchial Thermoplasty System (Asthmatx, Inc., Sunnyvale, CA now part of Boston Scientific) was approved by the U.S. FDA through the premarket approval (PMA) process (P080032) for use in adults with severe and persistent asthma whose symptoms are not adequately controlled with inhaled corticosteroids and LABAs. 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 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. FDA product code: OOY.

Centers for Medicare and Medicaid Services (CMS)
No national coverage determination.

Rationale/Source

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

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To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

For conditions such as asthma, where there are subjective outcomes such as self-reported symptoms and frequency of as-needed medication, placebo- or sham-controlled randomized trials are needed to demonstrate that the intervention has a benefit beyond the placebo effect.

BRONCHIAL THERMOPLASTY FOR THE TREATMENT OF ASTHMA

Clinical Context and Test Purpose

The purpose of bronchial thermoplasty in patients who have asthma refractory to standard treatment is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does bronchial thermoplasty improve health outcomes in patients with treatment-refractory asthma?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest is individuals with treatment-refractory asthma. Asthma symptoms can vary between individuals but may include bronchial hyperresponsiveness, airway inflammation, and reversible airflow obstruction. For adults with persistent and severe asthma whose symptoms are not adequately controlled with low-dose inhaled corticosteroids and LABAs, bronchial thermoplasty may be an add-on treatment.

Interventions

The therapy being considered is bronchial thermoplasty as an add-on treatment in patients whose asthma is not adequately controlled with medical management.

Bronchial thermoplasty delivers thermal energy to tissue in the distal airways in an attempt to reduce excess smooth muscle, which causes airway constriction in active disease. Radiofrequency energy is applied through a catheter and a flexible bronchoscope. A typical full course of treatment consists of three,

1-hour sessions, given 3 weeks apart under moderate sedation. All accessible airways distal to the main stem bronchus that are 3 to 10 mm in diameter are treated once, except those in the right middle lobe; the lower lobes are treated first followed by the upper lung.

Comparators
Currently, clinical response to continued medial management is being used to make decisions about the use of bronchial thermoplasty for treatment-refractory asthma. Continued medical management of asthma consists of environmental control, patient education, management of comorbidities, and regular follow-up for affected patients, as well as a stepped approach to medication treatment.

Outcomes
Beneficial outcomes are symptom relief, improvement in quality of life, reductions in medication adverse events and hospitalizations, and treatment-related morbidity. Instruments such as Asthma Quality of Life Questionnaire (AQLQ) score may be used to assess improvements in asthma symptoms.

Potential harms include periprocedural risk and risk for exacerbation of asthma during the treatment phase.

Timing
Short-term and long-term outcomes are important.

Short-term results are evaluated from weeks posttreatment to 12 months. Long-term follow-up studies have evaluated patients receiving bronchial thermoplasty up to 5 years posttreatment.

Setting
Patients would be treated in the outpatient setting by a pulmonologist.

Randomized Controlled Trials
There are 3 industry-sponsored RCTs have evaluated the efficacy and safety of bronchial thermoplasty. The study characteristics and results are summarized in Tables 1 and 2.

Research in Severe Asthma Trial
Pavord et al (2007) published the initial results of the Research in Severe Asthma (RISA) trial. Participants met multiple criteria for severe uncontrolled asthma. After a 2-week run-in period, participants were randomized to a control group that received continued medical management alone or to medical management plus treatment with the Alair Bronchial Thermoplasty System.

The primary objective of RISA was to determine the safety of bronchial thermoplasty. The rates of procedure and postprocedure respiratory adverse events as well as more 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). No overall statistical analysis was done that compared serious adverse events in the 2 groups.

Secondary objectives included evaluation of the effect of bronchial thermoplasty on asthma symptoms and daily medication requirements as an indication of efficacy. At 52 weeks, bronchial thermoplasty patients had a significantly greater improvement in β-agonist use than control patients (decrease of 26 puffs per week vs 6 puffs per week, respectively, $p<0.05$). There were no significant differences between groups in other efficacy variables including morning and evening peak expiratory flow, symptom scores, number of symptom-free days, percent predicted improvement in FEV_1, and quality of life measures. The small sample size limited the power to detect differences in the efficacy outcomes.

Pavord et al (2013) published 5-year safety data on 14 (82%) of the 17 patients randomized to bronchial thermoplasty in the RISA trial. All 14 patients completed the 3-year evaluation, and 12 patients completed evaluations at 4 and 5 years. As previously described, safety outcomes were the primary outcomes of RISA. In year 1, 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 2, 3, 4, and 5 were 5 (36%), 7 (50%), 2 (17%), and 5 (42%), respectively. Also, during years 2 to 5, there were 11 respiratory-related hospitalizations in 5 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 Trial

Cox et al (2007) published findings of the Asthma Intervention Research (AIR) trial, which was designed to evaluate symptom control and adverse events following bronchial thermoplasty in patients with moderate-to-severe persistent asthma. Participants were randomized to medical management with inhaled corticosteroids and LABA or to the same medical management strategy plus bronchial thermoplasty. At the end of the follow-up visits at 3, 6, and 12 months, there was a 2-week period of abstinence from LABA, 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 the rate of mild exacerbations from the baseline 2-week abstinence period. An exacerbation was defined as the occurrence on 2 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 3 additional puffs of rescue medication compared with the week before the abstinence period, or nocturnal awakening caused by asthma symptoms. The trial was powered to detect a difference between groups of 8 mild exacerbations per person per year. Data were available at 3 months for 100 (89%) of 112 patients and at 12 months for 101 (90%) patients; all patients were included in the safety analysis.

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 2 groups in the posttreatment period. Posttreatment, 3 patients in the bronchial thermoplasty group required hospitalization and 2 patients in the control group required a total of 3 hospitalizations. A trial limitation is the lack of a sham intervention and, consequently, an inability to blind patients to treatment group.

Thomson et al (2011) published 5-year data from the AIR trial. All trial participants who completed the 1-year follow-up visit were invited to participate in the extension study; 45 (87%) of 52 in the bronchial thermoplasty group and 24 (49%) of 49 in the control group opted to participate. Follow-up was done on an annual basis. Patients in the control group were followed for 2 additional years, and patients in the bronchial thermoplasty group were followed for 5 years. Twenty-one (88%) of 24 patients in the control group and 42 (93%) of 45 in the bronchial thermoplasty group completed the final follow-up. No instances of pneumothorax, intubation, mechanical ventilation, cardiac arrhythmias, or death were reported during the extension study. In the first year (year 2 of the study), the rate of hospitalizations was 3 (7%) of 45 in the bronchial thermoplasty group and 0 in the control group (p=0.55). In year 3, the rate of hospitalizations in the bronchial thermoplasty group was again 3 (7%) of 45, and 1 (5%) of 21 patients in the control group (p=1.00). Rates of emergency department visits in year 2 were 3 (7%) and 3 (12.5%) in the bronchial thermoplasty and control groups, respectively (p=0.41); in year 3, rates were 3 (5%) and 3 (5%), respectively (p=1.00). There was 1 hospitalization each of years 4 and 5 in the bronchial thermoplasty group.

In the extension study of the AIR trial, 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 2 groups. The incidence of respiratory adverse events during year 2 was 24 (53%) of 45 in the bronchial thermoplasty group and 13 (54%) of 24 in the control group. During year 3, incidence was 24 (56%) of 43 in the bronchial thermoplasty group and 12 (57%) of 21 in the control group; differences between groups were not statistically significant in year 2 or 3. The incidence of respiratory adverse events in the bronchial thermoplasty group was similar in subsequent years; rates were 23 (53%) of 43 in year 4 and 22 (52%) of 42 in year 5.

The Thomson study also reported on 2 measures of lung function: postbronchodilator FEV_1 and forced vital capacity. Exact numbers were not reported, but postbronchodilator FEV_1 did not go below 80% of predicted in either group during years 2 to 5. The group comparisons of safety and efficacy in this follow-up trial were limited by the differential rate of follow-up between the 2 groups, with a lower percentage of patients in the control group agreeing to participate in the follow-up study.

Asthma Intervention Research 2 Trial

AIR2 was an RCT evaluating the efficacy of bronchial thermoplasty at 30 sites in 6 countries (including the United States); findings were published by Castro et al (2010). Unlike the other 2 RCTs, the control condition was a sham intervention, and the trial was double-blind. 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 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. (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 regimens 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 end point; there the target was 96.4% to adjust for 2 interim looks at the data. The prior for the analysis was not reported in the article.

Participants and outcome assessments were blinded, but the intervention team was unblinded. 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 population. One hundred eighty-five participants in the treatment group and 97 in the sham control group underwent the second bronchoscopy, and the same numbers of patients had the third bronchoscopy (it is not clear whether they were the same patients).

The superiority of bronchial thermoplasty was not achieved in the intention-to-treat population for the primary effectiveness outcome, mean change in the integrated AQLQ score. Mean standard deviation (SD) change was 1.35 (1.10) in the bronchial thermoplasty group and 1.16 (1.23) in the sham control group. Using Bayesian analysis, the PPS was 96%. This did not surpass the target PPS of 96.4%. However, the superiority of bronchial thermoplasty on a related outcome was achieved. In the intention-to-treat population, the percentage of patients achieving an AQLQ score change of 0.5 or greater (ie, at least the minimally important difference) was 79% in the bronchial thermoplasty group and 64% in the control group. The PPS at 99.6% surpassed the target probability for secondary outcomes of 95%. Additional analysis of data from the active treatment group suggested 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, 4.1 vs 5.1, respectively).

Several secondary outcomes favored bronchial thermoplasty over the sham control group. They included a reduction in the proportion of patients reporting asthma worsening during follow-up (27.3% vs 42.9%, respectively; PPS=99.7%) and a reduction in the number of emergency department visits (0.07 vs 0.43 visits per person per year, respectively; PPS=99.9%). Moreover, there was a reduction in severe exacerbations of 0.47 per person per year in the bronchial thermoplasty group compared with 0.70 per person per year in the control group (PPS=95.5%). There were no significant differences between groups in

other secondary efficacy outcomes, including morning peak expiratory flow, number of symptom-free days, symptom score, and rescue medication use.

For safety outcomes, during the treatment phase, there was a higher rate of respiratory adverse events in the active treatment group (85% of participants; mean, 1.0 events per bronchoscopy) compared with the sham group (76% of participants; mean, 0.7 events per bronchoscopy). A total of 16 (8.4%) patients in the active treatment group required 19 hospitalizations for respiratory symptoms during the treatment phase compared with 2 (2%) patients in the sham group, who required 1 hospitalization each. However, during the posttreatment 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 trial, 5 (2.6%) patients in the bronchial thermoplasty group had a total of 6 hospitalizations for respiratory symptoms, and 4 (4.1%) patients in the sham group had 12 hospitalizations (1 patient had 9 hospitalizations).

In the AIR2 trial, the sham group had a relatively high response rate (eg, 64% experienced a clinically significant increase in the AQLQ score). Blinding appeared to be initially successful and remained so for the sham group. 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.

Two- and 5-year follow-up data on patients in the treatment group of the AIR2 trial have been published. Castro et al (2011) reported on 2-year data on 166 (87%) of 190 patients randomized to the bronchial thermoplasty group. In the second year after treatment, the proportion of participants who experienced severe exacerbations was 23.0% (95% confidence interval [CI], 16.6% to 29.5%). This compares with a 30.9% (95% CI, 24.2% to 37.7%) rate of exacerbations during year 1. The proportion who experienced asthma adverse events was 28.7% (95% CI, 22.1% to 35.3%) in year 1 and 26.5% (95% CI, 19.8% to 33.2%) in year 2. Wechsler et al (2013) reported on 5-year data for 162 patients in the AIR2 trial (85% of those randomized to the treatment group). In a matched-pair analysis including the 162 study completers and the same group in previous years, the rate of severe exacerbations in years 1, 2, 3, 4, and 5 were 30.9%, 23.5%, 34.0%, 36.4%, and 21.6%, respectively. The proportion of patients 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 patients who experienced adverse asthma events (at least ≥2 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 1 hospitalization for respiratory adverse events these same years was 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%. These follow-up studies are limited in that follow-up data were not collected on patients randomized to the sham group, and therefore outcomes (eg, the rate of exacerbations, the rate of hospitalizations) cannot be compared in patients who did and did not receive bronchial thermoplasty.

Table 1. Summary of Key RCT Characteristics

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Pavord et al (2007); RISA	U.K., Brazil, Canada	8	2004-2006	• ≥18 y with uncontrolled asthma refractory to high-dose ICS[a] and LABA[b] • FEV_1 ≥50% predicted • Airway hyper-responsiveness[c] • Abstinence from smoking for 1 y • Smoking history ≤0 pack-years	• 17 medical management and BT • Weeks 0-6: 3 treatments at least 3 wk apart • Weeks 6-22: steroid stable • Weeks 22-36: protocol defined steroid wean • Weeks 36-52: investigator-led steroid reduction	• 17 medical management alone • ICS dose tapered in 3 stages by 20%-25% of baseline dose every 4 wk to minimal dose of fluticasone propionate 100-600 mg/d or equivalent
Cox et al (2007); AIR	U.K., Brazil, Canada, Denmark	11	2002-2005	• 18-65 y with moderate-to-severe persistent asthma requiring daily ICS[d] and LABA[b] • FEV_1 60%-80% of predicted • Airway hyper-responsiveness • Stable asthma 6 wk prior to enrollment • No current or recent respiratory infection[e]	• 56 medical management and BT (3 treatments at least 3 wk apart) • Follow-up at 3, 6, and 12 mo,[f] then 2-wk LABA abstinence	• 56 medical management alone • Follow-up at 3, 6, and 12 mo,[f] then 2-wk LABA abstinence
Castro et al (2010); AIR2	U.S., EU, Canada, Australia	30	2000-2015	• ≥2 d asthma symptoms during 4-wk baseline required high initial dosage of ICS[g] • Baseline AQLQ score ≤6.25	• 196 received BT (3 treatments at least 3 wk apart)	• 101 received sham procedure

AIR: Asthma Intervention Research Trial, AQLQ: Asthma Quality of Life Questionnaire; BT: bronchial thermoplasty, FEV_1: forced expiratory volume at 1 minute, ICS: inhaled corticosteroids, LABA: long-acting β-agonist, RCT: randomized controlled trial, RISA: Research in Severe Asthma.
[a] Treatment of fluticasone propionate ≥750 μg/d or equivalent.
[b] Treatment of salmeterol ≥100 μg/d or equivalent.
[c] Demonstrated by challenge with methacholine or reversible bronchoconstriction during prior 12 mo.
[e] No more than 2 respiratory infections requiring treatment in past year and required to undergo a 2-wk baseline test period without LABAs; eligibility depended on worsening asthma control during that time.
[f] Between data collection periods, patients could use all maintenance therapies
[g] Treatment of beclomethasone ≥1000 μg or equivalent.

Table 2. Summary of Key RCT Results

Study	Respiratory AE (No. of Events)	Serious AE (Hospitalization)[b]	Reduction in SABA (puffs per 7 days)[c]	% Reduction in OCS Dose[d]	% Reduction in ICS Dose[d]
Pavord et al (2007)[4]; RISA					
BT (n=15)[a]	136	7	-26.6 (40.1)	63.6 (45.4)	28.6 (30.4)
MM (n=17)	57	0	-1.5 (11.7)	26.2 (40.7)	20 (32.9)
Effect (95% CI); p			NR (NR); <0.05	NR (NR); 0.12	NR (NR); 0.059

	Change in Rate of Exacerbations[e]
Cox et al (2007)[6]; AIR	
BT (n=52)[f]	
Baseline	0.35 (0.32)
12 months	0.18 (0.31)
MM (n=49)[f]	
Baseline	0.28 (0.31)
12 months	0.31 (0.41)
Effect (95% CI); p	NR (NR); 0.03
	Change in AQLQ[h]
Castro et al (2010)[8]; AIR2	
BT (n=190)[g]	
Baseline	4.30 (1.17)
12 months	5.66 (1.06)
Mean change	1.35 (1.10)
BT sham (n=98)[g]	
Baseline	4.31 (1.21)
12 months	5.48 (1.15)
Mean change	1.16 (1.23)

AE: adverse events; AQLQ: Asthma Quality of Life Questionnaire; BT: bronchial thermoplasty; CI: confidence interval; ICS: inhaled corticosteroid; MM: medical management; NR: not reported; OCS: oral corticosteroid; SABA: short-acting β-agonist.
[a] There were 2 withdrawals from BT group prior to first treatment.
[b] There were no deaths or serious AEs other than hospitalization related to respiratory events in either group.
[c] Results at 22 wk.
[d] Results at 52 wk.
[e] Change from baseline in mean number of mild exacerbations per subject per week at 12 mo.
[f] Analyses based on participants available for evaluation at 12 mo.
[g] Intention-to-treat analyses based on participants who underwent at least 1 bronchoscopy procedure in either arm.
[h] Change from baseline in integrated AQLQ score at 12 months with higher score (0-7) indicating better quality of life. A score change of ≥0.5 defines minimal important difference.

Post-FDA Approval Clinical Trial Evaluating Bronchial Thermoplasty in Severe Persistent Asthma

Chupp et al (2017) compared 3-year follow-up results from 190 patients in the AIR2 trial with a subgroup (n=190) from a prospective nonrandomized clinical study (Post-FDA Approval Clinical Trial Evaluating Bronchial Thermoplasty in Severe Persistent Asthma [PAS2]). PAS2 is an ongoing open-label trial of the Alair system required for post premarket approval. Of those enrolled, 168 patients from PAS2 reached 3 years of follow-up and were compared with 165 patients from AIR2 who also had 3 years of follow-up. The primary outcome was comparing 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 3 was compared with the 12 months before treatment (PAS2, 55% reduction; AIR2, 72.3% reduction; p<0.001); 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.

A TEC Assessment (2014) assessed bronchial thermoplasty as a treatment for inadequately controlled severe asthma. The Assessment included the 3 published RCTs discussed and concluded, "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.

Observational and Nonrandomized Studies
Several observational and nonrandomized studies were identified that provide data on safety outcomes and incidence of short-term adverse events.

Burn et al (2017) published a rigorous U.K. registry study that focused on safety outcomes. The study combined data from 2 sources, the U.K. Difficult Asthma Registry and the Hospital Episode Statistics warehouse, and included patients treated with bronchial thermoplasty 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 2 databases could be matched. Most patients had 3 bronchial thermoplasty treatment sessions. Data from the matched cohort were used to calculate event rates for 4 binary safety outcomes. Procedural complications were reported in 17 (11%) of 152 procedures in 13 (22%) patients; emergency department readmissions within 30 days of the initial hospitalization were reported for 15 (11.8%) patients; and accident and emergency visits (ie, emergency department) for any reason were reported for 13 (8.6%) patients. For the fourth 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 1 of the 4 safety issues. The authors noted that the relatively high rate of safety events might have been related to older patients with more severe disease being treated in clinical practice compared with patients included in clinical trials.

Langton et al (2017) published a single-center, observational study of 24 patients who had severe uncontrolled asthma and were treated with bronchial thermoplasty. Primary response was measured by change in 5-item Asthma Control Questionnaire (ACQ-5) scores at 6 months after treatment. The mean ACQ-5 score of the group was 3.3 (SD=1.1) at baseline, which improved to 1.5 (SD=1.1) at 6 months ($p<0.001$). For 21 patients, the change achieved the minimal clinically significant improvement (defined as an ACQ-5 improvement ≥0.5). Authors also reported deterioration in postbronchodilator FEV_1: 24 hours after treatment, FEV_1 decreased by a mean of 166 mL (95% CI, 102 to 224 mL; $p<0.001$). The predictors of acute change in FEV_1 were age ($p=0.02$) and a number of activations (ie, more activations predicted worsened FEV_1 postprocedure; $p=0.01$). Patients deemed responders according to ACQ-5 improvement had a mean of 221 (SD=45) activations, while those clinically deemed nonresponders had a mean of 139

(SD=11) activations (p<0.01). There were significantly more activations applied to upper lobe (78.8) than in the with the right (40.1) or left (42.8; p<0.001) lower lobes, which aligns with the significant deterioration in FEV_1 (≥15%) in 60% of patients treated in upper lobe (p=0.009). Patients whose right or left lower lobes were treated were quicker to return to baseline FEV_1 levels by day seven postprocedure compared with those whose upper lobes were treated. While the study was limited by its small size and observational nature, it provides data on the aggravating effect radiofrequency activations may have on FEV_1, especially on upper lobes.

D'Hooghe et al (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). The primary outcome was radiologic abnormalities following bronchial thermoplasty, and a large percentage of the cohort showed 1 of 4 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 2 of every 3 patients). Seventy-three percent of abnormal results resolved within 6 weeks, and 100% resolved 6 months postprocedure.

SUMMARY OF EVIDENCE

added to medical management, the evidence includes 3 RCTs and observational studies. Relevant outcomes are symptoms, quality of life, hospitalizations, and treatment-related morbidity. Early studies (RISA, AIR) investigated safety outcomes, finding similar rates of adverse events and exacerbations between the bronchial thermoplasty and control groups. These trials were limited by their lack of sham control. The AIR2 trial is the largest of the 3 published RCTs, and the only one double-blinded and sham-controlled, 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 of mean change in the quality of life score but was found to be superior on a related outcome, improvement in the quality of life of at least 0.5 points on the Asthma Quality of Life Questionnaire. There was a high response rate in the sham group of the AIR2 trial, suggesting a large placebo effect, particularly for subjective outcomes such as quality of life. There are no long-term sham-controlled efficacy data. Findings on adverse events from the 3 trials have suggested that bronchial thermoplasty is associated with a relatively high rate of adverse events, including hospitalizations during the treatment period, but not in the posttreatment period. Safety data up to 5 years have been reported in the RCTs for patients treated with bronchial thermoplasty but not for control patients. Safety data from a U.K. registry study, published in 2016, found that 20% of bronchial thermoplasty procedures were associated with a safety event (ie, procedural complications, emergency respiratory readmissions, emergency department visits, and/or postprocedure overnight stays). Conclusions cannot be drawn about the effect of bronchial thermoplasty on the net health outcome due to the limited amount of sham-controlled data (1 RCT) on short-term efficacy, the uncertain degree of treatment benefit in that single sham-controlled trial, the lack of long-term sham-controlled data in the face of a high initial

placebo response, and the presence of substantial adverse events. Also, there is a lack of data on patient selection factors for this procedure and, as a result, it is not possible to determine whether there are patient subgroups that might benefit. The evidence is insufficient to determine the effects of the technology on health outcomes.

References

1. Blue Cross and Blue Shield Association, Medical Policy Reference Manual, "Bronchial Thermoplasty", 7.01.127, 6:2018.
2. Centers for Disease Control and Prevention. Asthma FastStats. http://www.cdc.gov/asthma/faststats.html. Accessed May 12, 2016.
3. National Heart Lung and Blood Institute. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma (EPR-3). 2007; http://www.nhlbi.nih.gov/health-pro/guidelines/current/asthma-guidelines. Accessed May 12, 2016.
4. Pavord ID, Cox G, Thomson NC, et al. Safety and efficacy of bronchial thermoplasty in symptomatic, severe asthma. Am J Respir Crit Care Med. Dec 15 2007;176(12):1185-1191. PMID 17901415
5. Pavord ID, Thomson NC, Niven RM, et al. Safety of bronchial thermoplasty in patients with severe refractory asthma. Ann Allergy Asthma Immunol. Nov 2013;111(5):402-407. PMID 24125149
6. Cox G, Thomson NC, Rubin AS, et al. Asthma control during the year after bronchial thermoplasty. N Engl J Med. Mar 29 2007;356(13):1327-1337. PMID 17392302
7. Thomson NC, Rubin AS, Niven RM, et al. Long-term (5 year) safety of bronchial thermoplasty: Asthma Intervention Research (AIR) trial. BMC Pulm Med 2011;11:8. PMID 21314924
8. Castro M, Rubin AS, Laviolette M, et al. Effectiveness and safety of bronchial thermoplasty in the treatment of severe asthma: a multicenter, randomized, double-blind, sham-controlled clinical trial. Am J Respir Crit Care Med. Jan 15 2010;181(2):116-124. PMID 19815809
9. Castro M, Rubin A, Laviolette M, et al. Persistence of effectiveness of bronchial thermoplasty in patients with severe asthma. Ann Allergy Asthma Immunol. Jul 2011;107(1):65-70. PMID 21704887
10. Wechsler ME, Laviolette M, Rubin AS, et al. Bronchial thermoplasty: Long-term safety and effectiveness in patients with severe persistent asthma. J Allergy Clin Immunol. Dec 2013;132(6):1295-1302. PMID 23998657
11. Zhou JP, Feng Y, Wang Q, et al. Long-term efficacy and safety of bronchial thermoplasty in patients with moderate-to-severe persistent asthma: a systemic review and meta-analysis. J Asthma. Feb 2016;53(1):94-100. PMID 26383773
12. Blue Cross Blue Shield AsssociationTechnology Evaluation Center (TEC). Bronchial thermoplasty for treatment of inadequately controlled severe asthma. TEC Assessments 2014;Volume 29,Tab 12. PMID 25962190.
13. Torrego A, Sola I, Munoz AM, et al. Bronchial thermoplasty for moderate or severe persistent asthma in adults. Cochrane Database Syst Rev. 2014;3:CD009910. PMID 24585221
14. Wu Q, Xing Y, Zhou X, et al. Meta-analysis of the efficacy and safety of bronchial thermoplasty in patients with moderate-to-severe persistent asthma. J Int Med Res. 2011;39(1):10-22. PMID 21672303
15. Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. 2016; http://ginasthma.org/2016-gina-report-global-strategy-for-asthma-management-and-prevention/. Accessed May 12, 2016.
16. Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J. Feb 2014;43(2):343-373. PMID 24337046
17. American College of Chest Physicians (ACCP). Position Statement for Coverage and Payment for Bronchial Thermoplasty. 2014; http://www.chestnet.org/News/CHEST-News/2014/05/Position-Statement-for-Coverage-and-Payment-for-Bronchial-Thermoplasty. Accessed May 12, 2016.
18. British Thoracic Society Guidelines, Scottish Intercollegiate Guidelines Network (SIGN). SIGN 141: British guideline on the management of asthma. 2014; http://www.sign.ac.uk/guidelines/fulltext/141/. Accessed May 12, 2016.
19. Arrigo R, Failla G, Scichilone N, et al. How effective and safe is bronchial thermoplasty in "real life" asthmatics compared to those enrolled in randomized clinical trials? Biomed Res Int. 2016;2016:9132198. PMID 27672663
20. Bicknell S, Chaudhuri R, Lee N, et al. Effectiveness of bronchial thermoplasty in severe asthma in 'real life' patients compared with those recruited to clinical trials in the same centre. Ther Adv Respir Dis. Dec 2015;9(6):267-271. PMID 26307767
21. Langton D, Sha J, Ing A, et al. Bronchial thermoplasty in severe asthma in Australia. Intern Med J. May 2017;47(5):536-541. PMID 28101900

22. Burn J, Sims AJ, Keltie K, et al. Procedural and short-term safety of bronchial thermoplasty in clinical practice: evidence from a national registry and Hospital Episode Statistics. J Asthma. Dec 01 2016:0. PMID 27905828
23. National Institute for Health and Care Excellence (NICE). Bronchial thermoplasty for severe asthma [IPG419]. 2012; https://www.nice.org.uk/guidance/IPG419. Accessed May 31, 2017.
24. Chupp G, Laviolette M, Cohn L, et al. Long-term outcomes of bronchial thermoplasty in subjects with severe asthma: a comparison of 3-year follow-up results from two prospective multicentre studies. *Eur Respir J.* Aug 2017;50(2). PMID 28860266
25. Langton D, Sha J, Ing A, et al. Bronchial thermoplasty: activations predict response. *Respir Res.* Jul 4 2017;18(1):134. PMID 28676053
26. d'Hooghe JNS, van den Berk IAH, Annema JT, et al. Acute radiological abnormalities after bronchial thermoplasty: a prospective cohort trial. *Respiration.* Jul 2017;94(3):258-262. PMID 28675890

Policy History

Original Effective Date: 07/21/2010
Current Effective Date: 09/19/2018

07/01/2010	Medical Policy Committee review
07/21/2010	Medical Policy Implementation Committee approval. New policy.
07/07/2011	Medical Policy Committee review
07/20/2011	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/02/2012	Medical Policy Committee review
08/15/2012	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/01/2013	Medical Policy Committee review
08/21/2013	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/07/2014	Medical Policy Committee review
08/20/2014	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
09/03/2015	Medical Policy Committee review
09/23/2015	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
09/08/2016	Medical Policy Committee review
09/21/2016	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
09/07/2017	Medical Policy Committee review
09/20/2017	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
09/06/2018	Medical Policy Committee review
09/19/2018	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 09/2019

Coding

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	31660, 31661
HCPCS	No codes
ICD-10 Diagnosis	J44.0-J44.9 J45.20-J45.22 J45.30-J45.32 J45.40-J45.42 J45.50-J45.52 J45.901-J45.998

*****Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

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