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Understanding the pathophysiology of severe asthma to generate new therapeutic opportunities

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Although asthma is defined in terms of reversibility of airflow obstruction, as the disease becomes more severe and chronic, it adopts different characteristics, including a degree of fixed airflow obstruction and corticosteroid refractoriness. Underlying these phenotypes is evidence of airway wall remodeling, which should be distinguished from the increase in smooth muscle linked to airways hyperresponsiveness. Aberrant epithelial-mesenchymal communication leads to a chronic wound scenario, which is characterized by activation of the epithelial-mesenchymal trophic unit, epithelial damage, the laying down of new matrix, and greater involvement of neutrophils in the inflammatory response. In allergic asthmatic patients who remain symptomatic despite high-dose corticosteroid therapy, blockade of IgE with omalizumab confers appreciable clinical benefit. Chronic severe asthma is also accompanied by a marked increase in TNF-α production that might contribute to corticosteroid refractoriness. Based on this, TNF blockade with the soluble fusion protein entanercept produces improvement in asthma symptoms, lung function, and quality of life paralleled by a marked reduction in airways hyperresponsiveness. Identification of novel susceptibility genes, such as a disintegrin and metalloprotease 33 (ADAM33), will provide further targets against which to direct novel therapies for asthma, especially at the more severe end of the disease spectrum. (J Allergy Clin Immunol 2006;117: 496-506.)

Key words: *Severe asthma, airway remodeling, tumor necrosis factor, etanercept, anti-IgE, omalizumab, a disintegrin and metalloprotease 33, airway responsiveness, new treatments*

Abbreviations used
ADAM: A disintegrin and metalloprotease
APP: Amyloid precursor peptide
BAL: Bronchoalveolar lavage
BHR: Bronchial hyperresponsiveness
COPD: Chronic obstructive pulmonary disease
ECM: Extracellular matrix
EMTU: Epithelial-mesenchymal trophic unit
LABA: Long-acting β_2-agonist
LTRA: Leukotriene receptor antagonist
SNP: Single nucleotide polymorphism
TIMP: Tissue inhibitor of metalloprotease

Asthma is a disorder of the conducting airways characterized by T_H2-mediated inflammation and enhanced mediator release. In mild disease the inflammatory response, attendant bronchial hyperresponsiveness (BHR), and variable airflow obstruction are highly responsive to inhaled corticosteroids, positioning these drugs as first-line controller therapy for this disease. However, in persistent and severe asthma inhaled corticosteroids are only partially effective, and patients often require intermittent or continuous oral corticosteroids. This severe end of the disease spectrum accounts for approximately 10% of the asthmatic population.[1] It is these patients who have the highest morbidity and mortality and account for approximately 30% of the health cost of this disease through unscheduled doctor visits, hospital admissions, and corticosteroid side effects. Although a wide range of other treatments are used in these patients that include cytotoxic agents and nebulized bronchodilators, these are of variable benefit, with appreciable side effects.[2] Thus severe corticosteroid-refractory asthma represents a major unmet clinical need.[3]

Because of difficulty in accessing the airways in patients with severe asthma, it is only recently that additional insight has been gained into the underlying

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mechanisms that separate refractory asthma from that which is highly corticosteroid responsive. The first important point to note is the level of heterogeneity of severe disease.[2] On the one hand, there is extensive evidence of inflammation spreading to involve all the airways, including the most peripheral, with some alveolar involvement,[4] whereas on the other hand, there are cases in which there is scant evidence of inflammation but an increase in smooth muscle, extensive remodeling of the airway epithelium and walls, or both[2] and also many intermediate phenotypes. As the disease adopts a more chronic phenotype, despite high-dose inhaled corticosteroids, the degree of bronchodilator reversibility becomes progressively impaired because of a combination of matrix deposition and reduced access of inhaled aerosols to airways obstructed by mucus and cell debris. When inflammation is present, its character also changes to involve neutrophils either alone or in addition to eosinophils.[5,6] It had been widely thought that the neutrophilia was the result of chronic corticosteroid therapy. Although oral (but not inhaled) corticosteroids induce a circulating and sputum neutrophilia,[7] presumably through their capacity to release neutrophil precursors from the bone marrow and their capacity to inhibit apoptosis, there is increasing evidence that in severe asthma the neutrophils are in an activated state and therefore likely to contribute to tissue damage.[8]

Longitudinal cohort studies have established that a proportion of severe asthma has its origins in childhood and tracks throughout life.[9,10] A combination of computed tomographic imaging and bronchial biopsy studies have shown that severe asthma in childhood also exhibits features of airway remodeling,[11] comprising epithelial injury and matrix deposition,[12] as well as eosinophilic-neutrophilic inflammation.[13] These findings, which occur early in the natural history of severe asthma, indicate that genetic and environmental factors might exert their effects early in life,[14] although in wheezing babies evidence of remodeling is not present.[15]

When compared with mild disease, severe asthma has a number of associated features that include high prevalence of sinusitis, intolerance to nonsteroidal anti-inflammatory drugs, increased body mass index, and psychiatric disorders.[2,5,16] Early-onset severe asthma has a high incidence of accompanying atopy with associated disorders, such as eczema, food allergy, and rhinitis,[17] whereas late-onset asthma is characterized by less atopy[6] but a greater association with occupational exposures[18] and a clinical presentation that is frequently confused with that of chronic bronchitis with frequent infectious exacerbations.[19]

From a clinical perspective, lack of adherence to treatment is an important cause for increased asthma severity. There is now strong evidence that a high proportion of patients with severe disease can see improvement through attention to treatment adherence.[20] Asthma guidelines recommend a combination of an inhaled corticosteroid and a long-acting β_2-agonist (LABA), usually administered twice daily.[21] The clinical trial base for this approach is extensive, although for some patients, the replacement of a LABA with a leukotriene receptor antagonist (LTRA) or the addition of an LTRA[22,23] produces further benefit, especially in those patients shown to be intolerant to nonsteroidal anti-inflammatory drugs.[24] There is little doubt that the uptake of inhaled corticosteroids is the principal factor in the decreasing asthma mortality in countries in which this has been observed,[25] although recently some concerns over the widespread use of inhaled LABAs, as well as short-acting β_2-agonists, have emerged.[26] As a rule, LABAs should not be used without an inhaled corticosteroid, and in children with severe asthma, in whom LABAs are reportedly less effective,[27] an LTRA is frequently effective.

Although there continues to be an ongoing debate about the principal mechanisms of corticosteroid-refractory asthma, several abnormalities have emerged.[28] These include the capacity of certain cytokines, such as TNF-α and IL-1β, to activate p38 mitogen-activated protein kinase, thereby interfering with nuclear localization of glucocorticosteroid receptors,[29] reduced acetylation of a lysine residue in histone 4 leading to impaired activation of anti-inflammatory genes,[30] and cytokine induction of an alternatively spliced variant of the glucocorticosteroid receptor (β-variant) that is capable of binding to DNA but not to corticosteroids, thereby acting as a dominant-negative inhibitor.[31,32] Of considerable interest is the recent finding that tobacco smoking markedly impairs corticosteroid responsiveness in asthma,[33] although responsiveness to other controller therapies, such as LTRAs, are said to remain intact.[34] The most likely mechanism that explains this is reduced histone deacetylase activity, as recently described in corticosteroid refractoriness in chronic obstructive pulmonary disease (COPD).[35]

The recognition that current asthma therapy is failing to control the disease in a significant proportion of patients with severe asthma has created an opportunity for novel therapeutic approaches. Although a number of strategies targeting therapy at specific aspects of the inflammatory response, such as IL-4, IL-5, and IL-10, have not resulted in the predicted clinical benefits,[36] there is a reason to be optimistic about some new approaches both in controlling severe chronic asthma and in preventing exacerbations.

TARGETING IgE

IgE has long been known as a major therapeutic target in atopic disease after its discovery in 1967; however, only recently has this become possible in severe atopic asthma with the introduction of neutralizing IgG biologic agents targeted to that part of the IgE molecule that interacts with the high- and low-affinity IgE receptor. Once it was shown that anti-IgE therapy was highly effective at reducing free IgE in the circulation by forming small complexes,[37] the way was open to generate a therapeutic agent that could be used in severe allergic asthma. The result was omalizumab, an IgG1 mAb administered once or twice monthly as a subcutaneous injection. Extensive clinical trials have confirmed the efficacy of omalizumab in severe allergic asthma, both in increasing disease control and reducing