

Severity and control of severe asthma

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In national and international guidelines, the term *severe asthma* applies to patients who have regular, almost daily symptoms of asthma, requiring frequent doses of rescue β_2 -agonist, with significant impairment of lung function. If already on inhaled corticosteroid, a lesser level of any of these features places patients in this category.^{1,2} According to convention, the *severity* of a disease is considered to be a property of the disease, reflecting the grade of pathophysiologic abnormality, whereas *control* refers to reduction of the clinical manifestations of disease achieved with treatment, and reflects adequacy of treatment. The distinction between severity and control is complicated in asthma because, as argued by Stoloff and Boushey³ in their paper in this issue, a third element, responsiveness to corticosteroids, relates to treatment but serves as one of the defining characteristics of severe asthma. This complex relationship is well illustrated in the Gaining Optimal Asthma Control (GOAL) study, in which an attempt was made to achieve complete control of asthma in all subjects by using increasing doses of inhaled corticosteroids.⁴ At study entry, three-quarters of patients fulfilled the criteria for severe asthma, and two-thirds were on low (<500 μ g) or medium doses of inhaled corticosteroids (500-1000 μ g beclomethasone dipropionate or equivalent/d). Control was assessed using 2 composite measures with clinical and spirometric endpoints (total and well controlled) based on guideline goals of treatment. As expected, the proportion of patients achieving either level of control at the end of the study (after 12 months of dose escalation to a maximum of fluticasone 1000 μ g/d or the combination of salmeterol and fluticasone 1000 μ g/d) was lowest in those previously on inhaled corticosteroids. With fluticasone, total control was achieved in 40% of steroid-free patients, in 29% of those previously on low-dose corticosteroid, and in only 16% of those previously on medium doses of inhaled corticosteroid. The definition of well controlled asthma was fulfilled in 70%, 60%, and 47%, respectively, in the 3 groups. In those who did not achieve either of these levels of control—

Abbreviations used

ATS: American Thoracic Society

GC: Glucocorticoid receptor

that is, who demonstrated refractoriness to inhaled corticosteroids—administration of a 2-week course of prednisone at the study end enabled a small percentage of these refractory patients to achieve the target levels of control.⁴ These results confirm that refractoriness to both inhaled corticosteroids and systemic asthma is common in severe asthma.

The GOAL study illustrates 2 other features of corticosteroid refractoriness. First, refractoriness is relative and seldom complete. Although almost a half of patients with severe asthma did not achieve the definition of well controlled asthma, even with high doses of inhaled corticosteroids, almost all patients demonstrated significant clinical improvement in 1 or several conventional clinical endpoints and health status. Second, relative refractoriness to inhaled steroids does not indicate refractoriness to other controller drugs. Approximately 10% more patients responded (were not refractory) to salmeterol/fluticasone than to fluticasone alone, providing encouragement that refractoriness may be overcome by use of combinations of controllers and that there is scope for development of new treatments to supplement the role of corticosteroids in severe corticosteroid-refractory asthma.⁴

Stoloff and Boushey³ also point to the need to consider what they term “future risk” in asthma—the tendencies to develop permanent limitation of airflow and to experience severe life-threatening exacerbations, both of which are features of severe asthma and might on occasions not be predicted from interval assessments of control. The latter is more likely in patients in whom treatment is suboptimal and control only partial as in refractory asthma. In general, however, and even in refractory asthma, there is a strong inverse relationship between assessed levels of control and the frequency of severe exacerbations.^{3,5} Methods for identifying patients at risk of unpredictable attacks are required, and patients with these tendencies deserve special status as subgroups of severe asthma.

The challenge of defining subgroups or clinical phenotypes in severe asthma, which is thought to represent approximately 10% of patients with asthma, has been addressed by task forces from both the American Thoracic Society (ATS)⁶ and the European Respiratory Society.⁷ Termed “refractory asthma” by the ATS Taskforce and “difficult/treatment refractory” asthma by the European

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Respiratory Society, both groups identified the need for a special approach to such patients in terms of clinical investigation and treatment, and for gaining understanding of differences in pathophysiology and potential for developing new treatments. Task force recommendations for treating these patients are described in the articles by Moore and Peters⁸ and Wenzel and Szefer⁹ in this issue, and include confirming the diagnosis of asthma (excluding vocal cord dysfunction, chronic obstructive pulmonary disease, and other similar diagnoses), addressing aggravating factors and comorbidity (for example, gastroesophageal reflux, sinusitis, and psychiatric comorbidity), and checking all aspects of previous and current therapy (ensuring correct dosing, adherence, inhaler technique, understanding and use of medicines). Adjustments to treatment include the options of a trial of oral corticosteroids, the addition of other forms of controller treatment (leukotriene inhibitors, methylxanthines, anti-IgE therapy), and treatments with more doubtful efficacy (anti-TNF α therapy,¹⁰ methotrexate, cyclosporine, rapamycin, and macrolides). In general however, gains from these additional treatments are small, but they can be significant if they spare patients the complications of long-term use of high doses of corticosteroids or reduce life-threatening events.

Further progress in distinguishing phenotypes of severe asthma has come from examination of pathology, pathophysiology, and pharmacogenetics. Progress in this field has been substantial and is reviewed in several papers in this issue of the journal.¹⁰⁻¹³ The CD4⁺ T-helper lymphocyte is viewed as the pivotal cell type in mediating airway inflammation in asthma. Dysregulation of cytokine production by mononuclear cells associated with reduced suppression by corticosteroids has been observed in corticosteroid-refractory asthma.¹⁰⁻¹² Gelfand and Dakham¹³ draw attention to a small subset of CD8⁺ effector memory T lymphocytes (accounting for less than 1% of cells in bronchoalveolar lavage fluid but present in the airway submucosa) that may be relatively resistant to the effects of corticosteroids and play an important role in the maintenance and progression of asthma. These cells are attracted to the site of inflammation by leukotriene B₄, for which they have a high-affinity receptor, and are an important source of IL-13, a key mediator of ongoing allergic inflammation and mucus hypersecretion.¹³

Studies of inflammatory cell profiles in sputum and bronchoalveolar lavage fluid in severe asthma and their relationship with corticosteroid refractoriness have not yielded consistent results.^{8-10,12-15} Although elevated sputum eosinophil levels may be found in severe and treatment-refractory asthma, the frequency and levels of airway eosinophilia are not significantly different in mild-moderate versus severe asthma.¹⁶ On the other hand, strong associations between neutrophilic inflammation of the airways and both severe and corticosteroid-refractory asthma have been described. It has been speculated that in some patients, neutrophils may gradually replace eosinophils during treatment, because corticosteroids are less effective in reducing or even facilitating the arrival and survival of neutrophils in asthmatic airways.^{10,15}

However, the overall inconsistency of results in these studies suggests that inflammatory cells are at most contributory rather than central to the mechanisms responsible for refractory asthma.

Other potential reasons for corticosteroid refractoriness are changes in the complex pathways through which glucocorticoids are processed and exert their action.¹² In their comprehensive review of the molecular basis for corticosteroid action, Ito et al¹² draw attention to several potential mechanisms for resistance to glucocorticoids in asthma. At a molecular level, these include reduced numbers of glucocorticoid receptors (GC) in inflammatory cells, altered affinity of the ligand for GC, and reduced ability of the GC to bind to DNA or competition from inflammatory transcription factors for binding with DNA. The significance of these observations is that they open possibilities for interventions aimed at reversing corticosteroid refractoriness. Another possibility raised by the study of these mechanisms of action of corticosteroids is the prospect of developing molecules with the favorable properties of corticosteroids and improved safety. Most of the major anti-inflammatory effects of glucocorticoids are achieved by mechanisms classed as transrepression that suppress the production of inflammatory mediators. By contrast, the basis for the development of at least some of the side effects of corticosteroids, like glucose intolerance and glaucoma, involves transactivation. There is therefore the prospect of developing dissociated corticosteroids in which only anti-inflammatory are retained. Several nonsteroidal selective glucocorticoid receptor agonists are now in development.¹²

It should be apparent from these reviews of mechanisms in severe refractory asthma why detailed investigation and clinical phenotyping of each patient is essential. This should preferably be supervised by a health professional with special expertise in asthma management. The clinical characterization usually involves several visits and a sequence of investigations and trials of therapy, with careful monitoring of the effects of therapy, preferably using a validated instrument like the Asthma Therapy Assessment Questionnaire,⁵ the Asthma Control Test,¹⁷ or the Asthma Control Questionnaire.¹⁸ These provide numerical values for control and serve as sensitive indicators for the assessment of the effects of treatment. Recent reports on the clinical utility of measurements of exhaled nitric oxide^{8,19-21} and induced sputum examination^{8,22} in corticosteroid-responsive asthma confirm their value in establishing clinical phenotypes and in guiding selection of appropriate doses of treatment. Although their role in the management of refractory asthma has not been tested in a randomized trial, they are widely used and may be considered standard practice in these patients.

The new American Academy of Allergy, Asthma and Immunology and American College of Allergy, Asthma and Immunology practice parameter recommendation for the management of asthma is that treatment decisions be driven by assessments of control with the goal of achieving and maintaining control.²³ Although this objective is realistic for the majority of asthma patients

including those with severe asthma, a significant proportion will not achieve this goal of control. Research into the clinical phenotypes and mechanisms of disease in this group of patients is relatively new but has provided many important insights and promise of treatments to supplement inhaled corticosteroids to which these patients are partially refractory. The reviews in this edition of the Journal provide a valuable record of progress in this field.

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