Safety of investigative bronchoscopy in the Severe Asthma Research Program

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Background: Investigative bronchoscopy was performed in a subset of participants in the Severe Asthma Research Program to gain insights into the pathobiology of severe disease. We evaluated the safety aspects of this procedure in this cohort with specific focus on patients with severe asthma.

Objective: To evaluate prospectively changes in lung function and the frequency of adverse events related to investigative bronchoscopy.

Methods: Bronchoscopy was performed by using a common manual of procedures. A subset of very severe asthma was defined by severe airflow obstruction, chronic oral corticosteroid use, and recent asthma exacerbations. Subjects were monitored for changes in lung function and contacted by telephone for 3 days after the procedure.

Results: A total of 436 subjects underwent bronchoscopy (97 normal, 196 not severe, 102 severe, and 41 very severe asthma). Nine subjects were evaluated in hospital settings after bronchoscopy; 7 of these were respiratory-related events. Recent emergency department visits, chronic oral corticosteroid use, and a history of pneumonia were more frequent in subjects who had asthma exacerbations after bronchoscopy. The fall in FEV_1 after bronchoscopy was similar in the severe and milder asthma groups. Prebronchodilator FEV_1 was the strongest predictor of change in FEV_1 after bronchoscopy with larger decreases observed in subjects with better lung function.

Conclusion: Bronchoscopy in subjects with severe asthma was well tolerated. Asthma exacerbations were rare, and reduction in pulmonary function after the procedure was similar to that in subjects with less severe asthma. With proper precautions, investigative bronchoscopy can be performed safely in severe asthma. (J Allergy Clin Immunol 2011;128:328-36.)

Key words: *Investigative bronchoscopy, safety, severe asthma, exacerbation*

Airway inflammation is a central component of asthma.[1,2] Bronchoscopy has provided an investigative approach to obtain airway fluids and mucosal biopsies, which has been critical to demonstrate the pattern and persistence of inflammation in

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Abbreviations used
ATS: American Thoracic Society
BAL: Bronchoalveolar lavage
BMI: Body mass index
DSMB: Data safety monitoring board
ED: Emergency department
HCU: Health care utilization
MoP: Severe Asthma Research Program Manual of Procedures
SARP: Severe Asthma Research Program
VSA: Very severe asthma

asthma and begin to identify the link between these features and altered pathophysiology. Investigative bronchoscopy has provided a major step forward to understand more fully airway mechanisms of asthma as these studies focus on the target organ of disease, the lung.[3,4] To date, the majority of bronchoscopy studies have been performed in patients with mild to moderate disease. Severe asthma remains poorly understood and is a phenotype of asthma with greater morbidity. Extending investigative bronchoscopy to patients with more severe disease promises to provide a critical opportunity to gain novel insight into what is anticipated to be a unique histopathology. It may provide clues to what causes greater severity in this population, and act as a stimulus to the development of more effective therapeutic interventions.

The lack of data assessing the safety of investigative bronchoscopy in patients with more severe asthma has been a limitation in the use of this research technique to understand better the pathophysiology of severe disease.[5] There are few published studies evaluating the safety of investigative bronchoscopy in asthma and the effects of this procedure on physiologic changes, and even fewer on the effects of the procedure on short-term asthma control.[6-11] Collectively, only a small number of subjects with asthma and severe airflow obstruction have been included in previous studies, and most patients were not being treated with high doses of inhaled or oral corticosteroids at the time of the bronchoscopy.

In 2001, the National Heart, Lung, and Blood Institute established the Severe Asthma Research Program (SARP) at 9 sites in the United States and 1 in the United Kingdom. A major goal of the SARP was to identify and characterize a large number of subjects with severe asthma to establish the clinical characteristics of severe disease and understand pathobiologic mechanisms important in severe asthma compared with milder disease. To accomplish these goals, subjects with asthma of all levels of disease severity were recruited and underwent a comprehensive characterization to identify clinical phenotypes through which severe asthma might be defined.[12] To explore and define the pathobiology of severe asthma in these well characterized patients, it was necessary to obtain samples from the airways to describe patterns of inflammation and what processes may be dysregulated in severe asthma. Although many subjects underwent sputum induction for evaluation of airway inflammatory cells and soluble mediators,[13] this procedure preferentially samples the large proximal airways and does not allow assessment of inflammation more peripherally or unique features of airways remodeling. To explore differences in submucosal inflammation and architectural changes in the airway, investigative bronchoscopy was incorporated as a key component of the SARP.

Because subjects with increasingly severe asthma would undergo bronchoscopy, a subcommittee of investigators was appointed to develop common procedures for study and to maximize safety of subjects. The bronchoscopy section of the SARP Manual of Procedures (MoP) provides a detailed uniform approach to preprocedure assessment of underlying severity of asthma; ongoing evaluation for disease stability before, during, and after bronchoscopy; and consistent postprocedure follow-up to assess the occurrence of adverse effects. The aim of this study was to evaluate prospectively changes in pulmonary function and the frequency of respiratory-related events, including hospital-based health care utilization (HCU) and need for oral corticosteroids in subjects with not severe and severe asthma undergoing investigative bronchoscopy in SARP.

METHODS

SARP

After establishing standard operating procedures, including a review by an independent data safety monitoring board (DSMB) and approval by the institutional review boards at each site, subjects underwent a comprehensive phenotypic characterization as previously described.[12] Briefly, after subjects provided written informed consent, clinical staff administered questionnaires (asthma symptoms, medication use, medical history, and HCU), performed allergen skin prick testing, and performed a comprehensive pulmonary function evaluation on several days including baseline prebronchodilator spirometry, response to short-acting β-agonists (2-8 puffs albuterol), and methacholine challenge. After review of clinical data by investigators, a subset of subjects with severe and not severe asthma and normal healthy subjects were recruited for investigative bronchoscopy studies (see inclusion criteria in Table I).

Bronchoscopy MoP

Before initiation of bronchoscopy studies, a subcommittee of investigators was appointed to develop a MoP for investigative bronchoscopy. An independent DSMB reviewed the MoP with ongoing oversight by this committee through review of clinical site experience and adverse events. The institutional review board at each clinical site also reviewed and approved the bronchoscopy MoP. The entire bronchoscopy MoP is provided as an attachment in an online data supplement (see this article's Table E1 in the Online Repository at www.jacionline.org for table of contents of MoP). Clinical sites were required to complete several phases wherein investigators requested permission to perform bronchoscopy on subjects with increasingly severe airflow obstruction using a stepwise algorithm. A subset of the severe asthma group was defined *a priori* as having very severe asthma (VSA) on the basis of baseline severe airflow obstruction (FEV_1 <60 % predicted after bronchodilators), a therapeutic requirement of chronic oral corticosteroids, and recent or intensive HCU in the past year (see criteria in Table II). Individual centers were required to demonstrate bronchoscopy experience with subjects with severe asthma before progressing to VSA, and their request was reviewed and approved by the bronchoscopy subcommittee before being sent to the DSMB for further review. Only after the formal approval by the DSMB did any site proceed to the next level of asthma severity.

Bronchoscopy procedures

All subjects received albuterol before the bronchoscopy, and spirometry was performed before (prealbuterol FEV_1% predicted) and after (postalbuterol FEV_1% predicted) administration. Each center was then allowed to follow its standard operating procedures and institutional rules with regard to conscious sedation (choice of drug and route of administration), local anesthesia (nebulized, atomized, or topical lidocaine), and the use of supplemental oxygen. Bronchoscopic procedures were performed in accordance