Severe asthma: Lessons from the Severe Asthma Research Program

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Severe asthma affects only a small percentage of the asthma population. However, these patients remain poorly understood and difficult to treat. Because the numbers are relatively small (10% or less of the asthma population), a network approach with shared protocols, samples, and data provides a unique opportunity to recruit the numbers of subjects necessary to perform adequately powered studies. The Severe Asthma Network (Severe Asthma Research Program) was established by the National Heart, Lung, and Blood Institute in 2001 to advance collectively the study of severe asthma to determine factors that differentiated these patients or subjects from those with milder asthma. Nearly 800 subjects have been recruited in less than 4 years to begin to address these differences. Future studies will specifically evaluate the role of inflammatory/oxidative processes, infection, genetics, and the distal lung in the pathogenesis of severe asthma. (J Allergy Clin Immunol 2007;119:14-21.)

Key words: Asthma, allergy, phenotypes, corticosteroids

Asthma afflicts 6% to 8% of the United States population, making it one of the most common chronic diseases in the country. Although most patients have mild-to-moderate asthma that responds to inhaled corticosteroids,1-4 there are subpopulations of patients with asthma with severe disease whose symptoms and control are believed to be largely unresponsive to treatment, including high-dose inhaled and systemic corticosteroids.5 The care of these individuals is often difficult from both a patient and provider perspective. Although some progress has been made in understanding the disease, considerable gaps remain to be filled.

THE NEED FOR NETWORKING TO ADDRESS SEVERE ASTHMA MECHANISMS

Severe asthma represents approximately 10% of all subjects with asthma. This subset of patients has greater morbidity and a disproportionate need for health care support compared with the less severe subset.6 The frequency of severe asthma makes study of this group difficult, because a single center is unlikely to have a sufficient number of subjects for evaluation. However, given both the clinical and economic importance of this asthma phenotype and the lack of established animal models, the study of these patients is imperative to uncover the mechanisms of disease and the factors that determine asthma severity. It is an opportunity to discover novel information that may lead to more effective therapy not only for subpopulations of patients with severe asthma but also potentially for all levels of severity of this respiratory disease.7 Further, in contrast with a single-center approach, a collaborative approach allows enrollment of greater numbers of subjects, a greater diversity of subjects, and greater opportunity to define the disease and its phenotypes rigorously across large numbers of subjects.
For all these reasons, the National Institutes of Health and the Lung Division of the National Heart, Lung, and Blood Institute held a workshop in 2000 on severe asthma to define the characteristics, mechanistic factors, potential approaches for study and treatment, and future research needs and directions of severe asthma. On the basis of the recommendations of this workshop, a collaborative program was established to investigate the mechanistic bases for severe asthma and how this phenotype may differ from mild-to-moderate asthma in human patients. Eight sites were funded in 2001—the University of Virginia (subsites at Cleveland and Emory University), Brigham and Women’s Hospital, Imperial College, National Jewish Medical and Research Center, the University of Pittsburgh, Wake Forest University, Washington University, and the University of Wisconsin—forming the Severe Asthma Research Program (SARP). Each had submitted a unique research proposal on the mechanisms that may distinguish severe from nonsevere asthma. Unlike most if not all other National Heart, Lung, and Blood Institute networks, the were no a priori defined interactions among the sites, nor any protocols initially developed that were shared across the sites.

However, as with any networked project, or “confederation,” in the case of SARP, there was the need to establish consistent investigative protocols across all sites and to have appropriate safety mechanisms in place to perform investigative bronchoscopy in these high-risk population. An administrative structure (Steering Committee, Data Coordinating Center, National Institutes of Health and Data Safety Monitoring Board), a working definition of severe asthma, and a detailed clinical questionnaire were established, along with development of a Manual of Procedures, which includes a uniform investigative approach to the conduct of pulmonary functions, skin testing, bronchoprovocation, sputum collection, and, perhaps most importantly, the conduct of bronchoscopy.

**DEFINING SEVERE ASTHMA**

The definition of asthma, *per se*, remains clinically and physiologically based, dependent on appropriate symptoms and the presence of reversible airflow limitation. This general definition allows for the capture of numerous syndromes able to meet such criteria. This general definition of asthma makes precise definitions of severe asthma even more difficult. Guidelines for the Diagnosis and Management of Asthma and the Global Initiative on Asthma classify asthma severity on the basis of symptoms, need for rescue therapy, and lung function to provide a severity-based stratification that is commonly used in clinical trials and clinical practice. However, these criteria have not been validated and do not necessarily include information on medication use or healthcare utilization, and hence may not be accurate to identify a subject with severe asthma.

An American Thoracic Society (ATS) Workshop on Refractory Asthma, the proceedings of which were published in 2000, developed a working definition of severe/refractory asthma to promote unified approaches to the disease in clinical practice and research. The definition attempted to capture only those patients who had received “appropriate/guidelines” evaluation and high doses of asthma/anti-inflammatory therapy. These medications were either (1) required to maintain some degree of asthma control or (2) despite their use, inadequate to maintain acceptable control. The workshop proposed a definition of refractory or severe asthma based on 2 major and 7 minor characteristics (Table I), which the SARP Steering Committee adopted.

The SARP has now enrolled nearly 800 patients/subjects across the 8 centers, at least 250 of whom meet the ATS criteria for severe asthma, with the remaining serving as controls. Evaluating these subjects further, it is apparent that a group of patients with severe asthma has indeed been captured. Not only do the vast majority of subjects with severe asthma have a history of exacerbations, but also these exacerbations are more severe and more frequent, with 12% of the severe population having had an intensive care unit stay in the previous year. Further, nearly 70% reported a deterioration in their asthma control with reduction in their corticosteroid dose. Although only 2 minor criteria were required to meet ATS criteria for severe disease, most of the severe asthma population continued to have 5 to 6 minor criteria, despite being on high doses of controller medications. Although all minor criteria increased in frequency as the disease severity increased, the 2 minor criteria that best

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**TABLE I. ATS workshop consensus for definition of severe/refractory asthma**

<table>
<thead>
<tr>
<th>Requires 1 or both major criteria and 2 minor criteria</th>
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<tr>
<td><strong>Major criteria</strong></td>
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<tr>
<td>To achieve control to level of mild-moderate persistent asthma:</td>
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<tr>
<td>1. Treatment with continuous or near continuous (≥50% of year) oral corticosteroids</td>
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<tr>
<td>2. Requirement for treatment with high-dose inhaled corticosteroids</td>
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<tr>
<td><strong>Minor criteria</strong></td>
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<tr>
<td>1. Requirement for additional daily treatment with a controller medication, eg, long-acting β-agonist, theophylline, or leukotriene antagonist</td>
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<td>2. Asthma symptoms requiring short-acting β-agonist use on a daily or near daily basis</td>
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<td>3. Persistent airflow obstruction (FEV&lt;sub&gt;1&lt;/sub&gt; &lt;80% predicted; diurnal peak expiratory flow variability &gt;20%)</td>
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<td>4. One or more urgent care visits for asthma per year</td>
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<td>5. Three or more oral steroid bursts per year</td>
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<td>6. Prompt deterioration with ≤25% reduction in oral or inhaled corticosteroid dose</td>
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<td>7. Near-fatal asthma event in the past</td>
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*Requires that other conditions have been excluded, exacerbating factors treated, and patient believed to be generally compliant.

discriminated both mild and moderate asthma from severe asthma were 3 or more exacerbations requiring treatment with oral corticosteroids in the previous year and a history of endotracheal intubation. Thus, the SARP database would appear to have validated the ATS workshop definition of severe asthma, and in fact, this definition was adopted by a consortium of experts in severe asthma in February 2006.14

**RISK FACTORS FOR SEVERE ASTHMA**

As noted, the commonality of definition of severe asthma across centers allows for uniform analysis of epidemiologic and pathologic factors associated with and possibly contributory to severe asthma. In the initial SARP database, many clinical factors were found to be associated with severe asthma. Although many had been associated with severe asthma in the past, some factors that might have been predicted to associate with severe asthma, such as a lower bronchodilator response and postbronchodilator FEV₁, were not significantly different between subjects with moderate and severe asthma. Given previous theories that severe asthma is, in fact, a type of chronic obstructive pulmonary disease (COPD) with poor reversibility, this finding was surprising. However, our findings suggest that unlike COPD, some of the physiologic abnormalities in severe asthma may in fact remain nearly fully reversible and amenable to therapy. Interestingly, in the SARP cohort, a maximum bronchodilator response, using up to 8 puffs of albuterol, was used to obtain a postbronchodilator FEV₁. It is not likely that this degree of reversibility would have been seen with the typical 2 to 4 puffs of albuterol.

Two additional factors that have widely been associated with severe asthma, female sex and obesity, were also not strikingly different between the subjects with severe asthma and subjects with moderate asthma and similar lung function, but subjects with less severe asthma had significantly less urgent health care utilization and symptoms and lower corticosteroid use. Although women were predominant in all asthma severity classes, they were not more highly represented in the severe asthma group. This is in sharp contrast to the European Network for Understanding the Mechanisms of Severe Asthma (ENFUMOSA), in which females were overrepresented in the group with severe asthma.15 Whether these differences are a result of variations in definitions or referral patterns for severe asthma in the United States versus Europe awaits further analysis (see Table II for additional comparisons). Similarly, severe asthma has been believed to be a disease associated with obesity. However, the group with moderate asthma studied in SARP was equally as obese as the severe population. Although further study is necessary, this lack of association with severity may underscore the need to differentiate issues carefully regarding severity versus control of asthma.

Similar to ENFUMOSA, SARP found atopy (by skin testing) to be significantly less prevalent in severe disease, whereas a history of aspirin sensitivity was more common in subjects with severe asthma. The apparent inverse relationship of atopy and severity, now replicated in 2 cohorts of subjects with severe asthma (ENFUMOSA and SARP), remains intriguing, and at least initially, counterintuitive.13,15 However, it may suggest that the adaptive immune response, manifested by atopy/allergy, in fact has some protective or reparative qualities associated with it, at least over time, that limit the development of progressively severe disease. Alternatively, it may reflect the infusion of a group with a later/adult onset of asthma who have reversible airflow limitation, but without an association with atopy. The increased percentage of aspirin-sensitive subjects with asthma in this severe group, a phenotype associated with less atopy and adult onset, may also contribute to this lower level of atopy.

Consistent with previous studies, gastroesophageal reflux, sinusitis, and use of nasal corticosteroids were all higher in subjects with severe asthma.16,17 Asthma exacerbations associated with menses were also more common in the women with severe asthma. In contrast with other cohorts, however, and after application of logistic regression analysis to the risk factors associated with severe asthma, only prebronchodilator FEV₁ (% predicted), less atopy, history of pneumonia, symptoms with physical activity, and low blood basophils independently predicted severe asthma. Although the low blood basophils are difficult to interpret, this association may be a result of the suppressive effect of corticosteroids on these cells. Intriguingly, the history of pneumonia may tie into alterations in innate immunity. A further study of subjects with asthma suggested that “neutrophilic” asthma, as identified by sputum, showed greater evidence for activation of innate responses compared with nonneutrophilic asthma.18 However, whether asthma, especially severe asthma, predisposes to pneumonia or follows the occurrence of pneumonia remains unknown.19

**SARP AND SEVERE ASTHMA PHENOTYPES**

Because SARP consists of such a large database of subjects, in addition to overall predictive elements for severe asthma, risk factors for the development of
phenotypes of severe asthma (ie, frequent exacerbators, low FEV1) can be addressed. In an abstract presented in 2005, risk factors for the development of severe (intensive care unit or intubation) exacerbations were also analyzed. The risk factors were somewhat different from those for severe asthma, in general. Although FEV1 (%) predicted remained a risk factor, being an African American was highly predictive of severe exacerbations, as has been shown by others. A history of aspirin sensitivity or asthma symptoms with menses were also independently predictive of severe exacerbations. In addition to the presence of severe asthma, a history of pneumonia was also predictive of severe exacerbations. The risk factors differ somewhat from previously reported risk factors for exacerbations in a difficult-to-control asthma population. In that study, sinus-nasal disease and psychologic dysfunctioning were the only independent risk factors. However, the sample size (n = 39 subjects with difficult asthma) was considerably smaller as well.

Phenotypes of severe asthma have also been proposed on the basis of age at onset of disease. SARPs were also able to confirm the previous association of allergy and atopy with childhood, as opposed to later onset (>12 years old) severe asthma. In addition, the SARPs data set supported the lower lung function in subjects with adult-onset severe asthma compared with early childhood onset, while adding that subjects with adult-onset severe asthma had a greater likelihood of sinus disease and a more likely history of pneumonia than early-onset disease. This greater history of pneumonia in subjects with later-onset asthma, although again supporting an altered innate response, could also support the theory that the development of severe asthma occurs after an infectious process (especially because the likelihood of pneumonia appears to be greater in people with shorter duration of disease).

Although SARPs has not focused on pediatric asthma, 1 of the subsites (Emory University) has actively studied children (6-17 years old) with severe asthma in both a cross-sectional and a longitudinal format, which can be compared with the adults with severe asthma. In contrast with the adults, children with severe asthma are a more homogeneous population, with a strong preponderance of atopy/allergy (as would be expected with early-onset disease), and higher values of exhaled nitric oxide than subjects with less severe asthma. Similar to exacerbation-prone asthma in adults, there was a significantly greater percentage of African Americans among the children with severe asthma, and these children remained highly symptomatic and prone to exacerbations despite high doses of both inhaled and systemic corticosteroids prospectively over a 6-month period (Fig 1).

**SARP APPROACHES TO UNDERSTANDING THE PATHOBIOLOGY OF SEVERE ASTHMA**

Although each of the 8 initial sites had a specific hypothesis and aims, the utility of the network is to provide access to samples and data that enhance the power to address questions that may require more than the numbers of subjects available at a given site. The initial areas of interest for the SARP sites are shown in Fig 2. In general terms, these included the role of genetics and the environment (specifically respiratory viruses) on the development of inflammation (specifically oxidant/antioxidant contributions) and remodeling, especially in the epithelium and distal lung. Finally, the role of anti-inflammatory compounds, specifically corticosteroids and lipoxins, in the pathobiology of severe asthma was also addressed. To date, studies have been published in relation to the role of oxidants/antioxidants, lipoxins, and distal lung fibroblasts, whereas another has addressed the lower corticosteroid response in severe asthma PBMCs.

**Oxidants/antioxidants**

Inflammation has been associated with an imbalance in oxidation/reduction. In network-wide studies (134 total subjects), but arising primarily out of the University of Virginia/Cleveland Clinics, subjects with asthma were shown to have lower levels of circulating superoxide dismutase (SOD) activity, a reducing enzyme that lowers the tissue oxidative load. These levels were correlated with lower levels of lung function, but not severity classification. The authors went on to show that the manganese or copper-zinc superoxide dismutase activity was not different between subjects with asthma and normal subjects. Further, serum SOD activity had an inverse correlation with circulating levels of 3-bromotyrosine, a posttranslational modification of proteins produced by the eosinophil peroxidase system of eosinophils. *In vitro* studies then
confirmed that 3-bromotyrosine was able to inactivate SOD enzymes, suggesting a mechanism by which the lower antioxidant activity may be arising. Studies such as this in such large numbers of subjects would be very difficult to accomplish without the presence of the SARP network.

**Role of distal lung**

Studies by Sally Wenzel considered the role of distal lung inflammation and remodeling in severe asthma. Previous studies from this investigator suggest that a certain type of mast cells (chymase+ mast cells) are increased in the distal airways of patients with severe asthma compared with normal autopsy distal lung (and more recently, milder asthma as well).28 Therefore, it was hypothesized that matrix/resident cell differences may exist in the distal lung/airways that predispose to regional differences. Following initial observations that fibroblasts from the distal lung (obtained from transbronchial biopsies) appeared to behave in a markedly different manner from those obtained from the proximal airways (endobronchial biopsies), a formal comparison of these 2 potential fibroblast phenotypes was undertaken.29 Fibroblasts from the distal lung proliferated more rapidly and produced significantly more α-smooth muscle actin (consistent with a more myofibroblast-like cells) at baseline and in response to TGF-β than cells from the proximal airways. In contrast, airway fibroblasts produced significantly more profibrotic factors, such as procollagen I, tissue inhibitor of metalloproteinase 1, and the eosinophilic chemokine, eotaxin 1, in response to TGF-β and/or IL-13, compared with distal lung fibroblasts. These differences were not dependent on disease or disease severity, with similar findings seen in 2 sets of fibroblasts available from normal subjects. Despite this lack of intrinsic difference between fibroblasts across severity or disease type, because subjects with severe asthma have been reported to have higher levels of TGF-β in both the proximal and distal lung, and Th2 cytokines remain associated with asthmatic inflammation, these regional fibroblast differences could support a mechanism by which inflammation and remodeling differ in the proximal and distal lung. Further studies will explore the mechanisms by which these differences support mast cell/eosinophilic inflammation and matrix turnover.

**Role of anti-inflammatory compounds: Corticosteroids and lipoxins**

Poor responsiveness to corticosteroids has long been associated with severe asthma. However, controversy remains as to the cause of the poor responsiveness. In studies from the Imperial College site (19 subjects with mild-moderate and 16 with severe asthma), the ability of *in vitro* corticosteroids to suppress LPS induced cytokine levels in PBMCs was diminished in subjects with severe as opposed to mild-moderate asthma.30 IL-1β, IL-8, and macrophage inhibitory protein 1α were the least suppressed by corticosteroids in these patients and could explain a more active innate and even neutrophilic process, as has previously been observed in severe asthma.31 Finally, the levels of nuclear histone deacetylase (HDAC) were also lower in the severe asthmatic PBMCs than in cells from the subjects with milder asthma and normal controls (Fig 3). Through effects on gene regulation, HDAC activity has been associated previously with poor responsiveness to corticosteroids in both subjects with asthma and subjects with COPD.32,33 These findings may explain a common mechanism for at least some of the corticosteroid refractoriness seen in the both asthma and COPD.

Lipoxins, like corticosteroids, are naturally occurring mediators, formed from interactions between products of the 5-lipoxygenase and 15-lipoxygenase enzymes, which are believed to have potent anti-inflammatory effects. Previous studies have suggested that lipoxin A4 levels are diminished in sputum from subjects with severe compared with milder asthma.34 In studies from Brigham and Women’s Hospital, serum lipoxin A4 levels, present in low picogram amounts, were found to be lower at baseline in subjects with severe asthma compared with milder asthma. In activated whole blood, mean lipoxin A4 levels were decreased in severe compared with moderate asthma.
(0.4 [SD, 0.4] ng/mL vs 1.8 [SD, 0.8] ng/mL; \( P = .001 \)). In sharp contrast, mean levels of cysteinyl leukotrienes were increased in samples from severe compared with moderate asthma, altering the balance in the direction of leukotrienes. This imbalance in lipoxygenase-derived eicosanoid biosynthesis also correlated with the degree of airflow obstruction. Although additional studies of lung fluid are needed, these results support the deficiency of additional anti-inflammatory elements such as lipoxins in maintaining the chronic inflammatory state of asthma, and severe asthma in particular.

**Epithelial cell responses in severe asthma**

Studies primarily from Washington University provide evidence of abnormal epithelial and lamina reticularis thickening in subjects with severe asthma in comparison with mild-moderate asthma, chronic bronchitis, and normal controls. Those studies suggest that in severe asthma, the airway epithelium decreases or completely shuts off retinoblastoma expression, which is believed to be indicative of a proliferative response. Although the trigger for this proliferative response is not identified, prime candidates include viral infection or other forms of chronic injury. Interestingly, in concert with this proliferation, there was increased epithelial apoptosis and decreased cell death suppression, as demonstrated by a decrease in B-cell lymphoma/leukemia-2 (Bcl-2). This death response in the airway epithelium could also be promoted by proapoptotic factors or viral infection resulting in epithelial desquamation and damage. The role of this unchecked proliferative response in the airway obstruction associated with asthma requires further study.

**BRONCHOSCOPIC, IMAGING, AND GENETIC STUDIES**

Bronchoscopic studies of subjects with severe asthma have been performed only in limited sites and with limited safety data available. One of the primary tasks of SARP was to confirm that it was possible to sample the lungs safely in subjects with severe asthma compared with subjects with less severe disease. To confirm the safety of bronchoscopy in the severe asthma population, rigorous standards were developed for the performance of bronchoscopy across sites. To date, the safety of bronchoscopy in more than 60 subjects with severe asthma compared with nearly 100 subjects with mild-moderate asthma has been evaluated. Although adverse events were more common in severe asthma, including more prolonged shortness of breath and need for \( \beta \)-agonists (and systemic corticosteroids) in severe asthma compared with milder asthma, the overall incidence of severe adverse events (and their level of severity) was low.

No studies have yet been published comparing the pathology of mucosal biopsies across sites. However, given the large numbers of samples available, the centralized processing and analysis, and the extensive phenotypic characterization of the subjects, comprehensive data will soon be reported. This should prove valuable, because there is currently considerable variability in the literature regarding pathologic markers for severe asthma. Although a predominance of neutrophilic inflammation has been reported in severe compared with milder asthma, this finding is not always seen. Other than increased TGF-\( \beta \) expression in subjects with severe asthma, no studies have consistently demonstrated increases in specific cytokines, chemokines, or other factors. In fact, differentiation of asthma on the basis of the presence or absence of airway eosinophils (or neutrophils) has been suggested to be helpful in addressing specific phenotypes of asthma and severe asthma. The uniformity of procedures across centers and the overall size of SARP will allow sufficient power to distinguish phenotypes and the associated immunopathologic processes and genotypes better. In addition to bronchoscopy, 50% of the sites are also performing sputum induction and analysis, which will eventually allow comparison of the 2 approaches to airway evaluation.

**Imaging**

Computed tomography (CT) scanning has increasingly been recognized as a method to evaluate airway structural and parenchymal changes in lung disease. With the ability to digitize and quantify the images, objective assessment of both the airways and parenchyma have become possible. Although the airways have widely been reported to be thickened in asthma, and increasingly so in severe disease, much remains to be learned regarding the relationship of airway and parenchymal disease. In SARP, CT scans have been performed at half of the sites using a predefined protocol and analysis through Dr Eric Hoffman and the University of Iowa. More than 100 scans have been preliminarily evaluated, at functional residual capacity and total lung capacity, for objective analysis of both the airways and the parenchyma. Limited data have been presented at the ATS meeting in 2006, focusing specifically on the parenchymal changes, as recorded by overall degree of hyperlucency. Airway wall and luminal studies are in progress.

The distribution of CT hyperlucency scores in severe asthma suggests the existence of 2 subgroups, those with air trapping and those without. Air trapping in the lung parenchyma, measured as the number of CT image voxels (the smallest volumetric image measurable by CT scanning), \(< 850 \text{ Hounsfield units} \), a measure of voxel density, was evaluated. Subjects with 10% or more of their total lung density at the hyperlucent/air trapped level of \(< 850 \text{ Hounsfield units} \) were compared with those with \(< 10\% \) of their lung in this range. The existence of air trapping at functional residual capacity was greater in severe asthma and was associated with longer duration of disease, a greater incidence of severe/ICU exacerbations, and a lower FEV\(_1 \) (% predicted). Asthma with air trapping also had lower midrange flows (forced expiratory flow at 25% to 75% of forced vital capacity % predicted), suggesting more distal airways disease and greater numbers of neutrophils in sputum and bronchoalveolar lavage fluid.

In the future, studies from SARP will identify and characterize regional air trapping and its relationship to fixed
and dynamic airway wall and luminal dimensions. It is likely that the findings of imaging, similar to those of age at onset, may allow for identification of key subpopulations in asthma and severe asthma. Future studies will use the size of the SARP population and the extensive nature of the studies being performed to link genetic and pathobiologic processes to these clinical and radiologic phenotypes.

Genetics

Although other population studies of cross-sections of populations with asthma have suggested that polymorphisms in IL-4, IL-4 receptor α, TGF-β1, and a detensin and metallopeptinase (ADAM)-33 are linked with severity of disease, lower lung function, or severe exacerbations of asthma, SARP is the first patient database to focus specifically on the severe asthma subgroup. This focus allows the recruitment of large enough numbers of subjects to conduct meaningful genetic association studies. The Wake Forest University site serves as the genetics data center for SARP and has now processed more than 600 samples. However, in addition to simple association studies, the depth of the SARP data allows for a number of additional evaluations. First, with another 5 years of recruitment and well more than 1000 subjects with asthma (500 or more of whom will have severe disease), genotype analysis can be applied to the severe asthma phenotypes identified in some of the pathobiologic studies. Because the vast majority of subjects will have lung cells and tissue in addition to the usual serum/plasma, many of the genetic findings can be further evaluated at the functional level. Using both the pre-SARP and SARP National Jewish and the non-National Jewish SARP cohort, studies have been reported to suggest that previously identified polymorphisms in IL-4 receptor α are linked with both a high level of severe (intensive care unit/intubation) exacerbations and lower FEV1.43 Uniquely, in the large numbers of subjects studied by bronchoscopy over the years at National Jewish, these same polymorphisms were associated not only with lung function and exacerbations but also with mast cell numbers and their phenotypes in the airway tissue. The large (hundreds) of bronchoscopies performed with standardized acquisition and analysis will allow further studies to explore mechanisms by which certain genotypes may influence severe asthma phenotypes.

CONCLUSION

Severe asthma remains poorly understood. It is likely that some of the reasons for this lack of information relate to the multiple phenotypes that contribute to this overall population of patients with asthma. The presence of networks such as SARP (and others in Europe) will provide both the numbers of subjects and the depth of analysis required to elucidate the pathobiologic and genetic mechanisms behind these phenotypes and eventually to improve their treatment.

REFERENCES


