

New insights into the pathogenesis of severe corticosteroid-dependent asthma

**Bart Vrugt, MD,^a Ratko Djukanović, MD, PhD,^b Aad Bron, MD,^c
and René Aalbers, MD, PhD^d** *Utrecht and Groningen, The Netherlands,
Southampton, United Kingdom, and Davos, Switzerland*

Severe asthma is characterized by persistent T-cell activation, as demonstrated in both peripheral blood and bronchial mucosa. Endobronchial biopsy specimens of patients with severe, corticosteroid-dependent asthma revealed increased expression of CD25+ on mucosal T cells. Increased immunoreactivity for IL-5 further supports the evidence that the inflammatory response is orchestrated by T_{H2}-type T cells. Peripheral blood eosinophils and total serum IgE levels were increased in the absence of allergen and despite optimal treatment. The chemokine IL-8 may also be an aggravating factor in severe asthma; as well as being a potent chemotactic and activating factor for neutrophils, it may also be chemoattractant for eosinophils. We have recently detected increased levels of free IL-8 in the peripheral blood of patients with chronic severe asthma but not in healthy control subjects or in patients with mild asthma, even after allergen challenge. In patients with severe asthma there may be an imbalance between IL-8 production and the blocking capacity of IL-8 autoantibodies. Higher levels of IL-8 complexed to IgA autoantibody and increased numbers of activated T cells were also found in patients with unstable asthma compared with patients who had severe but stable disease. We conclude that IL-8 may provide an additional marker of asthma severity and corticosteroid responsiveness. (J Allergy Clin Immunol 1996;98:S22-6.)

Key words: Endobronchial biopsy, interleukin-8, severe asthma, T cell

During the past decade, considerable progress has been made in our understanding of the pathophysiologic mechanisms underlying the clinical picture of asthma. It is now clear that mucosal inflammation is a consistent finding in patients with asthma and is closely related to its main physiologic abnormalities, bronchial hyperresponsiveness and variable airflow limitation.¹ Postmortem studies of persons who have died of asthma have shown desquamation of the epithelium, deposition of collagen beneath the basement membrane, vasodilation, and widespread infiltration of the airway wall with mononuclear cells and eosinophils.² The use of bronchoalveolar lavage (BAL) and endobronchial biopsy specimens has confirmed the presence of an active inflammatory process in the airways of patients with mild and

Abbreviations used

BAL: Bronchoalveolar lavage
IL-2R: Interleukin-2 receptor

moderately severe asthma, with evidence of mast cell degranulation,³ an increased number of eosinophils,^{4,5} and activated T lymphocytes.^{6,7} In addition, a clear correlation of cellular findings with indices of disease activity has been demonstrated repeatedly. Bronchoscopy studies of the early- and late-phase responses have shown evidence that mast cell degranulation occurs very soon after challenge and that an influx of neutrophils, eosinophils, and lymphocytes occurs 3 to 4 hours after allergic stimulation.^{1,3,8} This has led to the concept that the immediate response after allergen challenge is mediated by mast cells, whereas eosinophils are the predominant cells in the late asthmatic reaction. The finding of increased expression of the T_{H2}-type cytokines associated with the late phase has suggested that the T cell orchestrates the allergic inflammatory reaction.¹

From ^aAcademic Hospital, Utrecht, The Netherlands,

^bSouthampton General Hospital, Southampton, United Kingdom, ^cDutch Asthma Centre, Davos, Switzerland, and

^dMartini Hospital, Groningen, The Netherlands.

Reprint requests: René Aalbers, MD, Martini Hospital, Van Swietenlaan 4, 9728 NZ Groningen, The Netherlands.

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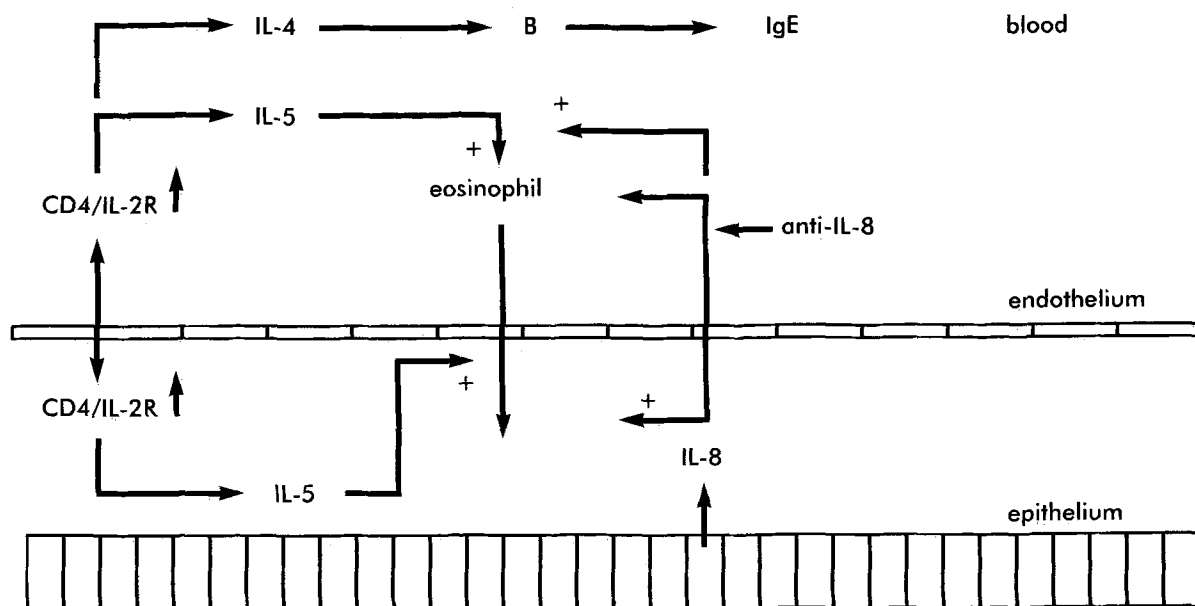


FIG. 1. Hypothesis for the interaction between the CD4 IL-2R T cell, eosinophil activation, and the cytokine IL-8, leading to an enhancement of the inflammatory response. Two mechanisms are suggested. First, T-cell activation characterized by increased cell surface expression of IL-2R (CD25) is associated with the release of IL-5 and leads to an accumulation of activated eosinophils in the bronchial mucosa. Second, increased levels of IL-8 in bronchial epithelial cells are potent chemoattractants for cytokine-primed eosinophils.

T-lymphocyte activation is characterized by increased cell surface expression of IL-2 receptor (IL-2R) (CD25) and class II histocompatibility leukocyte antigen and is associated with the release of various cytokines, such as IL-3, IL-4, IL-5, and granulocyte-macrophage colony-stimulating factor. These cytokines are crucial for the recruitment and activation of mast cells and eosinophils in asthmatic airways. In particular, IL-4 and IL-5 are central to allergic inflammation in patients with asthma. IL-4 is involved in the IgG-IgE isotype switch, whereas IL-5 promotes the differentiation, recruitment, activation, and vascular adherence of eosinophils.⁹ In mice, CD4⁺ T cells can be subdivided according to their cytokine profile into T_{H1} cells, producing IL-2 and interferon- γ , and T_{H2} cells, producing IL-4, IL-5, and IL-10.¹⁰ Several studies have indicated that this classification can be extended to human T cells.^{10, 11} Compelling evidence indicates that the inflammatory response in airways of humans with asthma is orchestrated by a T_{H2}-type T-helper cell.¹¹ With use of in situ hybridization, increased levels of mRNA for IL-4 and IL-5 but not for interferon- γ have been demonstrated in BAL fluid cells¹¹ and bronchial biopsy specimens¹² obtained from patients with stable

asthma compared with that of healthy control subjects.

CORTICOSTEROIDS IN SEVERE ASTHMA

Despite the considerable improvement in therapy for patients with asthma, epidemiologic studies indicate that the prevalence of severe asthma has increased and now accounts for approximately 10% of the total asthma population.¹³ Among the wide spectrum of antiasthmatic drugs, corticosteroids are the most potent antiinflammatory drugs currently available.⁹ Numerous studies have confirmed their long-term clinical efficacy,^{14, 15} and their antiinflammatory effects have been investigated intensively.⁹ Corticosteroids reduce T-cell proliferation and activation by inhibiting IL-2 production and suppressing IL-2R gene expression.⁹ Corticosteroids have been shown to reduce the number of BAL fluid cells transcribing mRNA for IL-4 and IL-5, and this was accompanied by a decrease in the number of eosinophils and clinical improvement.¹⁶ The suppressive action on T cells and cytokine release may explain the reduction in the numbers of mast cells and the depletion of eosinophils observed in the airways of patients with mild asthma after treatment with inhaled corticosteroids.¹⁵

The cause of decreased corticosteroid sensitivity has yet to be clarified. Although glucocorticoid receptor dysfunction and antilipocortin antibodies have been proposed as possible causes of corticosteroid resistance, no differences in glucocorticoid receptor function and antilipocortin antibodies have as yet been reported in corticosteroid-resistant patients compared with that in corticosteroid-sensitive persons.⁹ However, a growing body of evidence shows that persistent T-cell activation¹⁷ and a decreased *in vitro* sensitivity of T cells to the antiproliferative effects of dexamethasone¹⁸ are prominent features of corticosteroid-resistant asthma. In peripheral blood from corticosteroid-resistant patients who showed no satisfactory clinical response to 2 weeks of treatment with oral corticosteroids, increased numbers of CD4+ cells bearing surface IL-2R and elevated levels of soluble IL-2R have been demonstrated compared with that in the blood of corticosteroid-sensitive patients.¹⁷ In agreement with these observations, increased serum levels of IL-5 have been detected in patients with stable corticosteroid-dependent asthma.¹⁹

POTENTIAL MARKERS OF DISEASE SEVERITY

The role of IL-5 in eosinophil functioning is well established, but recent advances in understanding leukocyte traffic have revealed a number of other chemotactic cytokines, referred to as chemokines, that are likely to be important in allergic inflammation and asthma because they possess a degree of specificity for the recruitment of eosinophils.²⁰ The best described chemokine, IL-8, has been recognized as the major neutrophil chemotactic and activating factor and is associated with a number of pulmonary diseases in which neutrophils are implicated.²⁰ Although neutrophils may be relevant to the pathogenesis of asthma, the eosinophil seems to be fundamental to the inflammatory changes found in airways of patients with asthma.^{1, 4, 5} Recent studies have provided circumstantial evidence that IL-8 is a potent chemoattractant for cytokine (IL-3, IL-4, IL-5, and granulocyte-macrophage colony-stimulating factor)-primed eosinophils *in vitro*.²⁰ Marini et al.²¹ have demonstrated increased levels of IL-8 and IL-8 mRNA in bronchial epithelial cells isolated from patients with asthma compared with control subjects. These observations have been confirmed by *in vivo* studies that have shown increased expression of IL-8 on bronchial epithelium of biopsy specimens obtained from patients with symptomatic asthma²² and elevated levels of IL-8 in BAL from patients with both allergic and nonallergic asthma.²³

Adding to the complexity of the cytokine network, the discovery of IL-8 autoantibodies provides a homeostatic control mechanism that serves to limit the bioavailability of free IL-8 in peripheral blood²⁴ and airways.²⁵ Recently we detected free IL-8 in peripheral blood of patients with severe asthma but not in healthy persons or in patients with mild disease, not even after allergen challenge, which suggests that in patients with severe asthma, IL-8 production exceeds the blocking capacity of these autoantibodies.²⁶ The levels of IL-8 complexed to anti-IL-8 IgA were significantly higher in patients having an exacerbation compared with patients with severe asthma who were clinically stable at the time that measurements were performed. Similarly, higher numbers of activated T cells and increased levels of IL-8 complexed to IgA autoantibody were found in patients with unstable asthma compared with patients with stable disease, and a highly significant correlation was found between levels of free IL-8 and eosinophilic cationic protein. In view of the relationship of IL-8 with eosinophil and T-cell activation in patients with severe asthma, the determination of IL-8 and its autoantibodies may provide an additional marker of disease severity and corticosteroid responsiveness in patients with severe asthma.

BIOPSY FINDINGS IN SEVERE ASTHMA

Initially, studies of severe asthma were restricted to testing of blood and provided only an indirect reflection of the ongoing process in the bronchial mucosa. This prompted us to perform fiberoptic bronchoscopy with endobronchial biopsies in a number of patients with severe corticosteroid-dependent asthma who had been referred to the Dutch Asthma Centre in Davos, Switzerland (altitude 1560 m) because of unstable disease.²⁷ Although most persons with asthma benefit from a stay in this low humidity, hypoallergenic environment,²⁸ the asthma of the patients studied had remained unstable as judged by decreased lung function, persistent complaints of dyspnea, including nocturnal asthma, and increased variability in peak expiratory flow. Immunohistochemical analysis of bronchial biopsy specimens revealed an increased expression of CD25, co-localized to T cells, compared with specimens from patients with mild asthma and healthy control subjects.²⁹ The number of CD25+ cells showed a highly significant correlation with disease severity. These findings were accompanied by increased immunoreactivity for IL-5 in the bronchial mucosa compared with that of patients with mild asthma and a high

eosinophil blood count and increased levels of total serum IgE, despite optimal treatment and the lack of allergen. In contrast to previous observations in biopsy specimens obtained from patients with mild asthma after treatment with inhaled corticosteroids,¹⁵ in the patients with severe asthma, corticosteroids failed to deplete the bronchial mucosa of eosinophils.

In conclusion, severe corticosteroid-dependent asthma is characterized by persistent T-cell activation in both peripheral blood and bronchial mucosa, with a subsequent increase in the release of cytokines such as IL-5. Although IL-8 may be an aggravating factor in patients with severe asthma, further studies are required to elucidate its precise role in the pathogenesis of this type of asthma.

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