SYNDROMES OF SEVERE ASTHMA

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INTRODUCTION

Asthma is a disease of the respiratory system characterized by hyper-responsiveness to bronchoconstructing stimuli, inflammation, and changes to the respiratory epithelium. Although it is estimated that 5-7% of the population of Europe and North America are affected by asthma in most of these individuals the disease is mild and easily managed. In a subset of asthmatics however the disease process is either refractory to therapy or requires persistent utilization of systemic anti-inflammatory medication, usually corticosteroids, in order to maintain reasonable control of symptoms. These patients have been referred to in the literature as having "severe asthma", "steroid-dependent asthma", "difficult to control asthma", "poorly controlled asthma", "brittle asthma", "irreversible asthma", or "steroid-resistant asthma" though the latter term is thought to represent a distinct entity by some experts. Both the American Thoracic Society and the European Respiratory Society are currently working on definitions to encompass these terms and "refractory asthma" may emerge as the over-arching phrase to encompass such patients (1, 2).

Depending on the definition utilized it is thought that anywhere between 1-15% of asthmatics would fit the criteria for severe asthma. It is likely that a significant and disproportionate amount of the estimated $6.2 billion spent in the United States on asthma care each year is accounted for by such patients. This review will concentrate on recent developments in the study of patients with severe asthma, specifically several clinically distinct syndromes of severe asthma including steroid resistant asthma, Chürg-Strauss syndrome, aspirin related syndromes of asthma which may be severe, and allergic bronchopulmonary aspergillosis (ABPA). Although any seriously ill patient with an exacerbation of asthma might be considered to have "severe" asthma, patients with "asthma in extremis" will be viewed as a separate group for the purposes of this discussion and will be covered only as pertinent.

Definition of Severe Asthma

The Expert Panel Report II "Guidelines for the Diagnosis and Management of Asthma" was released by the National Heart Lung Blood Institute in February, 1997. It classified asthma severity into four distinct groups based on symptoms, lung function, and use of short acting beta-2 agonists (Table 1) prior to the onset of optimal therapy. Patients with severe persistent asthma have continual symptoms and evidence of moderate-severe obstructive lung disease on pulmonary function testing. However many of these patients respond well to inhaled corticosteroids and a long acting inhaled B2-agonist. As such it is likely that the NIH guidelines would over-estimate the prevalence of severe asthma. A study in young male Israeli military recruits found that 6% had asthma but only 1% of these individuals were considered steroid dependent with an FEV1 <50% predicted (3). A study in Australia which defined severe asthma as severe hyper-reactivity to a low dose of inhaled histamine found that 12% of asthmatics evidenced severe asthma (4).

TABLE 1

Classification of Asthma Severity

	Mild Intermittent	Mild Persistent	Moderate Persistent	Severe Persistent
Frequency of symptoms	≤2x wk	>2x wk <1x day	Daily	Continual
Exacerbations	Brief/mild	May affect activity	Affects activity	Frequent/ severe
Nighttime asthma symptoms	≤2x mo	>2x mo	>1x wk	Frequent
Lung function				
FEV_1 or FEF	>80%	≥80%	>60<80%	≤60%
% PEF variability	<20%	20% to 30%	>30%	>30%

While a precise definition of "severe" or refractory asthma is difficult the current attempts by the ATS and ERS are likely to encompass prior efforts to define this entity but stress the amount of medication necessary to treat the patients on a chronic basis. As such for the purposes of this discussion severe asthma will be considered to be present in patients who require 10 mg/day of Prednisone or more to control their disease on a chronic basis or those individuals who require unusually high doses of inhaled corticosteroids (for example >1500 µg/day of inhaled fluticasone (Flovent)).

The Phenotype of Patients with Severe Asthma

A recent study in Europe, which will be presented at the 1999 ATS Meeting (5, 6), was conducted by ENFUMOSA (European Network for Understanding Mechanisms of Severe Asthma). Patients with severe asthma treated with >1500 µg/day of inhaled steroids for one year with either a) one course of oral steroids during the previous year; b) daily use of <5 mg/day Prednisone; or c) history of one or more near fatal attacks during the past 5 years were compared to patients with stable asthma on <1000 µg/day inhaled steroids. All patients had a smoking history of <5 pack years. The study was conducted in the outpatient clinics of 13 specialized hospitals in 9 European countries (Table 2). One hundred seventy-eight patients with severe asthma were compared to 149 stable asthmatics. Several striking clinical features were observed. First a disproportionate number of patients with severe asthma were women (RR 2.67 (1.57-4.55) $p<0.001$). More asthma triggers were identified in the severe asthma group ($p<0.01$) as were more frequent hospitalizations ($p=0.001$). Women with severe asthma had an increase in asthma symptoms associated with sinusitis and their pre-menstrual

period. Men had an increase in symptoms related to exercise. In both men and women aspirin induced exacerbation of symptoms was significantly more frequent in severe asthmatics (RR 4.61 and 3.53 respectively).

TABLE 2

Clinical Characteristics of Severe Asthma (Compared to Mild Asthma)

Women (79%)	RR 2.67 p<0.001
Number of triggers	p=0.01
Sinusitis	RR 4.14
Aspirin	RR 3.53
Pre-menstrual period	RR 3.97
Men	
Exercise	RR 6.03
Aspirin	RR 4.61

- Holgate, et al
ENFUMOSA, 1999 ATS Meeting

Attempts to characterize the airway histology and inflammatory cell profile in the lower respiratory track of patients with severe asthma have been made by a number of investigators with somewhat conflicting results. The inflammatory process in asthma is generally thought to be characterized by marked airway eosinophilia driven by cytokines such as IL-4, IL-5 and other mediators associated with allergic responses (see below). However some investigators have suggested that a neutrophilic inflammatory process may predominate in severe asthmatics (7-10). Wenzel and colleagues reported an increase in airway neutrophils obtained by bronchoscopy in patients with severe asthma on oral corticosteroids as compared to patients with mild/moderate asthma. Similar findings have been described in patients with acute episodes of status asthmaticus. However these studies are complicated by a number of super-imposed variables including the fact that corticosteroids are known to inhibit neutrophil apoptosis (11). A recent study from San Francisco found no evidence for an increase in sputum neutrophils, an accepted mirror of bronchial lavage in asthmatics, in a group of patients with chronic severe asthma (12).

It is widely thought that one of the hallmarks of severe asthma is an irreversible "remodeling" of the airways characterized by changes in the type and amount of smooth muscle, thickening of the sub-basement membrane and alterations in the glandular components of the airway (13-16). However the few studies conducted to date suggest that a thickened sub-basement membrane is found in all asthmatics and that collagen-derived fibrosis does not differ in severe asthmatics. Similar studies looking at enzymes potentially involved in airway remodeling such as matrix metalloproteinase 2 and 9 have

also failed to distinguish between severe and mild asthma (17). Studies evaluating levels of IL-4, GM-CSF and TGF-B in severe asthma have at times suggested a difference from milder forms of the disease but the data is not clear cut.

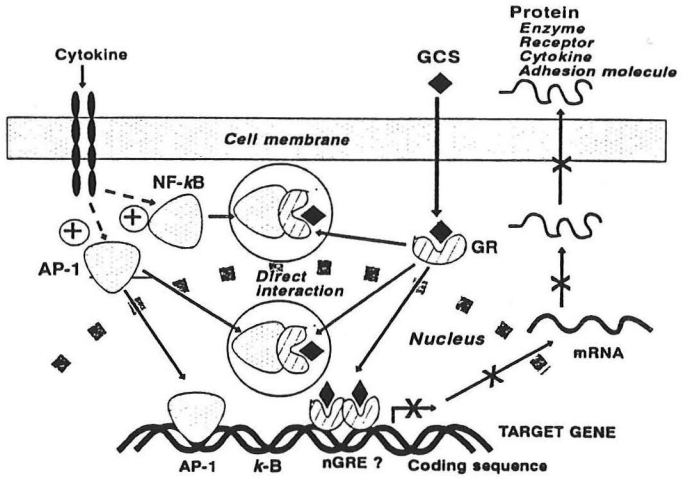
Pathogenesis of Asthma and the Response to Steroids

Severe asthma in large part is defined by a failure to respond to routine doses of inhaled corticosteroids. Therefore it is important to review current data regarding the pathogenesis of asthma and the mechanisms by which both inhaled and systemic corticosteroids impact the manifestations of the disease process.

Asthma, including severe asthma, is a multi-factoral process in which both genetic and environmental factors play a role. Numerous mediators of inflammation including pro-inflammatory cytokines, adhesion molecules, nitric oxide, and leukotrienes are likely to interact to produce the clinical spectrum of asthma. In addition polymorphisms in β2 adrenergic receptors, selective deficiencies in "anti-inflammatory" cytokines such as IL-10, and alterations in signaling proteins involved in modulating the effects of pro-inflammatory or anti-inflammatory cytokines in respiratory epithelium have also been implicated in the pathogenesis of asthma (18, 19). Nevertheless many investigators interested in asthma continue to focus on the role of a stereotypical response to allergens or antigens as being central to the pathogenesis of asthma.

In this hypothesis a T cell response to foreign antigen results in a cascade of inflammatory events resulting in the up-regulation of cytokines capable of recruiting additional inflammatory cells, expression of adhesion molecules which facilitate transmigration of these cells to the site of disease, and the production of pro-inflammatory enzymes such as inducible nitric oxide synthase (iNOS) and inducible cyclo-oxygenase (COX-2). The end-organ effects of "asthmatic cytokines" rely on the up-regulation of transcriptional activity for the downstream participants in the inflammatory cascade (Figure 1). Central to this up-regulation of gene transcription in asthma is believed to be two transcription factors, nuclear factor-Kappa B (NF-κB) and activator protein-1 (AP-1). The anti-inflammatory mechanism of corticosteroids in asthma is integrally linked to the interaction of the glucocorticoid receptor (GR) with these transcription factors (20-22).

FIGURE 1



Direct interaction between the transcription factors activator protein-1 (AP-1) and nuclear factor-kappa B (NF-κB) and the glucocorticoid receptor (GR) may result in mutual repression.

- Barnes et al
Am J Respir Crit Care Med 1998;157:S1-S53

Recent data has greatly elucidated the cytokines which are likely to play a key role in the asthmatic response (23-26). Utilizing a well characterized model of asthma produced in transgenic mice who develop airway hyper-responsiveness (AHR) and histological evidence of asthma in their airways following repeated exposure to ovalbumin, the cytokines involved in initiating asthma have been clarified.

Because of the critical role that IL-5 plays in the development of eosinophilia and the supposition that much of the asthma phenotype is related to airway eosinophilia, early attention focused on the impact of IL-5 in this model. Although a role for IL-5 in asthma may still be present the bulk of the data suggests that it is not responsible for the development of AHR or goblet cell hyperplasia, two key features of asthma. Using blocking antibodies to IL-5, antibodies to the IL-5 receptor, or transgenic mice incapable of producing IL-5 eosinophilia has been attenuated but not AHR or the non-eosinophil airway histology of asthma.

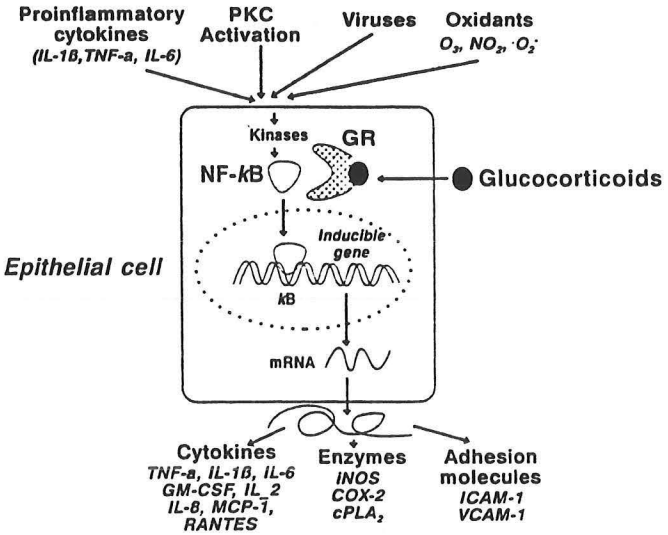
Interleukin-4 plays a central role in atopic responses. Antibodies to the IL-4 receptor have greatly attenuated the development of asthma in this model. However it was observed that when knockout mice incapable of making IL-4 were utilized that AHR and airway histology were only modestly attenuated. These observations have now been explained by the finding that IL-13, a cytokine closely related to IL-4, is capable of producing the asthma phenotype in this model. Both IL-13 and IL-4 utilize the alpha chain of the IL-4 receptor (IL-4Rα). Administration of blocking antibody to IL-13 significantly attenuates the development of asthma in this model. More importantly mice which lack IL-4Rα do not develop asthma even when exogenous IL-13 or IL-4 are

administered. Thus it would appear that IL-13 and IL-4 mediate the asthma phenotype through the IL-4Rα chain. Neither eosinophil number or IgE levels in airway are controlled through this pathway however. Linkage analysis studies have suggested that susceptibility to asthma maps to a region on human chromosome 5q25-31 which includes the genes for IL-4 and IL-13 as well as domains of IL-4Rα. Genes on other chromosomes are also likely to participate in the development of asthma.

Mechanism of Action of Glucocorticoids in Asthma

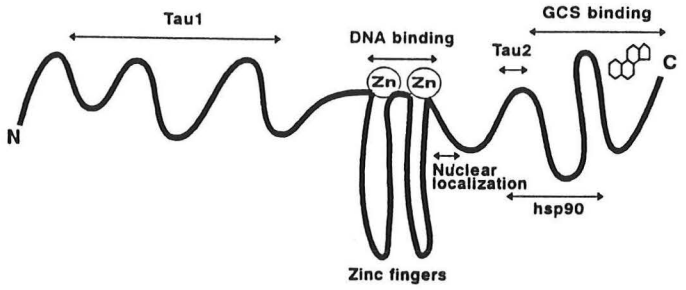
Glucocorticoids bind to glucocorticoid receptors (GR) which are present in the cytoplasm of respiratory cells (Figure 2). There is no evidence that different subtypes of GR are present in patients with severe asthma, though a variant form of GR which binds to DNA but not steroids has been identified (27). In its inactive form the GR is bound to a protein complex of "molecular chaperones", including two 90KD heat shock proteins and a 59KD immunophilin, which prevent the unoccupied GR from translocating from the cytoplasm to the nucleus. Following binding with the glucocorticoid these chaperones dissociate and allow the GR to reach the nucleus (28-30). The steroid binding portion of the GR is at the C-terminal end of the molecule (Figure 3). The GR contains two "zinc fingers" which bind to DNA following interaction with steroids. Several domains within the GR are important for trans-activation of transcription once the molecule has moved to the nucleus.

FIGURE 2



- Barnes et al
Am J Respir Crit Care Med 1998;157:S1-S53

FIGURE 3



Structure of the glucocorticoid receptor. Glucocorticosteroids (GCS) bind to the C-terminal end of the molecule.

- Barnes et al
Am J Respir Crit Care Med 1998;157:S1-S53

Once "activated" by glucocorticoids the GR forms a dimer that binds to DNA sites called glucocorticoid response elements (GRE). The result may be either activation or inhibition of gene transcription (Table 3). GR may also interact with other transcription factors via "leucine zipper" interactions (31, 32). Indeed these interactions are central to the anti-inflammatory effects of glucocorticoids.

TABLE 3

EFFECT OF CORTICOSTEROIDS ON GENE TRANSCRIPTION

Increased transcription
- Lipocortin-1
- β_2-Adrenoceptor
- Secretory leukocyte inhibitory protein
- Clara cell protein-10 (CC10, uteroglobin)
- IκB-α
- IL-1 receptor antagonist
- Neutral endopeptidase

Decreased transcription
- Cytokines
  (IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, IL-11, IL-12, IL-13, TNFα, GM-CSF, RANTES, MIP-1, eotaxin, SCF)
- Inducible nitric oxide synthase (iNOS)
- Inducible cyclo-oxygenase (COX-2)
- Inducible phospholipase A_2 (cPLA-$_2$)
- Endothelin-1
- NK_1-receptors
- Adhesion molecules (ICAM-1, VCAM-1)

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Many cytokines involved in asthma exert their effect through NF-κB (33-35). The GR, once bound to glucocorticoid, is capable of binding NF-κB and preventing its translocation to the nucleus. In addition glucocorticoids may directly increase the production of IκB, the inhibitor of NF-κB. Interactions have also been described with AP-1, a transcription factor particularly important for activation of lymphocytes by IL-2 (36-38). Other interactions between GR and transcription factors include signaling from β2 agonists via CREB (cyclic AMP responsive element beta) and CREB-binding protein (CBP) though the clinical effect of these interactions in asthma is less certain (39-41).

Steroid Resistant Asthma

By its nature the syndrome of "steroid-resistant asthma" is somewhat circular in its definition. Some authors have attempted to quantify this syndrome both clinically and through an attempt to understand the pharmacokinetics of steroid resistance. Carmichael and colleagues (42) in 1981 proposed that the syndrome be defined as individuals who have a morning FEV1 <70% predicted, a significant improvement (15%) in peak flow (PEF) or FEV1 after the administration of bronchodilators, but a failure to improve their FEV1 or PEF after taking 20 mg per day of Prednisone for 7 days. More recent definitions have utilized a failure to improve FEV1 or PEF after 14 days of 40 mg per day of Prednisone. It is generally thought that only 25% of patients with severe asthma fit this definition of steroid resistance.

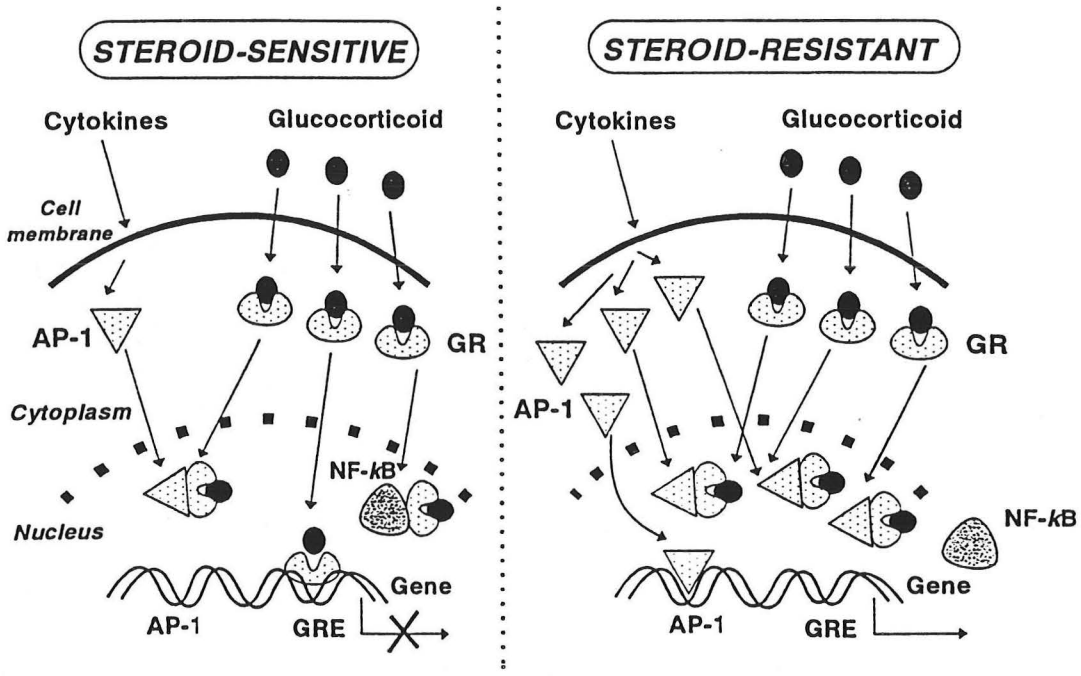
Several important observations about steroid resistant (SR) asthma have been made in recent years. First the clinical effects of "steroid resistance" are clearly confined to the lungs of SR patients. There is no evidence of Addison's disease, the patients have normal circulating cortisol and ACTH, and the syndrome is not associated with hypertension or signs of androgen excess (43). The rare syndrome of familial glucocorticoid resistance (44), a result of a point mutation in the GR in some patients, is not a predominant contributor to SR asthma.

Molecular characterization of the GR in these patients has failed to elucidate a difference from patients with steroid responsive asthma. Some investigators have attempted to divide SR asthma into two distinct types (45). Type 1 SR asthma is defined as a reduced affinity of the GR for steroids. This reduced affinity, which has been demonstrated using peripheral blood T cells from patients with SR asthma, normalized after 48 hours in culture suggesting the reduced affinity was acquired in the inflammatory milieu (both local and systemic) of asthma. Some investigators have suggested that the reduced affinity is secondary to IL-2 and IL-4, as the addition of these cytokines to culture of peripheral blood T cells from Type 1 SR asthmatics prevents the normalization of GR affinity for glucocorticoids (46).

Type II SR asthma is associated with a significantly decreased number of GR. This does not normalize with prolonged *in vitro* culture. These patients do not demonstrate elevated cortisol levels but are reported to have a lower incidence of steroid-related side effects, implying that patients with Type II SR asthma may have a true defect in steroid responsiveness.

More recently attention has focused on the role of transcription factors in SR asthma. The clearest data exists pertaining to altered function of AP-1 (47, 48). Normally AP-1 should be countered by the activated cytoplasmic GR (Figure 4). However there is evidence that hyper-activation of AP-1 may exist in SR asthma. These patients have been demonstrated to have increased activity of an enzyme, JNK kinase, which activates AP-1 by phosphorylating its components. The enhanced activity of AP-1 would result in a sequestering of the GR in the cytoplasm and thus block the anti-inflammatory effects on gene transcription mediated by glucocorticoids. Indeed a recent study suggests that SR asthmatics demonstrate enhanced phosphorylation of JNK and c-jun, a component of AP-1, following administration of steroids. In contrast steroid sensitive asthmatics demonstrate a reduced phosphorylation of JNK and c-jun in response to glucocorticoids. Similar abnormalities have not been demonstrated to date in pathways involving either NF-κB or CREB.

FIGURE 4



Proposed mechanism of primary steroid-resistance in asthma. Increased activation of activator protein-a (AP-1) results in the complexing of glucocorticoid receptors (GR), thus preventing the anti-inflammatory action of steroids.

- Barnes et al
Am J Respir Crit Care Med 1998;157:S1-S53

Chürg-Strauss Syndrome

Chürg-Strauss syndrome (CSS) or allergic granulomatosis is a disease process characterized by asthma, pulmonary and systemic small vessel vasculitis, extravascular granulomas and hyper-eosinophilia. Although some experts insist that histologic criteria including angiitis and extravascular granulomas with eosinophilic infiltrates be demonstrated, more recent attempts to define the disorder have utilized clinical findings. The American College of Rheumatology (49, 50) in 1990 and 1994 suggested a combination of clinical and histologic criteria for the diagnosis (Table 4).

TABLE 4

ACR CRITERIA FOR DIAGNOSIS OF CHÜRG-STRAUSS SYNDROME

1. Asthma
2. >10% eosinophils
3. Mono/polyneuropathy
4. Pulmonary infiltrates
5. Sinusitis or nasal polyps
6. Eosinophilic vasculitis on biopsy

(Need 4/6 criteria: 85% sensitive, 100% specific)

Viewed in a larger context CSS belongs to the group of systemic vasculitides such as microscopic polyarteritis and Wegener's granulomatosis. In approximately 60% of patients with CSS a positive ANCA (anti-neutrophilic cytoplasmic antibody) is present. In contrast to Wegener's the ANCA is directed against myeloperoxidase rather than anti-PR3. CSS, at least in its earlier stages, is usually easy to differentiate from either Wegener's or microscopic PAN by the presence of asthma, eosinophilia, and the tendency of renal disease to be mild.

Although CSS is a rare disorder in the general population, it is likely to account for 1-2% of cases of severe asthma (see below). Recently attention has focused on CSS because of the development of this disorder in patients with asthma treated with the leukotriene D_4 receptor antagonists (LTD_4RA) Accolate (zafirlukast) (51) or Singulair (montelukast) (52, 53). Indeed the manufacturers of these drugs have recently issued warnings to physicians concerning CSS. As such it is worth reviewing in detail the clinical presentation of CSS.

Clinical Course of CSS

It has been suggested that CSS has three phases (54, 55). The first is a prodromal period that may last decades and is characterized by allergic rhinitis, nasal polyposis, and later on asthma. The second phase is associated with marked tissue and peripheral blood eosinophilia, particularly eosinophilic gastroenteritis. This phase of the disease is often accompanied by spontaneous remissions and exacerbations. The

third phase of the disease is characterized by a systemic vasculitis. In this phase marked cardiac and GI involvement may occur. One of the hallmarks of this phase of the disease is a peripheral neuropathy, found in 50-75% of patients. Cranial nerve and CNS involvement is rare. In the literature it has been stated that systemic vasculitis emerges within a mean period of 3 years after the onset of asthma. A shorter duration between the onset of asthma and the development of the systemic vasculitis has been associated with a poorer prognosis. The constellation of eosinophilia, asthma requiring frequent utilization of oral steroids, and sinus disease or nasal polyposis, should always raise the possibility of CSS.

Incidence of CSS and the Role of LTD_4 Receptor Antagonists

Most cases of CSS in the literature have come from tertiary care centers. However two series (56, 57) have addressed the incidence of this disorder in the general population (Table 5). CSS is a rare disorder with an estimated annual incidence of between 2 - $4/10^6$ individuals. This is less than 30% of the incidence of Wegener's granulomatosis. In the asthmatic population however it has been estimated to range between 50 - $100/10^6$ individuals in the U.S. and U.K. respectively. If the higher estimate is utilized, all patients with CSS are considered to have severe asthma, and 1% of asthmatics have severe asthma then 1% of patients with severe asthma should have CSS. As such there was considerable anxiety when a cluster of cases of CSS were reported within months of the general release of Accolate in December, 1996. Similar cases have now been reported with Singulair.

TABLE 5

ESTIMATED ANNUAL INCIDENCE OF COMMON VASCULITIDES FROM 1988-1994

	Annual Incidence/10^6
Systemic rheumatoid vasculitis	12.5
Wegeners	8.5
Micropscopic PAN	2.4
Chürg Strauss	2.4
Henoch-Schonlein	1.2
SLE	3.6

- Watts et al
Semin. Arth. Rheum. 25:28-34, 1995

The relationship of CSS to these drugs is a smoldering question in the field of asthma therapy. It is important because LTD_4 receptor antagonists are now estimated to account for 10-15% of prescriptions written for the chronic control of asthma. In an initial clinical trial of Accolate in patients with mild asthma one case of eosinophilia and

neuropathy developed in 6243 patients, an incidence of $160/10^6$. Within 6 months of its release 12 cases of CSS had been reported in a cumulative patient population of 250,000 patient-years of exposure, yielding an annual incidence rate of $48/10^6$ patients (range 18 - $108/10^6$). This is clearly within the likely incidence of CSS amongst all asthmatics.

In most patients who developed the syndrome, a clear prodrome prior to the use of Accolate could be identified and the development of the disease was linked to the weaning of oral steroids. These patients were considered to have a forme fruste of CSS. However in at least one reported case oral steroids were not being used when the patient developed arthralgia, rash, pulmonary nodules and a pericardial effusion within 2 months of being started on Accolate (58). The majority of cases have developed within 3 months of the onset of therapy.

Several troubling issues remain regarding the role of LTD_4 RA in CSS. First although the contention of many is that CSS was simply unmasked as oral steroids were tapered following the institution of these drugs, it is noteworthy that the number of reports of CSS in patients tapered from oral steroids following utilization of inhaled steroids appears to be much less. Secondly, no cases have been reported with zilueton (Zyflo) a drug which attacks the leukotriene pathway by inhibiting 5-lipoygenase and thus the generation of all leukotrienes. Third, there are plausible mechanisms to explain the development of an eosinophil mediated disease in these patients. Levels of urinary (and serum) LTD_4 rise enormously in patients on LTD_4RA. Eosinophils and other cells are known to have receptors for LTD_4 which are likely not blocked by the antagonist to the high affinity LTD_4 receptor. Finally even those who believe that LTD_4RA do not play a causal role in CSS have stopped these drugs in patients with asthma in whom the syndrome develops.

According to the NHLBI guidelines LTD_4RA were supposed to be an option for therapy in patients with mild persistent asthma. It would appear that in this group of patients these drugs are not associated with an increased risk of CSS. However as the authors of a report of CSS amongst patients treated with Accolate noted "as use of the drug increases, adverse events that occur . . . in populations not examined in clinical trials may become manifest" (51). As such the safety of these drugs in patients with severe asthma is yet to be clarified.

Therapy and Prognosis of CSS

The cornerstone of therapy in CSS remains systemic corticosteroids. Many authors have also suggested the use of cyclophosphamide (cytoxan), particularly in ANCA-positive patients. No controlled trials are available. In one large series (59) a clinical remission of 89% was obtained following therapy. In the majority of patients between 10-15 mg/day of Prednisone was required indefinitely. During follow-up roughly 25% experienced relapses and overall 23% of patients died, with CSS thought to be directly responsible in half of those individuals. In most patients a decrease in serum eosinophil counts parallels clinical improvement. Recently it was reported that

interferon-alpha may be of benefit in some patients who are refractory to steroids, cytoxan, or methotrexate (60).

Severe Asthma Associated with Aspirin Sensitivity and Chronic Sinusitis

The relationship between asthma and sinus disease is complex and beyond the scope of this review. Both are common diseases. According to the National Health Survey sinusitis occurs in almost 15% of the U.S. population (61). Some authors contend that 80% of patients with asthma have some type of rhinitis, and 50-75% of children with asthma have abnormal sinus radiographs (62-64). In a similar fashion asthma associated with aspirin-induced worsening of symptoms has been estimated to occur in between 4-20% of all asthmatics (65, 66). In most patients with asthma and sinusitis, or asthma and aspirin sensitivity the disease is thought to be mild to moderate. However in patients with severe asthma the association of chronic sinusitis and aspirin sensitivity can be seen as a distinct entity. Indeed recent information suggests that aspirin sensitivity in patients with severe asthma may be associated with a markedly increased risk of vasculitis, possibly CSS.

The "aspirin triad" of asthma, chronic hyperplastic sinusitis (with or without polyposis) and aspirin intolerance (Samters' triad) is often associated with difficult to control asthma. The pathogenesis of this disorder remains uncertain but is thought to involve some abnormality of arachidonic acid metabolism (67, 68). The asthma in this process is made worse by aspirin or other NSAID's which tend to preferentially block the cyclo-oxygenase pathway and allow arachidonic acid to be metabolized predominantly through the lipoxygenase or epoxygenase pathway. However this mechanism is not clearly established (69). While aspirin makes the asthma worse, avoidance of aspirin is not associated with an improvement in asthma. Furthermore although there is anecdotal evidence that such patients respond well to leukotriene modulators there is a surprising lack of data using these drugs in controlled studies to support a leukotriene-driven mechanism.

Although bacterial infection may play a role in this disorder the literature would suggest that antibiotic therapy (70), while improving symptoms of sinus disease, has little impact on asthma in adults. In children however the improvement in asthma symptoms may be greater with aggressive therapy of sinus disease including surgery (71). The role of aggressive sinus surgery in adults is controversial though some patients do appear to benefit with reduced need for steroids to control their asthma (72, 73).

The diagnosis of aspirin sensitivity can be made by history or after aspirin challenge (74-77). These patients tend not to manifest marked atopic symptoms. Indeed no correlation has been established between bronchospasm induced by aspirin and that produced by either histamine or methacholine. Aspirin sensitivity can be confirmed by either challenge with small doses of oral aspirin or intravenous, intra-nasal or inhalational challenge with lysine-aspirin solution. Patients can be desensitized to

aspirin but the beneficial effect is short-lived. Repetitive desensitization has been reported to have some benefit on asthma symptoms though not in patients with severe asthma (78).

Preliminary data suggest that aspirin sensitivity may be a "red flag" in patients with severe asthma. As mentioned previously the ENFUMOSA study (5, 6) found a significantly higher risk of aspirin sensitivity in patients with severe asthma compared to patients with mild asthma. Another recent study searched the European Network on Aspirin-Induced Asthma (AIANE) registry for the incidence of CSS or other types of vasculitis (79). While it is unclear what the criteria were for including patients in this registry it is reasonable to speculate that a predominant number of these patients have moderate-severe asthma.

Out of 440 patients registered 23 had vasculitis. Six fulfilled the diagnostic criteria for CSS. Utilizing this lower number the incidence of CSS in these patients is roughly 2%, while vasculitis of any kind occurred in a stunning 5%. Further credence for the association between aspirin sensitivity and an increased risk of vasculitis comes from a report from Japan (80). In this study gastric biopsy was performed in 13 aspirin sensitive and 11 non-sensitive asthmatics following intravenous lysine-aspirin administration. Six of 13 aspirin sensitive patients demonstrated a marked eosinophilic infiltrate in gastric mucosa. In contrast only 1/11 non-aspirin sensitive asthmatics exhibited eosinophilic infiltration.

These reports strongly suggest that the presence of aspirin sensitivity in patients with severe asthma identifies a subgroup with a markedly increased incidence of vasculitis, including CSS. Although LTD_4RA are often touted as the ideal drug for patients with aspirin induced asthma it would appear that use of LTD_4RA in aspirin sensitive severe asthmatics would be unwise until more is known about the relationship between these drugs and CSS.

Allergic Bronchopulmonary Aspergillosis

Widely assumed to be the most common cause for asthma with pulmonary and systemic eosinophilia, allergic bronchopulmonary aspergillosis (ABPA) is a syndrome that is difficult to diagnose in patients with severe asthma who are on frequent courses of oral steroids. The accepted clinical criteria for diagnosing ABPA (Table 6) include features such as eosinophilia and IgE levels which are quickly altered by steroid therapy (81-86). The chest radiograph which classically shows mucus plugging, pulmonary infiltrates, and lobar atelectasis is also improved by steroid therapy. Central bronchiectasis, which is usually irreversible, may be a clue to the diagnosis in advanced cases.

TABLE 6

CRITERIA FOR DIAGNOSING ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS

Major
- Asthma
- Peripheral eosinophilia
- Recurrent CXR abnormalities
- Positive immediate reaction to skin prick test (A. fumigatus)
- Aspergillus precipitins

Minor
- Increased IgE level
- A. fumigatus in sputum
- Bronchial casts in sputum
- Bronchiectasis

A large number of patients with ABPA may have an impressive "wheal and flare" response to skin testing to aspergillus fumigatus antigen but this may also be affected by systemic steroids.

Although aspergillus can often be demonstrated in mucus from patients with ABPA, the fungus can also be found in specimens from patients without asthma. Invasive aspergillus disease does not occur in ABPA. Serum IgG precipitins to A. fumigatus are found in most patients with ABPA but are also found in 15% of asthmatics without ABPA. However a total IgE of >2000 in a patient with asthma is strongly suggestive of the diagnosis of ABPA.

In its latter stages ABPA has been associated with the development of fibrotic disease in the lung. In most patients however the diagnosis is suggested by an inability to be tapered completely off oral steroids. Once the diagnosis is established patients may be controlled with the indefinite use of low doses (5–10 mg/day) of Prednisone after an acute episode of asthma responds to higher doses. Total IgE level is utilized by many physicians to monitor the adequacy of therapy. There is little data reporting on the efficacy of high dose inhaled corticosteroids in patients with ABPA. Antifungal therapy has not significantly altered the clinical course of the disease in most reports (87, 88).

Clinical Approach to the Patient with Severe Asthma

A number of issues should be considered when evaluating a patient with inadequate response to routine doses of inhaled corticosteroids and long acting B-agonists (Table 7). Issues of compliance, improper use of inhalers, and environmental triggers must all be examined. The possibility that the disease process is something

other than asthma must be considered as well. In this regard one of the most useful procedures is the performance of lung volumes using either plethysmography or helium dilution. Asthma is an obstructive process that should result in an elevation in functional residual capacity (FRC) both in absolute terms and as a percentage of total lung volume. Simple spirometry may provide evidence of both obstruction and restriction in patients with marked air trapping and is inadequate to exclude a true restrictive process. A normal or reduced FRC would strongly mitigate against a diagnosis of severe asthma.

TABLE 7

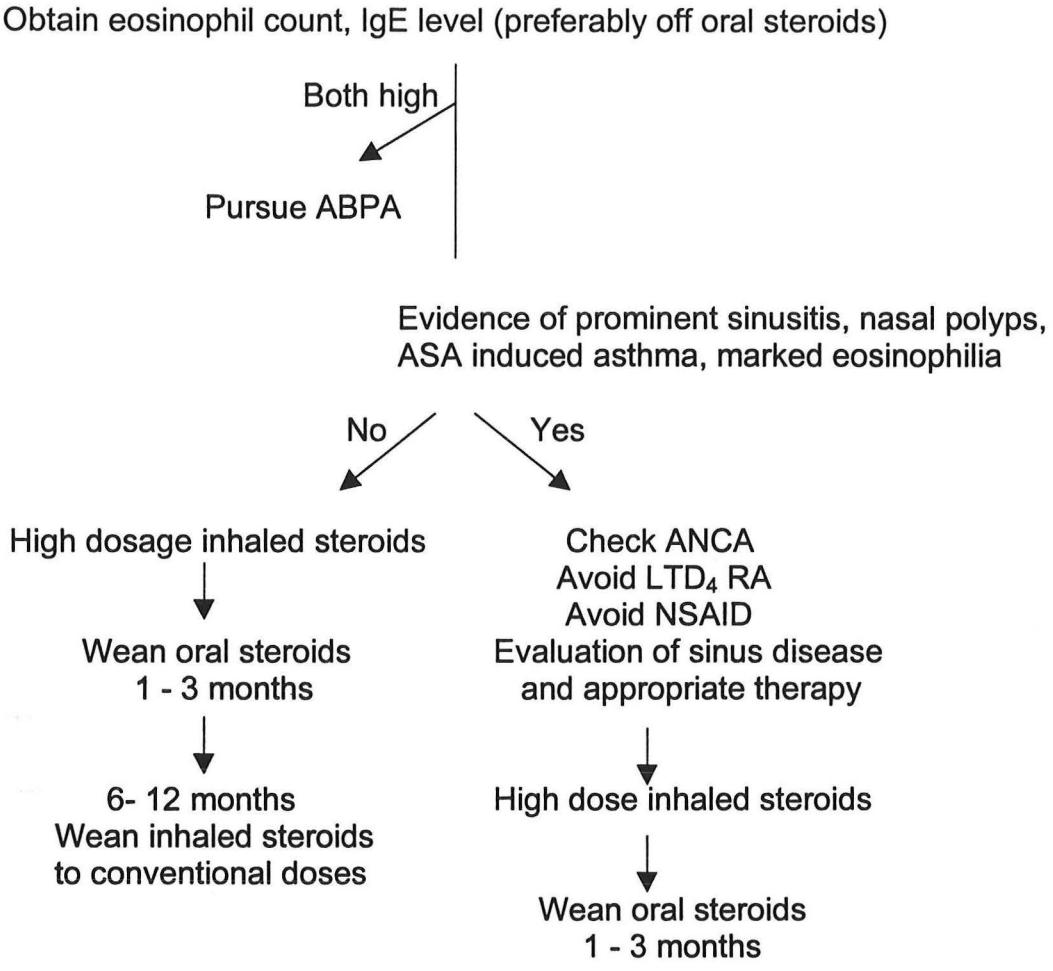
ISSUES TO CONSIDER IN ASTHMATICS REFRACTORY TO CONVENTIONAL THERAPY

1. Home/work environment - pets, ventilation system, metal/plastic fumes
2. Noncompliance or ineffective use of medication
3. Document disease objectively with peak flow meter
4. Drug-induced (B-blockers, NSAIDs)
5. Other types of lung disease

A suggested approach to the patient with severe asthma is shown in Figure 5. Several points bear special emphasis. First it is desirable though not always practical to perform serologic and hematologic studies while the patient is not receiving systemic corticosteroids. Secondly, as mentioned in a prior section, the finding of aspirin sensitivity or sinusitis in a patient with severe asthma should raise the possibility of CSS and LTD_4RA should be avoided in this group of patients. Third, the major goal of therapy is to wean the patient from oral steroids by utilizing high doses of inhaled corticosteroids. This final point contains several subtleties which merit further discussion.

FIGURE 5

CLINICAL APPROACH TO SEVERE ASTHMA



It is apparent from the literature that many patients with "steroid-dependent" asthma can be weaned from oral steroids with minimal difficulty. In one study utilizing methotrexate or placebo for severe asthma 40% of patients in the placebo group, who had regular contact with health providers during the study, had their dose of Prednisone tapered significantly (89). Thus a concerted effort to wean the dose of prednisone is likely to succeed in many patients regardless of the therapy utilized.

Recent data has also continued to underscore the likelihood that high doses of inhaled steroids have systemic effects owing to the absorption of these drugs from the respiratory track. At this Center we have seen one patient on 3000 µg/day of Flovent but no oral steroids who was overtly Cushingoid. Preliminary data from England (90) demonstrate that in 196 adults with asthma aged 20 – 40 a dose of inhaled steroids >1000 µg/day was independently associated with a significant reduction in bone mineral density in the lumbar spine and femoral neck. A smaller study from Chicago (91)

showed a bone mineral density more than 2 standard deviations below normal in 19% of young asthmatic women (mean age 36.5 ± 3.7) on inhaled steroids compared to control. Significant diffferences were observed for total body, lumbar spine and greater trochanter mineral density.

The long term side-effects of high dose inhaled corticosteroids remain unknown but are likely to be clinically significant. Although this is an important issue, i.e. the optimal dose of inhaled steroids in asthmatics who require indefinite therapy, it is of less concern in patients with severe asthma requiring systemic corticosteroids.

Any preparation of inhaled corticosteroid currently on the market can be utilized, though high dose therapy in the literature has primarily been given using inhaled fluticasone (Flovent) or budesonide (Pulmicort). Using the highest potency of Flovent available in the U.S., 220 ug/puff, it is possible to give therapy as 4-5 puffs twice a day, usually with a spacer device. Long acting inhaled B-agonists such as Serevent (Salmeterol) should also be a standard part of the patient's regimen.

In one study of patients (92) with severe asthma 69% of patients on 750 µg bid of Flovent and 88% of patients on 1000 µg bid were completely weaned off Prednisone during a 16 week trial compared to 3% of control subjects. Importantly this correlated with a highly significant improvement in airway physiology in patients on 1000 µg bid.

A follow-up study of these patients is now available in preliminary form (93). After the 16 week period 91 patients from this trial were entered into an open-label phase where they received 1000 µg bid and could be titrated to a minimum dose of 250 µg bid if deemed appropriate. Eighty-three of these patients were treated for 3-4 years. During the first year of therapy only 36% of the patients avoided a course of oral steroids. This improved however each year and by year 4 of the open-label phase 70% of patients did not require a course of Prednisone.

These data would suggest that in most patients with severe asthma inflammation in the airways may take several years to respond optimally to high dose therapy. However even patients with severe asthma may ultimately be weaned to more conventional doses of inhaled steroids.

Other therapies (94, 95) including methotrexate, gold, intravenous IgG and macrolide antibiotics have been utilized in patients with severe asthma. Many studies suggest that oral steroids can be tapered while using these agents but usually without any objective change in pulmonary function. Most of these drugs have not been compared with high dose inhaled steroid therapy. In general most of these drugs are limited by significant toxicity or expense.

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REFERENCES

1. National Asthma Education and Prevention Program Expert Panel Report 2: Guidelines for the Diagnosis and Management of Asthma. National Institutes of Health, National Heart, Lung, and Blood Institute, Publ. No. 97-4051, 1997.
2. Spahn JD, Leung DYM, Szefler SF. Difficult to control asthma: New insights and implications for management. In: Severe Asthma: Pathogenesis and Clinical Management, eds Szefler SJ, Leung DYM, Vol. 86 Lung Biology in Health and Disease (Exec Ed. C Lenfant), Marcel Dekker, Inc., New York, 1996, pp. 497-535.
3. Auerbach J, Springer C, Godfrey S. Total population survey of the frequency and severity of asthma in 17 year old boys in an urban area of Israel. Thorax 1993;48:139-141.
4. Woolcock AJ. Steroid resistant asthma: what is the clinical definition? Eur Respir J 1993;6:743-747.
5. Holgate, ST. A cross-sectional multicentre study to investigate the mechanisms of severe asthma. Am J Respir Crit Care Med 1999 ATS Meeting Supplement (In Press).
6. Holgate, ST for the ENFUMOSA (European Network for the Understanding the Mechanisms of Severe Asthma) Study Group. Clinical characteristics associated to severe asthma. Am J Respir Crit Care Med 1999 ATS Meeting Supplement (In Press).
7. Wenzel SE, Szefler SJ, Leung DYM, Sloan SI, Rex MD, Martin RJ. Bronchoscopic evaluation of severe asthma. Persistent inflammation associated with high dose glucocorticoids. Am J Respir Crit Care Med 1997;156:737-743.
8. Sur S, Crotty TB, Kephart GM, et al. Sudden-onset fatal asthma -- a distinct entity with few eosinophils and relatively more neutrophils in the airway submucosa? Am Rev Respir Dis 1993;148:713-719.
9. Fahy JV, Kim KW, Liu J. Prominent neutrophilic inflammation in sputum from subjects with asthma exacerbation. J Allergy Clin Immunol 1995;95:843-852.
10. Lamblin C., Gosset P, Tillie-Leblond I, et al. Bronchial neutrophilia in patients with noninfectious status asthmaticus. Am J. Respir Crit Care Med 1998;157:394-402.
11. Cox G. Glucocorticoid treatment inhibits apoptosis in human neutrophils. Am Assoc Immunologists 1995;154:4719-4725.
12. Khashayar R, Janson S, Lazarus SC, Fahy JV. Induced sputum cytology in chronic severe asthma; no evidence of neutrophilia. Am J Respir Crit Care Med 1999 ATS Meeting Supplement (In Press).
13. Chu HW, Halliday JL, Martin RJ, Leung DYM, Szefler SJ, Wenzel SE. Collagen deposition in large airways does not differentiate severe asthma from milder forms of the disease. Am J Respir Crit Care Med. 1997;155:A502.
14. Bousquet J, Lacoste J-Y, Chanez P, Vic P, Godard P, Francois-Bernard M. Bronchial elastic fibers in normal subjects and asthmatic patients. Am J Respir Crit Care Med 1996;153:1648-1654.

15. Laitinen A, Altraja A, Kampe M, Linden M, Virtanen I, Laitinen LA. Tenascin is increased in airway basement membrane of asthmatics and decreased by an inhaled steroid. Am J. Respir Crit Care Med 1997;156:951-958.
16. Kraft M, Djukanovic R, Wilson S, Holgate ST, Martin RJ. Alveolar tissue inflammation in asthma. Am J Respir Crit Care Med 1996;154:1505-1510.
17. Miranda T, Wright C, Chu HW, Kennedy JA, Kashem MA, Trudeau JB, Wenzel SE. Matrix metalloproteinase 2 and 9 (MMP-2, MMP-9) levels in the airways of severe asthmatics (SA) compared to moderate (MA) and Mild (MIA) asthmatics and normal controls (NC). Am J Respir Crit Care Med 1999 ATS Meeting Supplement (In Press).
18. Turki J, Pak J, Martin RJ, Liggett SB. Genetic polymorphisms of the B_2-adrenergic receptor in nocturnal and non-nocturnal asthma. J Clin Invest 95(4):1635-1641, 1995.
19. In KH, Asano K, Beier D, et al. Naturally occurring mutations in the human 5-lipoxygenase gene promoter that modify transcription factor binding and reporter gene transcription. J. Clin Invest 1997;99:1130-1137.
20. Barnes P.J. Mechanism of action of glucocorticoids in asthma. Am J Respir Crit Care Med 1996;154:S21-S27.
21. Scheinman RI, Gualberto A, Jewell CM, Cidlowski JA, Baldwin AS. Characterization of the mechanisms involved in trans-repression of NF-κB by activated glucocorticoid receptors. Mol Cell Biol 1996;15:943-953.
22. Adcock IM, Brown CR, Gelder, CM, Shirasaki H, Peters MJ, Barnes PJ. Effects of glucocorticoids on transcription factor activation in human peripheral blood mononuclear cells. Am J Physiol 1995;268:C331-C338.
23. Wills-Karp M, Luyimbazi J, Xu X, Schofield B, Neben TY, Karp CL, Donaldson DD. Interleukin-13: Central mediator of allergic asthma. Science 1998;282:2258-2361.
24. Grünig G, Warnock M, Wakil AE, Venkayya R, Brombacher F, Rennick DM, Sheppard D, Mohrs M, Donaldson DD, Locksley RM, Corry DB. Requirement for IL-13 independently of IL-4 in experimental asthma. Science 1998;282:2261-2263.
25. Leckie MJ, ten Brinke A, Lordan J, Khan J, Diamant Z, Walls CM, Cowley H, Hansel TT, Djukanovic R, Sterk PJ, Holgate ST, Barnes PJ. SB 240563, a humanized anti-IL-5 monoclonal antibody. Initial single dose safety and activity in patients with asthma. Am J Respir Crit Care Med 1999 ATS Meeting Supplement (In Press).
26. Eum, SY, Maghni K, Hamid Q, Eidelman DH, Martin JG. Involvement of eotaxin and IL-5 in the development of antigen-induced airway eosinophilia but not in airway hyperresponsiveness in mice. Am J Respir Crit Care Med 1999 ATS Meeting Supplement (In Press).
27. Bamberger CM, Bamberger AM, deCastr M, Chrousos GP. Glucocorticoid receptor β, a potential endogenous inhibitor of glucocorticoid action in humans. J Clin Invest 1995;95:2435-2441.
28. Muller M, Renkawitz R. The glucocorticoid receptor. Bio-chim Biophys Acta 1991;1088:171-182.

29. Encio PJ, Detgra-Wadleigh SD. The genomic structure of the human glucocorticoid receptor. J Biol Chem 1991;266:7182-7188.
30. Truss M, Beato M. Steroid hormone receptors: interaction with deoxyribonucleic acid and transcription factors. Endocr Rev 1993;14:459-479.
31. Ponta H, Cato ACB, Herrlick P. Interference of specific transcription factors. Biochem Biophys Acta 1992;1129:255-261.
32. Pfahl M. Nuclear receptor/AP-1 interaction. Endocr Rev 1993;14:651-658.
33. Ray A, Prefontaine KE. Physical association and functional antagonism between the p65 subunit of transcription factor NF-κB and the glucocorticoid receptor. Proc Natl Acad Sci USA 1994;91:752-756.
34. Barnes PJ, Karin M. Nuclear factor-KB: a pivotal transcription factor in chronic inflammation. N Engl J Med 1997;336:1066-1071.
35. Barnes PJ, Adcock IM. NF-κB: a pivotal role in asthma and a new target for therapy. Trends Pharmacol Sci 1997;18:46-50.
36. Yang Yen HF, Chambard JC, Sun YL, Smeal T, Schmidt TJ, Drouin J, Karin M. Transcriptional interference between c-Jun and the glucocorticoid receptor: mutual inhibition of DNA binding due to direct protein-protein interaction. Cell 1990;62:1205-1215.
37. Schüle R, Rangarajan P, Kliewer S, Ransone LJ, Bolado J, Yang N, Verma IM, Evans RM. Functional antagonism between oncoprotein c-Jun and the glucocorticoid receptor. Cell 1990;62:1217-1226.
38. Jonat C, Rahsdorf HJ, Park KK, Cato ACB, Gebel S, Ponta H, Herrlick P. Anti tumor promotion and antiinflammation: down-modulation of AP-1 (fos/jun) activity by glucocorticoid hormone. Cell 1990;62:1189-1204.
39. Imai E, Miner JN, Mitchell JA, Yamamoto KR, Granner DK. Glucocorticoid receptor-cAMP response element-binding protein interaction and the response of the phosphoenolpyruvate carboxykinase gene to glucocorticoids. J Biol Chem 1993;268:5353-5356.
40. Peters MJ, Adcock IM, Brown CR, Barnes PJ. Beta-adrenoceptor agonists interfere with glucocorticoid receptor DNA binding in rat lung. Eur J Pharmacol 1995;289:275-281.
41. Janknecht R, Hunter T. A growing coactivator network. Nature 1996;383:22-23.
42. Carmichael J, Paterson IC, Diaz P, Crompton GK, Kay AB, Grant IW. Corticosteroid resistance in chronic asthma. Br Med J 1981;282:1419-1422.
43. Lane SJ, Atkinson BA, Swaminathan R, Lee TH. Hypothalamic-pituitary-adrenal axis in corticosteroid-resistant bronchial asthma. Am J Respir Crit Care Med 1996;153:557-570.
44. Lamberts SWJ, Kioper JW, deJong FH. Familial and iatrogenic cortisol receptor resistance. J Steroid Biochem Mol Biol 1992;43:385-388.
45. Sher ER, Leung DY, Surs W, Kam JC, Zieg G, Kamada AK, Szefler SJ. Steroid-resistant asthma: cellular mechanisms contributing to inadequate response to glucocorticoid therapy. J Clin Invest 1994;93:33-39.
46. Kam JC, Szefler SJ, Surs W, Sher FR, Leung DYM. Combination of IL-2 and IL-4 reduces glucocorticoid-receptor binding affinity and T cell response to glucocorticoids. J. Immunol 1993;151:3460-3466.

47. Adcock IM, Lane SJ, Brown CR, Lee TH, Barnes PJ. Abnormal glucocorticoid receptor-activator protein 1 interaction in steroid-resistant asthma. J Exp Med 1996;182:1951-1958.
48. Adcock IM, Brady H, Lim S, Karin M, Barnes PJ. Increased JUN kinase activity in peripheral blood monocytes from steroid-resistant asthmatic subjects (Abstract). Am J. Respir Crit Care Med 1997;155:A288.
49. Hunder GG, Arend WP, Block DA. The American College of Rheumatology 1990 criteria for the classification of vasculitis: Introduction. Arthritis Rheum 1990;33:1065-1067.
50. Jeanette JC, Falk RJ, Andrassy K, et al: Nomenclature of systemic vasculitides. Proposal of an international consensus conference. Arthritis Rheum 1994;37:187-192.
51. Wechsler ME, Garpestad E, Flier SR, Kocher O, Weiland DA, Polito AJ, Klinek MM, Bigby TD, Wong GA, Helmers RA, Drazen JM. Pulmonary infiltrates, eosinophilia, and cardiomyopathy following corticosteroid withdrawal in patients with asthma receiving Zafirlukast. JAMA 1998;279:455-457.
52. Wechsler ME, Finn D, Jordan M, Gunawardena D, Drazen JM. Montelukast and the Churg-Strauss Syndrome. Am J Respir Crit Care Med 1999 ATS Meeting Supplement (In Press).
53. Haranath SP, Freston C, Fucci M, Lee E, Anwar MS. Montelukast associated Churg-Stauss Syndrome. Am J Respir Crit Care Med 1999 ATS Meeting Supplement (In Press).
54. Lanham et al. Systemic vasculitis with asthma and eosinophilia: a clinical approach to the Churg-Strauss syndrome. Medicine (Baltimore) 1984;63:65-81.
55. Lhote F, Cohen P, Guillevin L. Polyarteritis nodosa, microscopic polyangiitis and Churg-Strauss syndrome. Lupus 1997;7:238-258.
56. Kurland LT, Chuang TY, Hunder G. The epidemiology of systemic arteritis. In: Lawrence RC, Shulman LE (eds): The Epidemiology of the Rheumatic Diseases. New York, NY, Gower 1984, pp 196-205.
57. Watts RA, Carruthers DM, Scott DGI. Epidemiology of systemic vasculitis: changing incidence or definition: Semin Arthritis Rheum 1995;25:28-34.
58. Katz RS, Papernik M. Zafirlukast and Churg-Strauss syndrome. JAMA 1998;279:1949.
59. Cohen P et al and the French Polyarteritis Nodosa Study Group. Clinical aspects and long survival of 85 patients with Churg-Strauss syndrome. Arthritis Rheum 1995; 38(Supplement 9):S.391 (abstract 1438).
60. Tatsis E, Schnabel A, Gross WL. Interferon-α treatment of four patients with the Churg-Strauss syndrome. Ann Intern Med 1998;129:370-374.
61. Benson V, Marano MA, National Center for Health Statistics. Current estimates for the National Health Interview Survey-1993. Vital and health statistics. 10(190). Washington, DC: Government Printing Office, 1995.
62. Slavin RG. Sinopulmonary relationships. Am J Otolaryngol 1994:15:18-25.
63. Rachelefsky GS, Goldberg M, Katz RM, et al. Sinus disease in children with respiratory allergy. J Allergy Clin Immunol 1978;61:310-314.
64. Slavin RG, Cannon RE, Friedman WH, et al. Sinusitis and bronchial asthma. J Allergy Clin Immunol 1980;66:250-257.

65. Settipane GA. Asthma, aspirin intolerance and nasal polyps. N Engl Reg Allergy Proc 1986;7:32-37.
66. McDonald JR, Mathison DA, Stevenson DD. Aspirin intolerance in asthma, detection by oral challenge. J Allergy Clin Immunol 1972;50:198-207.
67. Sherman NA, Morris HG. Aspirin-induced shift in the metabolism of arachidonic acid. J allergy Clin Immunol 1983;71:A153.
68. Stevenson DD, Lewis RA. Proposed mechanisms of aspirin sensitivity reactions. J Allergy Clin Immunol 1987;80:788-790.
69. Nizankowska E, Sheridan AQ, Maile MH, et al. Pharmacological attempts to modulate leukotriene synthesis in aspirin-induced asthma. Agents Actions 1987;21:203-213.
70. Gwaltney JM, Scheld WM, Sande MA, Sydnow A. The microbial etiology and antimicrobial therapy of adults with acute community-acquired sinusitis: a fifteen-year experience at the University of Virginia an review of other selected studies. J Allergy Clin Immunol 1992;90:457-461.
71. Manning S, Wasserman R, Silver R, Phillips D. Results of endoscopic sinus surgery in pediatric patients with chronic sinusitis and asthma. Arch Otolaryngol Head Neck Surg 1994;120:1142-1145.
72. McFadden EA, Woodson BT, Fink JN, Toohill RJ. Surgical treatment of aspirin triad sinusitis. Am J Rhinology 1997;11:263-270.
73. Senior BA, Kennedy DW. Management of sinusitis in the asthmatic patient. Ann Allergy Asthma Immunol 1996;77:6-19.
74. Milewski M, Mastalerz L, Nizankowska E, Szczeklik A. Nasal provocation test with lysine-aspirin for diagnosis of aspirin-sensitive asthma. J Allergy Clin Immunol 1998;101:581-586.
75. Szczeklik A. Mechanism of aspirin-induced asthma. Allergy 1997;52:613-619.
76. Pleskow WW, Stevenson DD, Mathison DA, Simon RA, Schatz M, Zeiger RS. Aspirin-sensitive rhinosinusitis/asthma: spectrum of adverse reactions to aspirin. J Allergy Clin Immunol 1983;71:574-579.
77. Stevenson DD, Simon RA. Sensitivity to aspirin and nonsteroidal antiinflammatory drugs. In: Middleton E Jr, Reed CE, Ellis EF, Adkinson NF Jr, Yunginger JW, Busse WW, editors. Allergy: principles and practice. St. Louis: Mosby, Inc.; 1993, p. 1747-65.
78. Sweet JM, Stevenson DD, Simon RA, Mathison DA. Long-term effects of aspirin densensitization--Treatment for aspirin-sensitive rhinosinusitis-asthma. J. Allergy Clin Immunol 1990;85:59-65.
79. Szczeklik A, Schmitz-Schumann M. Churg-Strauss Syndrome (CSS) and aspirin-induced asthma (AIA). Am J Respir Crit Care Med 1999 ATS Meeting Supplement (In Press).
80. Toyoshima M, Chida K, Hayakawa H, Masuda M, Suda T, Sato J, Nakamura H. Eosinophilic gastritis as one of characteristic features in aspirin-induced asthmatics. Am J Respir Crit Care Med 1999 ATS Meeting Supplement (In Press).
81. Safirstein BH, D'Souza MF, Simon G, Tai EH-C, Pepys J. Five year follow-up of allergic bronchopulmonary aspergillosis. Am Rev Respir Dis 1973;108:450-459.

82. Rosenberg M, Patterson R, Mintzer R. Clinical and immunological criteria for the diagnosis of allergic bronchopulmonary aspergillosis. Ann Intern Med 1977;86:405-414.
83. Chapman BJ, Capewell S, Gibson R, Greening AP, Crompton GK. Pulmonary eosinophilia with and without allergic bronchopulmonary aspergillos. Thorax 1989;44:919-924.
84. Patterson R, Fink JN, Pruzansky JJ, et al. Serum immunoglobulin levels in pulmonary allergic aspergillosis and certain other lung diseases with special reference to immunoglobulin E. Am J Med 1973;54:16-22.
85. McCarthy DS, Simon G, Hargreave FE. The radiological appearances in allergic bronchopulmonary aspergillosis. Clin Radiol 1970;21:366-375.
86. Patterson R, Greenberger PA, Halwig JM, Liotta JL, Roberts M. Allergic bronchopulmonary aspergillosis. Natural history and classification of early disease by serologic and roentgenographic studies. Arch Intern Med 1986;146:916-918.
87. Crompton GK, Milne LJR. Treatment of bronchopulmonary aspergillosis with clotrimazole. Br J Dis Chest 1973;67:301-308.
88. Shale DJ, Faux JA, Lane DJ. Trial of ketaconazole in non-invasive pulmonary aspergillosis. Thorax 1987;42:26-31.
89. Erzurum SC, Leff JA, Cochran JE, Ackerson LM, Szefler SJ, Martin RJ, et al. Lack of benefit of methotrexate in severe, steroid-dependent asthma. A double-blind, placebo-controlled study. Ann Intern Med 1991;114:353-360.
90. Wong CA, Walsh LJ, Smith C, Wisniewski AF, Lewis SA, Hubbard R, Green DJ, Pringle M, Tattersfield AE. Long term effect of inhaled corticosteroids on bone mineral density in patients with asthma. Am J Respir Crit Care Med 1999 ATS Meeting Supplement (In Press).
91. Pogue NJ, Larson JL, Boileau RA, Main DM. Bone mineral density of asthmatic women treated with inhaled corticosteroids. Am J Respir Crit Care Med 1999 ATS Meeting Supplement (In Press).
92. Noonan M, Chervinsky P, Busse WW, et al. Fluticasone propionate reduces oral prednisone use while it improves asthma control and quality of life. Am J Respir Crit Care Med 1995;152:1467-1473.
93. Herje N, Duke S, Kellerman D, Harding S. Prednisone reduction maintained after 3-4 years of treatment with fluticasone propionate MDI. Am J Respir Crit Care Med 1999 ATS Meeting Supplement (In Press).
94. Jarjour N, McGill K, Busse WW, Gelfand E. Alternative anti-inflammatory and immunomodulatory therapy. In: Szefler SJ, Leung DYM, eds. Severe Asthma: Pathogenesis and Clinical Management. Lung Biology in Health and Diseases, Vol. 86, New York, Marcel Dekker, 1996; pp. 333-369.
95. Spector SL. Treatment of the unusually difficult asthmatic patient. Allergy and Asthma Proceedings 1997;153-155.