

Eosinophilic Phenotypes of Airway Disease

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Abstract

Our understanding of the clinical implications of eosinophilic airway inflammation has increased significantly over the last 20 years, aided by the development of noninvasive means to assess it. This pattern of airway inflammation can occur in a diverse range of airway diseases. It is associated with a positive response to

corticosteroids and a high risk of preventable exacerbations. Our new understanding of the role of eosinophilic airway inflammation has paved the way for the clinical development of a number of more specific inhibitors that may become new treatment options. Different definitions, ideas of disease, and adoption of biomarkers that are not well known are necessary to fully realize the potential of these treatments.

(Received in original form June 13, 2013; accepted in final form June 25, 2013)

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Ann Am Thorac Soc Vol 10, Supplement, pp S143–S149, Dec 2013

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DOI: 10.1513/AnnalsATS.201306-168AW

Internet address: www.atsjournals.org

Although the association of asthma and eosinophilic airway inflammation has been recognized for many years, it is only over the last 25 years that it has been seen as being of prime importance in the pathogenesis of the disease (Figure 1). Bronchoscopy studies in the mid to late 1980s have been particularly influential, showing evidence of eosinophilic airway inflammation even in subjects with mild asthma and correlations between measures of eosinophilic airway inflammation and airway responsiveness (1). A fundamentally important role for this inflammatory response is supported by the consistent observation that maneuvers that improve or worsen eosinophilic airway inflammation (i.e., treatment with inhaled corticosteroid, allergen challenge) are associated with parallel changes in airway responsiveness. It is also possible to construct plausible models whereby the eosinophilic inflammatory response and its consequences on the airway alter airway function in such a way as to promote airway hyperresponsiveness (2).

The paradigm illustrated in Figure 1 remains the prevalent view of the

relationship between eosinophilic airway inflammation and the disordered airway function and symptoms that characterize asthma. Guidelines for treatment continue to promote control of symptoms and optimization of lung function; they assume that if both are achieved then inflammation is controlled and the risk of exacerbations and long-term decline in lung function are minimized. However, over the last 20 years, the development and validation of widely applicable, noninvasive techniques to assess airway inflammation that are suitable for cross-sectional and longitudinal assessment of airway inflammation in almost all patients has led to new, clinically important insights into the relationship between airway inflammation and the clinical expression of disease. This review summarizes this new information and speculates on its clinical relevance. The focus is on eosinophilic airway inflammation, defined herein as an induced sputum differential eosinophil count of greater than 2%, because most of the clinically important developments have been in this area.

Eosinophilic Airway Inflammation Is Not Always Present in Asthma and Can Be Seen in Functionally Distinct Airway Diseases

A raised sputum eosinophil count is seen in 70 to 80% of corticosteroid-naïve patients with asthma, in 50% of corticosteroid-treated patients with symptomatic asthma (3), in 30 to 40% of patients with cough (4), and in up to 40% of patients with chronic obstructive pulmonary disease (COPD) (5). Within diagnostic categories, there is at best a weak association between symptoms, disordered airway function, and the degree of eosinophilic airway inflammation (5, 6). Thus, little can be deduced about the presence and severity of eosinophilic airway inflammation using a system that categorizes patients using a standard clinical assessment.

Dissociation between eosinophilic airway inflammation and airway hyperresponsiveness is most clearly seen in patients with eosinophilic bronchitis, a condition characterized by corticosteroid-responsive cough and the presence of sputum eosinophilia occurring in the

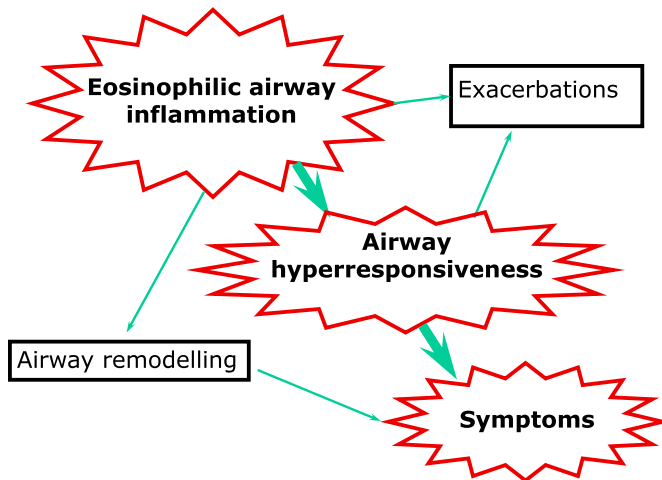


Figure 1. A traditional view showing eosinophilic airway inflammation as central to the pathophysiology of all aspects of asthma.

absence of variable airflow obstruction or airway hyperresponsiveness (7). As with asthma, the raised sputum eosinophil count seen in eosinophilic bronchitis returns toward normal after treatment with inhaled corticosteroids. However, eosinophilic bronchitis differs from asthma in that this improvement in eosinophilic airway inflammation after corticosteroid treatment is associated with a significant improvement in capsaicin cough sensitivity but with no change in the airway response to histamine (8, 9). Closer study of this condition may be informative because any difference in pathology between the two conditions is likely to give important clues to the features that are relevant to the different functional associations.

Studies suggest that the state of activation of eosinophilic lower airway inflammation in asthma and eosinophilic bronchitis is similar (10, 11), although patients with eosinophilic bronchitis have higher concentrations of histamine and prostaglandin D_2 in their sputum (12) and increased numbers of mast cells in bronchial brushings (11) when compared with patients with asthma. This finding has led us to hypothesize that there may be differences in the localization of mast cells within the airway wall between the two conditions; specifically, in asthma there is an increase in the number of mast cells in the airway smooth muscle, which is functionally linked to the development of airway hyperresponsiveness.

This view is supported by a comparative immunopathological study of

asthma and eosinophilic bronchitis (10) in which the traditional characteristics of the immunopathology of asthma, including a submucosal eosinophilia and thickening of the basement membrane and lamina reticularis, were also found in eosinophilic bronchitis. These are therefore unlikely to be critical factors causing airway hyperresponsiveness or variable airflow obstruction. However, increased mast cells within the airway smooth muscle were only seen in patients with asthma, supporting our hypothesis that localization of mast cells within the airway wall is a crucial determinant of the functional associations of airway inflammation with a predominantly epithelial infiltration resulting in a bronchitic illness and a smooth muscle infiltration resulting in the abnormalities of airway function that characterize asthma (Figure 2).

Eosinophilic Airway Inflammation as a Marker of Steroid-responsive Disease

Since the late 1950s, studies have consistently shown that the presence of eosinophilic airway inflammation is more closely associated with a positive response to corticosteroids than any other clinical measure. Moreover, a positive response to corticosteroids is seen irrespective of the pattern of airway disease in which eosinophilic airway inflammation occurs (5, 7, 9, 13–15). Thus, if the clinical question is whether a patient with chronic

respiratory symptoms should receive corticosteroid treatment or whether the intensity of this treatment should be increased, then the identification of eosinophilic airway inflammation would be a better basis for making this decision than the findings of other tests.

The sputum eosinophil count is also a better marker for titrating corticosteroid therapy than standard clinical measures. Studies in asthma (16, 17) and COPD (18) have shown that management strategies where decisions about corticosteroid use and dose are guided by the sputum eosinophil count result in a lower frequency of exacerbations and more economical use of corticosteroids than management guided by traditional clinical measures.

In nonsmokers, exhaled nitric oxide (FE_{NO}) levels correlate reasonably closely with the presence of eosinophilic airway inflammation assessed more directly (19–21). This is the most important feature of the test, and, apart from cigarette smoking, there appear to be no clinically important confounders of this relationship (19). A raised FE_{NO} level is a reliable indicator of a positive response to corticosteroids in a heterogeneous population of patients with symptoms suggesting airway disease (22) independent of the clinical diagnosis at presentation, in particular the label of asthma. The relationship between FE_{NO} levels, airway eosinophilia, and steroid responsiveness; the simplicity of the test; and the availability of an immediate result suggests a role for FE_{NO} in the identification of airway disease that should be treated with corticosteroids and titration of that treatment (23, 24). This has been investigated in a number of small studies in different populations. The findings show a consistent trend to reduction in asthma exacerbation of around 25% (23, 25, 26); in one study, better outcome for mother and unborn child was achieved with a significantly lower mean daily dose of inhaled corticosteroids (26). More definitive studies are required, and more needs to be learned about the optimum cutpoints for FE_{NO} as a marker of corticosteroid responsive airway disease and as a tool for asthma monitoring (27), but the evidence suggests that the use of regular FE_{NO} measurements is a promising way

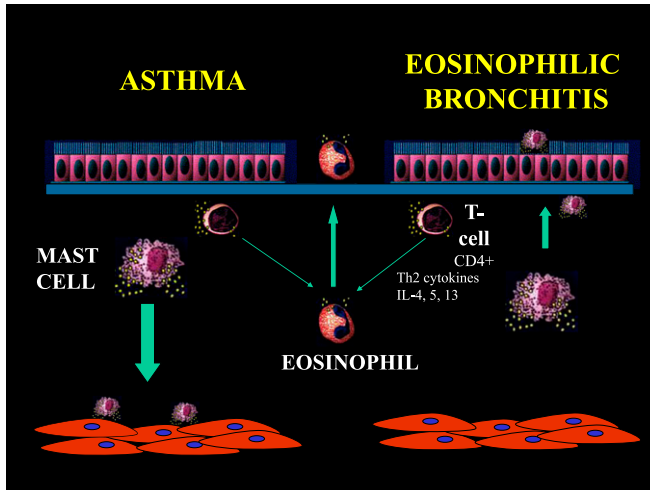


Figure 2. Localization of mast cells and eosinophils within the airway wall in eosinophilic bronchitis and asthma. Note microlocalization of mast cells within the airway smooth muscle in asthma but not in eosinophilic bronchitis.

to achieve more economical and effective use of inhaled corticosteroids.

Eosinophilic Airway Inflammation and Severe Exacerbations of Airway Disease

Exacerbations requiring courses of oral corticosteroids and hospital admissions are the most serious manifestation of airway disease, responsible for a high proportion of the cost to the health service in terms of consultations, medication use, and hospital stay. Better prevention and treatment strategies are urgently needed. The pathophysiology of exacerbations is complex and incompletely understood but likely involves mucosal edema, mucus hypersecretion, and impaction of the bronchial lumen with cellular debris as much as airway smooth muscle contraction.

Clinically, the cardinal feature of exacerbation is bronchoconstriction and a loss of response to bronchodilators (28).

It is increasingly recognized that the exacerbation frequency does not relate that closely to symptoms and measures of disordered airway function, suggesting that the mechanisms responsible for these features of asthma are different (28). This view is supported by the findings of the FACET study (29), which showed that higher-dose inhaled corticosteroids had a marked beneficial effect on exacerbation frequency but relatively little effect on symptoms and peak expiratory flow, whereas with the addition of long acting β_2 agonists the opposite was true.

The reduction in exacerbation frequency seen with additional corticosteroid treatment suggests that eosinophilic airway inflammation might be particularly important in the genesis of

exacerbations. In keeping with this, a raised sputum eosinophil count predicts the occurrence of an asthma exacerbation after inhaled corticosteroids are withdrawn (30), and a significant increase in the sputum eosinophil count occurs well before the onset of increased symptoms and worsening airflow obstruction (31). Finally, a management strategy that achieves control of eosinophilic airway inflammation as well as symptoms results in a marked reduction in severe asthma exacerbations but in no difference in control of day-to-day symptoms and simple tests of airway function (13). A *post hoc* subgroup analysis showed that all of the benefit occurred in the 65% of patients who had evidence of active eosinophilic airway inflammation during the trial.

These studies suggest that eosinophilic airway inflammation is more closely related to the genesis of asthma exacerbations than day-to-day symptoms and airway caliber. Although the above studies do not establish causation, their clear implication is that eosinophilic airway inflammation is a more valid surrogate marker of exacerbation frequency than other outcome measures.

The main conclusion to be drawn from our observations on the relationship between airway function and eosinophilic airway inflammation between patients is that, to a large extent, these features appear to be independently regulated and that our earlier paradigm of a simple and causal relationship between them needs to be modified (Figure 3).

The Development of New Treatments for Eosinophilic Airway Disease

Our new understanding of the relationship between eosinophilic airway inflammation and the clinical expression of airway disease has paved the way for the development of more selective inhibitors. IL-5 is crucial in eosinophil hematopoiesis, maturation, migration, activation, function, and survival. Due to the limited spectrum of cells that IL-5 acts on, selectively targeting IL-5 has been seen as a promising method for treating conditions in which eosinophils are thought to play a significant role, including asthma.

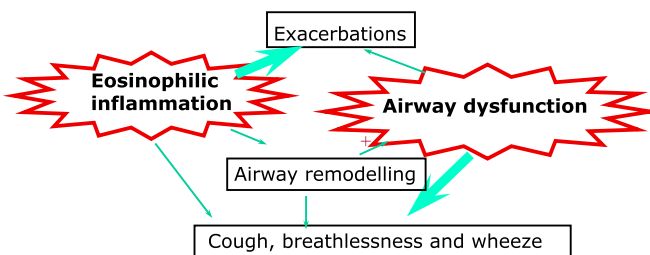


Figure 3. An alternative model in which eosinophilic airway inflammation is more closely linked to exacerbations and airway dysfunction (i.e., airflow obstruction and airway hyperresponsiveness) to symptoms.

The first IL-5 antagonist used in a randomized controlled trial in asthma is mepolizumab. Leckie and colleagues tested mepolizumab, a humanized monoclonal antibody against IL-5, in a small group of patients with mild atopic asthma (32). The main aim of this study was to assess tolerability of a single administration of the drug and its effect on eosinophils, allergen-induced asthma, and airway hyperresponsiveness. Results showed significant reduction in blood and sputum eosinophil levels in the treatment group but no effect on airway hyperresponsiveness or on the late asthmatic response. In a larger study, focused mostly on clinical outcomes, mepolizumab was tested on patients with persistent asthma who were symptomatic despite treatment with moderate-dose inhaled corticosteroids. In this study, mepolizumab had no effect on most clinical endpoints, including patient-reported symptom scores, lung function, or rescue medications use (33).

The disappointing effects of these early clinical trials suggested to many at the time that eosinophilic airway inflammation was not directly involved in the pathogenesis of key clinical outcomes in asthma. The alternative possibility that treatment did not have a sufficiently large effect on eosinophilic airway inflammation was unlikely because the effects of treatment on sputum and airway biopsy eosinophil numbers were at least as great as the effects seen with corticosteroids (34). However, the evidence outlined above of a closer link between eosinophilic airway inflammation and exacerbations than between symptoms and disordered airway function suggests a third possibility: treatment might have an isolated but clinically important effect on exacerbation risk.

Two recent studies have done a more rigorous evaluation of the effects of blocking IL-5 by making two important modifications to the clinical trial design: (1) treating patients with evidence of active eosinophilic airway inflammation rather than an arbitrary and unrelated clinical measure, such as a significant acute bronchodilator response, and (2) assessing the effect of treatment on asthma exacerbations, an outcome measure that is directly and potentially causally related to eosinophilic airway inflammation.

Nair and colleagues examined the effect of mepolizumab treatment for 26 weeks on asthma exacerbations and steroid dose reduction in a randomized control trial involving 20 subjects with severe eosinophilic asthma who had refractory symptoms despite treatment with oral and inhaled corticosteroid therapy (35). There was a significant difference in the exacerbation frequency between the two trial arms, with only one patient out of the nine in the mepolizumab group having an asthma exacerbation, which was noneosinophilic, compared with 10 patients out of the 11 in the placebo group. Furthermore, patients on mepolizumab were able to reduce their oral corticosteroid dose significantly more than those randomized to placebo. Haldar and colleagues enrolled 61 patients with recurrent exacerbations of asthma and

evidence of eosinophilic airway inflammation defined as a sputum eosinophil count greater than 3% on at least one occasion in the previous year (36). The asthma-related quality of life scores were significantly better in the mepolizumab group, although no difference was seen in asthma symptoms or airway function. The main effect of treatment was a 48% reduction in the number of severe asthma exacerbations requiring treatment with prednisolone (Figure 4).

The multicenter, GlaxoSmithKline-sponsored DREAM (Dose Ranging Efficacy and Safety with Mepolizumab in Severe Asthma) trial was conducted as a phase IIb drug trial to define the optimum dose of mepolizumab and to confirm the efficacy and safety in patients with eosinophilic asthma (37). The primary endpoint was the frequency of clinically significant exacerbation over the 1-year duration of the

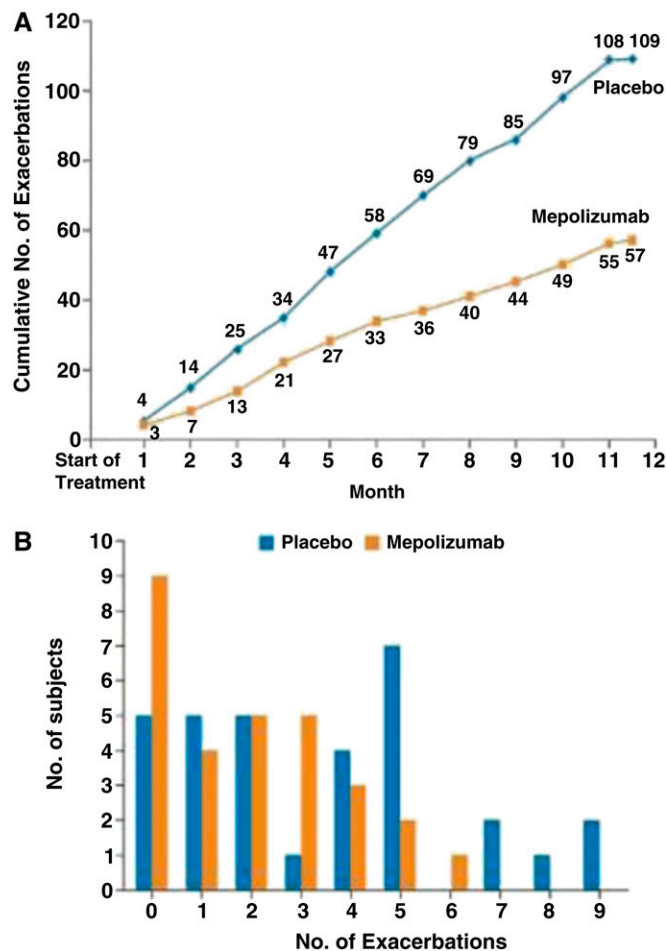


Figure 4. Cumulative severe exacerbation frequency (*top*) and exacerbation distribution (*bottom*) in patients receiving mepolizumab and placebo. Reprinted by permission from Reference 37.

treatment. A total of 621 patients were randomly assigned to receive placebo or one of three different doses of mepolizumab (75, 250, or 750 mg) in a parallel group, 12-month study. Subjects were required to have evidence of eosinophilic airway inflammation as suggested by one of more of the following documented in the previous year: a sputum eosinophil count greater than 3%, an exhaled nitric oxide concentration (FE_{NO}) of greater than 50 ppb, an asthma-related peripheral blood eosinophil count of greater than $0.3 \times 10^9/L$, and/or a prompt deterioration in asthma control after a 25% reduction in corticosteroid dose. Mepolizumab reduced severe exacerbations by about 50% in all the treatment groups compared with placebo, with no evidence of a dose-response effect. The blood and sputum eosinophil counts were reduced by treatment, and there was evidence of a dose-related effect on sputum eosinophil counts. No improvement in asthma symptoms, quality of life, FE_{NO} , or lung function was seen. The drug was shown to be safe and well tolerated. Testing the different baseline variables using multivariate methods established that only the degree of blood eosinophilia and exacerbation frequency in the previous 12 months were associated with the response to the drug.

Other types of IL-5 inhibitors have been used in clinical trials for asthma. Reslizumab is another monoclonal antibody that neutralizes IL-5 and, like mepolizumab, is administered intravenously. In a recent trial in patients with poorly controlled eosinophilic asthma, reslizumab was shown

to significantly improve FEV_1 (38). Additionally, patients in the reslizumab group had better asthma control, although the difference from the control group was not significant except in patients with concomitant nasal polyposis. Benralizumab is a monoclonal antibody that inhibits IL-5 by targeting IL-5R α and causing eosinophil cytotoxicity. Published clinical studies of benralizumab in asthma are limited, but a study of patients with mild atopic asthma, benralizumab induced profound eosinopenia (39). The theoretical ability of benralizumab to inhibit eosinophils more profoundly by targeting the common part of the IL-5R, thus blocking IL-5, IL-3, and GM-CSF signal transduction, raises the possibility that it might have more impact than monoclonal IL-5 antagonists, although this remains to be proven.

Other biological agents blocking aspects of TH-2 type inflammation have been investigated in asthma, including omalizumab (anti-IgE) and lebrikizumab (anti-IL-13.) (Table 1). These agents have in common a bigger effect on exacerbations than symptoms and lung function and a relatively selective effect in patients with evidence of activation of the TH-2 pathway (40, 41). Evidence is accumulating that inhibition of different aspects of the pathway results in subtly different effects on biomarkers and clinical measures and is predicted by different biomarkers (Table 1). In the future, it might be possible to select the optimum approach to an individual patient on the basis of a biomarker profile.

COPD is an inflammatory airway disease largely caused by smoking and,

similar to asthma, is characterized by exacerbations that contribute significantly to the morbidity of the disease. Although COPD is typically associated with sputum evidence of neutrophilic airway inflammation, up to a third of patients have evidence of eosinophilic airway inflammation. This eosinophilic group responded better to corticosteroid therapy than patients with noneosinophilic COPD (5, 42). IL-5 levels are increased in the sputum of these patients and are decreased with corticosteroid treatment (43). Thus, it is possible that treatment with biological agents inhibiting the TH-2 pathway would be helpful in this subgroup. One challenge with the clinical development of specific inhibitors of the TH-2 pathway has been that these drugs inhibit a pattern of airway inflammation, not conditions that are arbitrarily defined on the basis of physiological tests. Traditional markers of asthma, such as FEV_1 and the acute bronchodilator response, are not related to the efficacy of treatment (37). Different definitions and ideas of disease and the adoption of biomarkers that are not well known are necessary to fully realize the potential of these treatments.

Conclusions

Our understanding of the significance of eosinophilic airway inflammation in asthma has been greatly facilitated by the development of widely applicable noninvasive methods to assess airway inflammation. Observational studies have shown that eosinophilic airway inflammation is not always present in asthma, nor is it an exclusive feature of asthma. Its presence seems to be a marker of corticosteroid responsive disease, and it is closely linked to the occurrence of severe asthma exacerbations. However, it does not relate closely to the presence of symptoms or the extent of airway dysfunctions; recent evidence suggests that these features may be more closely linked to the site of localization of mast cells in the airway wall. The development of agents such as humanized monoclonal antibodies against IL-5 that are specific and effective inhibitors of eosinophilic airway inflammation offers the prospect of further refining our understanding of the role of this aspect of the inflammatory response in asthma and other airway diseases. ■

Table 1. Summary of the effects of different inhibitors of the TH-2 pathway on biomarkers and different clinical measures

Treatment	Effect on Outcome Measures			Potential Biomarkers
	FEV_1	Symptoms	Exacerbations	
Corticosteroids	++	++	++	Blood and sputum eosinophils, FE_{NO}
Anti-IL-5	0	0	++	Blood eosinophils, exacerbations
Anti-IL-13	+	0	?	FE_{NO} , periostin
CRTH2	+	+	?	?
antagonist				
Anti- α subunit	+	+	++	Blood eosinophils ? FE_{NO}
of				
IL-4 receptor				
(44)				
Anti-IgE	0	+	+	FE_{NO}

Definition of abbreviations: CRTH2 = chemoattractant receptor-homologous molecule expressed on Th2 cells; FE_{NO} = fraction of exhaled nitric oxide.

Author disclosures are available with the text of this article at www.atsjournals.org.

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