

Biomarkers in asthmatic patients: Has their time come to direct treatment?



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Asthma is a heterogeneous disease with multiple phenotypes that have variable risk factors and responses to therapeutics. Mild-to-moderate asthma often responds to traditional medications, whereas severe disease can be refractory to inhaled corticosteroids, long-acting β -agonists, and leukotriene receptor antagonists. There is robust research into the variable phenotypes of asthma. Biomarkers help define the specific pathophysiology of different asthma phenotypes and identify potential therapeutic targets. The following review will discuss the current use of biomarkers for the diagnosis of asthma, triaging the severity of a patient's disease, and the potential efficacy of treatments. This information can be used to define certain patient populations that are more likely to respond to inhaled corticosteroids or biologics. As knowledge of patient phenotypes and endotypes and biological agents to target specific classes of asthma emerge, the ability to provide personalized care to asthmatic patients will follow. (*J Allergy Clin Immunol* 2016;137:1317-24.)

Key words: Asthma, biomarkers, eosinophil, IgE, periostin, nitric oxide

Biomarkers, or biological markers, are traceable substances used to examine organ function or other aspects of health.¹ Medical biomarkers can also provide information about the pathophysiology of an underlying disease, the course of an illness, and/or the response to treatment.² At their best, biomarkers could inform us whether a disease is present or absent, define its severity, provide information about its progression, serve to select the most effective treatment, and/or serve as guidance about the affected subject's survival (Fig 1). With precision medicine on the forefront of patient care and the desire

Abbreviations used

FENO: Fraction of exhaled nitric oxide

ICS: Inhaled corticosteroid

to select the most effective treatments, biomarkers are needed to provide and play an important, expanding, and directive role by allowing physicians to predict the susceptibility, or responsiveness, of a given disease to a specific treatment. Asthma is at the forefront of this concept and for good reasons, but do we have the right biomarkers to meet this need at this time?

Biomarkers have long been an important and informative aspect of medicine, beginning with the simple measurement of body temperature to detect a fever and its significance to underlying health. The presence of a fever, for example, tells us about a change in a patient's health and possibly the underlying cause, an infection. The regression of a fever can also be informative as to the effectiveness of an intervention and indication that a patient is on the road to recovery. Blood pressure is another example of a longstanding and informative biomarker; it detects an underlying condition, hypertension, as well as risks for cardiac, renal, or neurologic disease, and is an obvious target guide for treatment. Although pulmonary function measurements tell us about the consequence of asthma and its severity and are a reflection of responsiveness to treatment, they do not always inform us about the underlying cause of disease or necessarily the factors contributing to these processes.

Biomarkers have been arbitrarily classified into 3 types.² Type 0 refers to a marker related to the natural history of the disease. At present, type 0 biomarkers in asthmatic patients are not available, but the Asthma Predictive Index is a helpful indicator of risk for disease in the unaffected child.³ Type 1 biomarkers reflect drug activity or act as markers of responsiveness and are taking on a greater importance as precision medicine comes into play with more biologics available for the treatment of asthma. Finally, type 2 biomarkers refer to surrogate markers, such as cholesterol, which might act as an indicator (or risk) of cardiovascular disease.

Physicians already use biomarkers to more effectively track disease progression,⁴ such as hemoglobin A1c, which not only measures the average blood sugar over time but also provides insight into the effectiveness of glycemic control agents. Moreover, hemoglobin A1c is a surrogate for the prognosis of disease and the likelihood of end-organ damage from diabetes.⁵ Similarly, physicians use a virologic biomarker, the CD4⁺ T-cell count, or the peripheral circulating viral load in the diagnosis, treatment, and prognosis of HIV.⁴ In particular, the viral load relates to disease etiology, severity, responsiveness to treatment, and survival. CD4⁺ T-cell counts can also serve to

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Disclosure of potential conflict of interest: W. W. Busse reports personal fees from AstraZeneca during the conduct of the study and personal fees from Novartis, GlaxoSmithKline, Genentech, Roche, Pfizer, Merck, Boehringer Ingelheim, Sanofi, Gilead, Teva, Takeda, Aerocrine, Boston Scientific, Circassia, and ICON outside the submitted work. A. Berry declares no relevant conflicts of interest.

Received for publication January 5, 2016; revised March 1, 2016; accepted for publication March 10, 2016.

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0091-6749/\$36.00

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<http://dx.doi.org/10.1016/j.jaci.2016.03.009>

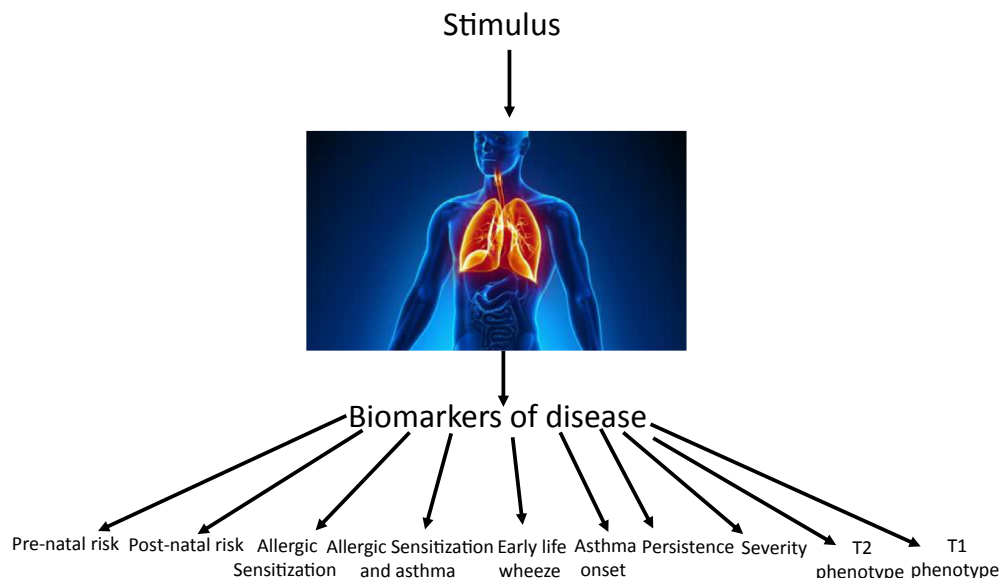


FIG 1. Potential biomarkers in relationship to asthma, beginning with prenatal risk for disease and extending to markers associated with treatment selection.

reflect the prognosis and guide responses to antiretroviral treatment in patients with AIDS.^{6,7} These biomarkers have clear clinical and practical relevance and have directed patient care toward improved outcomes.

Biomarkers in asthmatic patients have yet to reach the level of precision found with HbA1c levels or CD4⁺ counts. However, a number of biomarkers have been identified that help define asthma phenotypes and predict patient characteristics most likely to reflect responsiveness to specific therapies.

We will review the current but limited menu of biomarkers in asthmatic patients and how they might help define phenotypes and endotypes, predict disease severity, and select patient groups who will be most responsive to biologic therapies. To be most useful, biomarkers in asthmatic patients must first be vetted in large cohorts of patients, be readily accessible by measurements using standard methods to ensure widespread and accurate use, and display robust sensitivity, specificity, accuracy, and reproducibility.

WHAT HAS BEEN LEARNED AND WHAT INSIGHT HAS BEEN GAINED FROM BIOMARKERS IN ASTHMATIC PATIENTS?

Asthma is a heterogeneous disease, and for some patients, particularly those with severe disease, existing therapies have limited efficacy.⁸ This is not surprising because a wide variety of cells and inflammatory molecules act in concert in a complex manner to drive the development, severity, and pattern of inflammation in asthmatic patients and, theoretically, to eventually determine various clinical phenotypes of disease. From these efforts, it has been possible to identify biomarkers in asthmatic subpopulations and from this information gain greater insight into what treatments might be most effective.⁹ From these efforts, a small number of relevant biomarkers have emerged: eosinophil counts, fraction of exhaled nitric oxide (FENO) values, and periostin and IgE levels. However, as will be discussed, these 4 biomarkers have limitations because they are primarily important and related to patients with a T_H2-high, now referred to as T2 to

include both T_H2 cells and non-T_H2 cells as a source of cytokines, component to their asthma. Although they are helpful in this situation, a significant proportion of asthmatic patients do not express a T2 pattern and instead have, for example, neutrophils or no specific cell type involved in their airway dysfunction. Therefore the T2 markers, although highly meaningful, do not convey the full story.

EOSINOPHILS

Eosinophils are a longstanding feature or characteristic of asthma and, as a consequence, are considered fundamental to the pathophysiology of this disease, its severity, and possibly its etiology, at least in some patients.¹⁰ The histology of the lung in asthmatic patients is associated with and often characterized by eosinophilic infiltration of the airway. Based on the inflammatory capacity of the eosinophil, its presence has been believed to reflect airway injury, to contribute to airway hyperresponsiveness and remodeling, and to be a direct causative link to asthma pathophysiology.¹¹ Moreover, early studies that measured peripheral blood eosinophil counts found significant correlations between this cell's presence and disease severity, as well as a marker reflecting clinical improvement as their numbers decreased in response to treatment.^{12,13}

This cell's positioning as a relevant biomarker is supported by animal models for asthma, in which ablation of eosinophils after administration of mAbs directed toward IL-5 reduces airway inflammation and bronchial hyperresponsiveness after an allergen provocation.¹⁴ Based on these associative findings, the eosinophil was considered the causative cell of asthma, and its presence was considered an ultimate biomarker for asthma because it marked the presence of disease, its severity, and its responsiveness to treatment.

However, initial studies in broad-based asthmatic populations with anti-IL-5 mAb treatment found no effect on lung function, symptoms, or exacerbations despite a nearly total ablation of circulating eosinophils.¹⁵ These findings led to a reassessment of the significance of eosinophils to asthma, what their presence meant, and under what conditions this cell had a relationship

TABLE I. Baseline characteristics of subjects in the intention-to-treat population

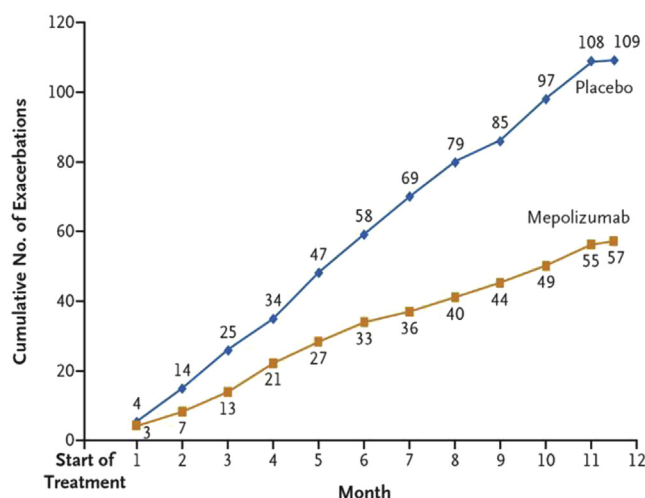
Characteristic	Mepolizumab (n = 29)	Placebo (n = 32)	P value
Age (y), mean	48	50	
Severe exacerbations per subject in previous year (no.)	5.5	5	.71
FEV ₁ after bronchodilator use (% predicted value)	78.1 ± 20.9	77.6 ± 24.1	.93
Eosinophil count in sputum (%)	6.84 ± 0.64	5.46 ± 0.75	.60
Eosinophil count in blood (×10 ⁻⁹ /L)	0.32 ± 0.38	0.35 ± 0.30	.57
Dose of ICS, beclomethasone dipropionate equivalent (μg), daily dose	2038	1711	
Use of oral prednisolone, regular use (% of subjects)	57.1	53.1	.80

and relevance to asthma. What has emerged is evidence that the eosinophil is a biomarker in asthma, representing a risk factor for exacerbations, but this relationship occurs under important and restrictive conditions: the persistent presence of eosinophils in either sputum or peripheral blood in the face of treatment with corticosteroids, either inhaled or systemic, and an absence of disease control.¹⁶

The Expert Panel Report 3 recommends inhaled corticosteroids (ICSs) as the principal anti-inflammatory or controller medication in asthmatic patients with an escalation in dose, usually in conjunction with long-acting β -agonists or leukotriene antagonists, as disease severity increases.¹⁷ For most patients with mild-to-moderate asthma, disease control can be achieved with this approach, and the use of biomarkers is not frequently necessary to guide treatment. For patients with more severe disease who continue to have frequent exacerbations despite adherence to appropriate therapy, the clinical situation is different, and biomarker monitoring might be needed to direct the selection of other therapeutics.

When Green et al¹⁸ asked whether an increase in the ICS dose to guideline care that could reduce sputum eosinophil numbers would affect asthma, they found asthma exacerbations (ie, the need for rescue systemic corticosteroids) were significantly reduced.^{18,19} Extending this concept, Halder et al²⁰ added mepolizumab, an anti-IL-5 mAb, to the treatment of asthmatic patients with severe asthma despite large doses of ICSs and, in many patients, systemic corticosteroids, along with persistent sputum and circulating eosinophils (Table I) with anti-IL-5 treatment, asthma exacerbations were reduced by approximately 50% (Fig 2).²⁰ Mepolizumab had limited effects on symptoms or lung function.²⁰ Consequently, an increased sputum eosinophil count emerged as a biomarker to indicate a risk for asthma exacerbations; however, the use of sputum analysis to assess eosinophil presence in asthmatic patients is often impractical in clinical practice.¹⁶

There is controversy as to the relative predictability of blood versus sputum eosinophil counts in relationship to asthma exacerbations. Although blood and sputum eosinophil counts in asthmatic patients correlate, earlier work indicated that sputum eosinophilia was more predictable than the blood eosinophil count for exacerbation.²¹ However, at present, the practicality of using sputum analysis to measure eosinophil counts has made this approach difficult.²² Most recently, Malinovschi et al²³ showed

**FIG 2.** Severe exacerbations during the course of the study comparing placebo versus mepolizumab. The cumulative number of severe exacerbations that occurred in each study group over the course of 50 weeks is shown. Reprinted with permission from Halder et al.²⁰

the reliability of blood eosinophil counts to indicate the risk for an asthma attack. This conclusion has largely been borne out with trials in which anti-IL-5 antibodies have been evaluated.²⁴⁻²⁶

Mepolizumab has been approved by the US Food and Drug Administration for the treatment of patients with severe asthma with frequent exacerbations despite other ongoing treatments. The outcome target of this treatment is principally to prevent exacerbations in patients with severe asthma. In the DREAM (Dose Ranging Efficacy and Safety with Mepolizumab) in severe asthma study all 3 concentrations (75, 250, and 750 mg) of mepolizumab tested reduced peripheral blood eosinophil counts and also prevented exacerbations by nearly 50%.²⁴ Moreover, in this large study mepolizumab reduced symptoms and led to a slight improvement in lung function. In a subsequent study mepolizumab was able to reduce the dose of maintenance systemic corticosteroids and still prevent exacerbations.²⁵ From the collective research to date, peripheral blood eosinophil counts of 150 eosinophils/mm³ or greater have emerged as a threshold marker of benefit from mepolizumab in patients already receiving corticosteroids, either inhaled or systemic, who still experience exacerbations.²⁶

Whether the most appropriate level of blood eosinophils is greater than 150 cells/mm³ in the face of corticosteroid treatment has not been universally established because some studies with other anti-IL-5 mAbs find benefit occurring primarily at higher levels (ie, 400 cells/ μ L).²⁷ However, there is general agreement that a persistence of peripheral blood eosinophils despite ongoing asthma controller treatment is a biomarker to indicate that an anti-IL-5 therapy might be effective and that its effectiveness is principally, but not exclusively, the prevention of exacerbations; the cut point for the peripheral blood eosinophil count to most accurately predict this response has yet to be fully determined and might vary depending on the IL-5 mAb, patient population, and outcome measured. There is also some remaining controversy that sputum eosinophils are the best source for this biomarker.

FENO

Nitric oxide is generated by airway epithelium and is a marker of T_H2 inflammation.^{28,29} Parameters for FENO measurements have been standardized by a joint American Thoracic

Society/European Respiratory Society workshop³⁰ and indicate that in patients with well-controlled asthma, the upper value of normal FENO is 25 ppb.^{31,32} However, the use of FENO in clinical practice and to reflect asthma phenotypes is more complex and nuanced. Patients with high FENO values are likely to benefit from ICSs, and values of greater than 50 ppb, particularly in the face of treatment, suggest corticosteroid-unresponsive asthma.³³ Because FENO values increase quickly once medication is stopped, this marker is often used to follow ICS medication adherence.³⁴ Clinically, a significant decrease in FENO values beginning 2 to 6 weeks after initiation of ICSs is defined as a change of 20% for starting values of greater than 50 ppb and 10 ppb for values of less than 50 ppb.^{30,35} If FENO values remain high despite corticosteroid treatment, levels of medication adherence need to be considered versus whether the underlying asthma represents a severe phenotype and unresponsiveness to usual treatment.

Like eosinophil counts, increased FENO values predict a risk for an asthma exacerbation,³⁶⁻³⁸ including exacerbations that might follow corticosteroid withdrawal. This association is particularly robust in children.^{37,39} Pijnenburg et al³⁹ found that an increase in FENO value of greater than 49 ppb occurring 4 weeks after discontinuation of ICSs predicts an asthma exacerbation, an association with a sensitivity of 71% and specificity of 93%.³⁹ Each doubling of the FENO value reflected an increased risk for an asthma exacerbation.

FENO values have many confounding factors. Although there is an association between FENO values and eosinophilic airway inflammation, the specificity of FENO to sputum eosinophilia is approximately 70%.⁴⁰ Most investigators believe these 2 biomarkers, although representing a similar T_H2 pathway, are distinct from one another. Both are equally effective in predicting responses of omalizumab and mepolizumab.⁴¹ Although corticosteroids reduce FENO values and sputum eosinophil counts, anti-IL-5 therapy reduces eosinophil counts without changing FENO values.²⁰ Interestingly, tobacco smoke decreased FENO values.⁴² FENO values are generally higher in patients with atopic disease with or without asthma.^{43,44} Obesity is associated with lower FENO values, and weight loss can result in an increase in FENO values.⁴⁵ Furthermore, there are demographic variations in FENO values that also confound its interpretation. As a rule, children have lower FENO values than adults by an average of 5 ppb.⁴⁶ Men have 25% higher FENO values than their female counterparts.⁴⁷ A complete description and understanding as to where and under what conditions FENO values play a biomarker role in asthmatic patients have yet to be established, but its ease of use promises expanded use in patients with more severe disease and in whom biological agents are being considered.

PERIOSTIN

The discovery of specific gene products generated by inflammatory cytokines, particularly T_H2 cytokines, is an example of a successful and practical development of new and potentially meaningful biomarkers in asthmatic patients. Woodruff et al⁴⁸ obtained bronchial brushings from asthmatic patients and control subjects and incubated these cells with IL-13; 3 gene products were induced by IL-13: periostin, CLCA1 (chloride channel regulation) and serpinB2. A subsequent analysis of bronchoalveolar lavage fluid from the subjects who were the source of epithelial cells found periostin

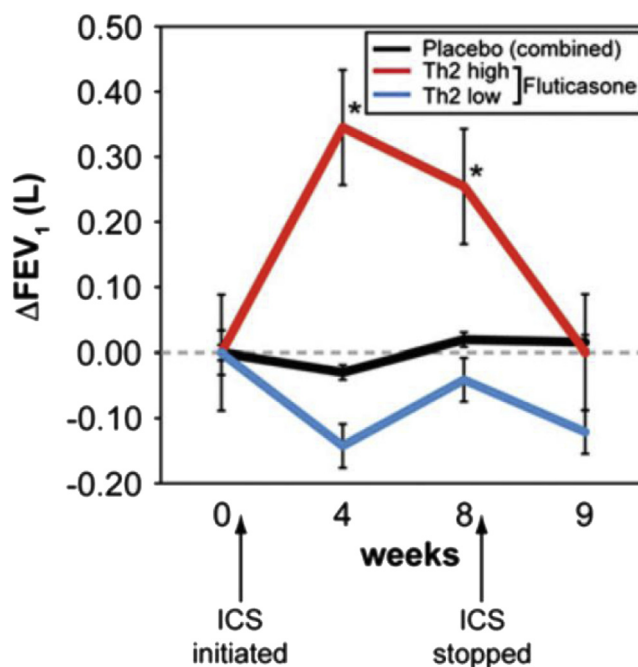


FIG 3. Responsiveness of T_H2-high asthma to ICSs and reproducibility of phenotypic markers after placebo in a randomized controlled trial. FEV₁ was measured at baseline (week 0), after 4 and 8 weeks of daily fluticasone (500 mg twice daily), and 1 week after the cessation of fluticasone (week 9). There was no significant change in FEV₁ in response to placebo at any time point in either group. Reprinted with permission of the American Thoracic Society (Copyright ©2016 American Thoracic Society) from Woodruff et al.⁴⁹ **P* < .05.

expression was higher in asthmatic patients than control subjects and that periostin levels were variable but greatest in bronchoalveolar lavage fluid, with increased concentrations of IL-4, IL-5, and IL-13. These findings suggest that increased periostin levels reflect a T_H2-high profile; in contrast, periostin levels represent a T_H2-low pattern in asthmatic patients whose mechanism of disease is not well defined. This concept was supported by assessing the response to ICSs in these 2 populations. Asthmatic patients with a T_H2-high profile and increased periostin levels had significant improvement in FEV₁, whereas the T_H2-low population did not (Fig 3).^{48,49}

Periostin is induced by IL-13, a pleiotropic T₂ cytokine, which is also produced by eosinophils, basophils, mast cells, activated T cells, and macrophages.⁵⁰ IL-13 also differentiates CD4⁺ lymphocytes into T_H2 cells. Subsets of asthmatic patients have increased IL-13 levels in their airways; periostin can be used to reflect and define T_H2 phenotypes.⁵¹ Further support for the clinical relevance of periostin has been found with the observation that an increased serum periostin level was found in patients with a greater increase in FEV₁ to anti-IL-13 mAb therapy.⁵² The administration of lebrikizumab, a humanized mAb against IL-13, improved FEV₁ values by 8.2% compared with placebo in patients with increased periostin levels; in patients with low periostin levels, improved FEV₁ was minimal (Fig 4).⁵² There was also a larger reduction in FENO values in the subgroup with high periostin levels than in the subgroup with low periostin levels to lebrikizumab (34.4% vs 4.3%).⁵³ Thus periostin might identify patients with an IL-13-dependent T₂ phenotype who will be most likely to benefit from anti-IL-13 therapy.

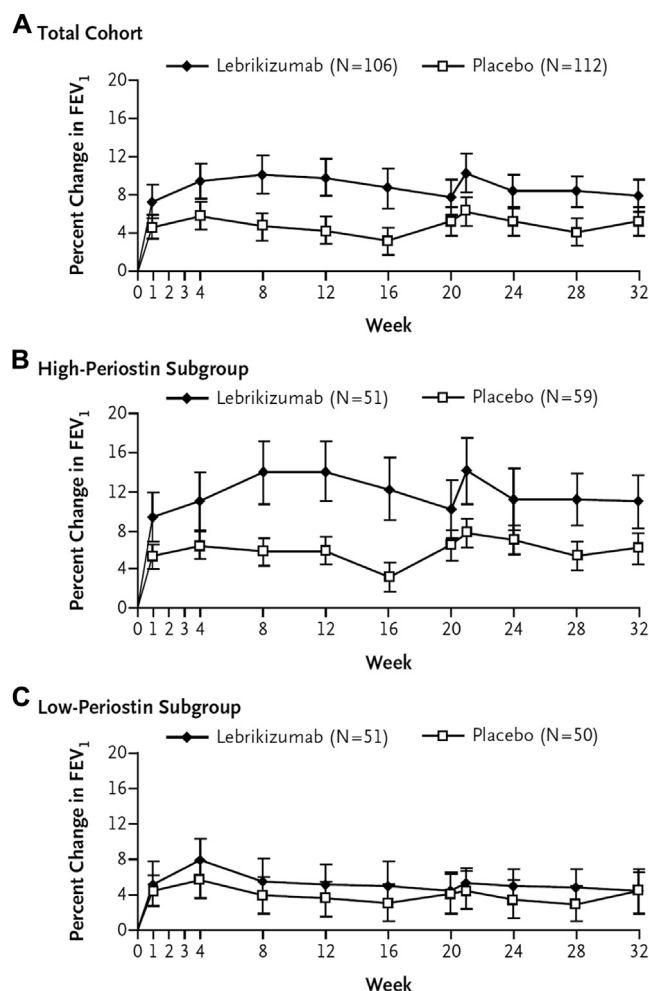


FIG 4. Relative change in FEV₁ in the intention-to-treat population. At week 12, the increase from baseline in FEV₁ was higher by 5.5 percentage points (95% CI, 0.8-10.2 percentage points) in the lebrikizumab group than in the placebo group (mean $\pm$ SE change, $9.8\% \pm 1.9\%$ vs $4.3\% \pm 1.5\%$; $P = .02$; **A**). In the subgroup of patients with high periostin levels, the relative increase from baseline FEV₁ was higher by 8.2 percentage points (95% CI, 1.0-15.4 percentage points) in the lebrikizumab group than in the placebo group (mean change, $14.0\% \pm 3.1\%$ vs $5.8\% \pm 2.1\%$; $P = .03$; **B**). Among patients in the subgroup with low periostin levels, the relative increase from baseline FEV₁ was higher by 1.6 percentage points (95% CI, -4.5 to 7.7 percentage points) in the lebrikizumab group than in the placebo group (mean change, $5.1\% \pm 2.4\%$ vs $3.5\% \pm 2.1\%$; $P = .61$; **C**). Reprinted with permission from Corren et al.⁵²

FENO values, eosinophil counts, and periostin levels reflect a T2 inflammatory response, and as such, there is obvious overlap between these individual biomarkers.^{24,52} In studies to evaluate mepolizumab and lebrikizumab, for example, there were increases in FENO values, as well as eosinophil counts²⁴ and periostin levels.⁵² Thus, at present, these markers have a general absence of specificity for components of T2 inflammation and are not precise in defining which treatment choice will be most effective.

Sorting out the relative domains and unique importance of these 3 biomarkers is important to more fully establish their individual or possibly collective predictive relevance in asthmatic patients. To begin to evaluate this question, Jia et al⁵⁴ used blood, sputum, and airway biopsy samples from 2 patient cohorts to identify systemic biomarkers of eosinophilic inflammation in

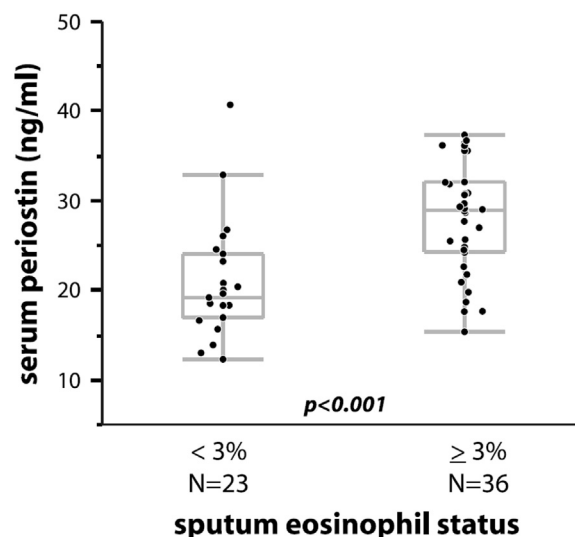


FIG 5. Peripheral blood periostin levels differentiate patients with severe uncontrolled asthma taking high-dose ICSs according to airway eosinophilic inflammation, as measured in sputum and dichotomized by sputum eosinophilia. Reprinted with permission from Jia et al.⁵⁴

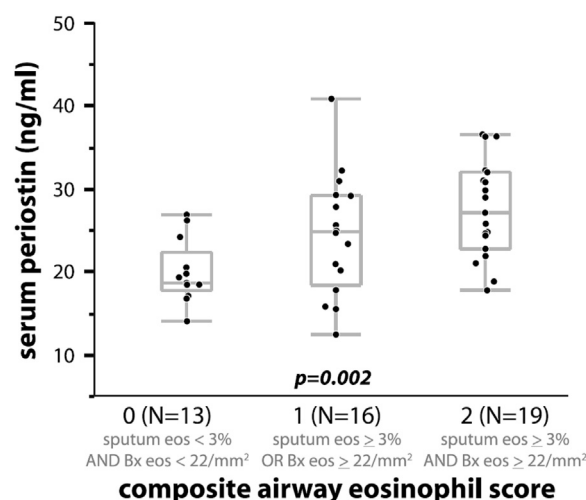


FIG 6. Peripheral blood periostin levels differentiate patients with severe uncontrolled asthma taking high-dose ICSs according to airway eosinophilic inflammation. The composite airway eosinophil score (sputum and biopsy eosinophil counts at 2 cut points) demonstrating a strong positive progression of increasing serum periostin levels with increasing scores is shown ($P < .002$, logistic regression). Bx, Biopsy. Reprinted with permission from Jia et al.⁵⁴

asthmatic patients. Although serum periostin levels paralleled markers of airway eosinophils (ie, biopsy specimens, sputum, or both), it was necessary to set cut points with eosinophil counts to see correlations (Fig 5).⁵⁴ When the sensitivity and specificity of periostin levels, FENO values, blood eosinophil counts, and IgE levels were evaluated in relationship to composite airway eosinophil status (ie, sputum and biopsy values), periostin levels had a good predictive relationship (Fig 6).⁵⁴ The findings of Jia et al⁵⁴ indicate the complexity and variability that exist between the described T_H2 biomarkers.

In addition, periostin has limitations to its use in certain patient populations because it is an extracellular matrix protein secreted

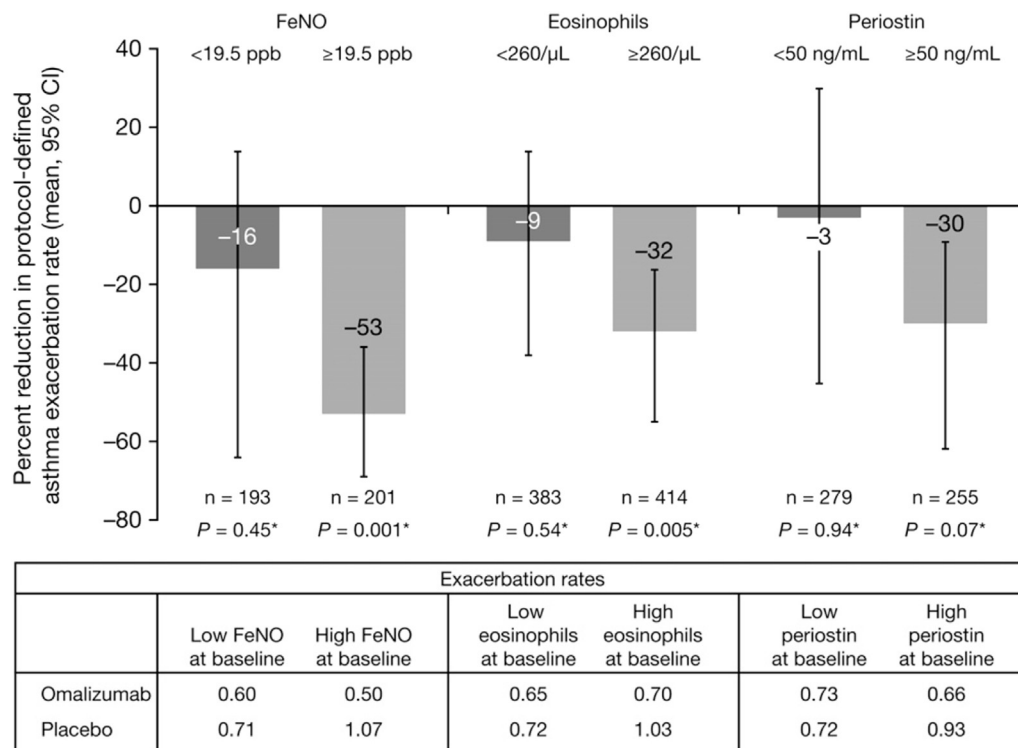


FIG 7. Mean percentage reduction (95% CI) in protocol-defined asthma exacerbation rate in the low-level and high-level biomarker subgroups (baseline FENO values, peripheral blood eosinophil counts, and serum periostin levels). *Exacerbation reduction *P* values; omalizumab versus placebo in each biomarker subgroup. Reprinted with permission of the American Thoracic Society (Copyright ©2016 American Thoracic Society) from Hanania et al.²⁸

by osteoblasts⁵⁵ and therefore is an unreliable biomarker in adults with osteoporosis or patients with recent bone fracture. Growing children will have increased periostin levels caused by high bone turnover. Certain tumor types, including glioblastoma and malignancies with bony metastasis, also result in increased periostin levels.^{56,57} Finally, increased periostin levels point to a T2 profile and are not limited to indicate benefit only for anti-IL-13 products.²⁸

IgE AND ANTIGEN-SPECIFIC IgE

A majority of asthmatic patients have allergic sensitizations. This is not surprising because the existence of allergen-specific IgE and allergen exposure are risk factors for disease expression and severity.⁵⁸ A National Institutes of Health workshop concluded that multiallergen screening to define atopy is an appropriate core biomarker for allergic sensitization in asthma clinical trials, and it is possible that this biomarker can establish which phenotype is likely to be responsive to interventions directed against T_H2 inflammation.^{59,60}

Increased serum IgE levels correlate with asthma severity in adults and children.⁶¹ The probability of wheeze and reduced FEV₁ also increases as specific serum IgE values increase. Data that link increase IgE levels to severe asthma appear more robust in children than in their adult counterparts.⁶²⁻⁶⁴ For example, the use of beclomethasone dipropionate as rescue treatment for children with mild persistent asthma identified children who benefited from ICSs as those with markers of allergic inflammation, increased IgE levels of greater than 350 μK/L, and positive skin test responses to allergens.^{62,65}

These findings suggest that in children increased antigen-specific IgE levels likely reflect a T2 profile. Based on the association of IgE levels with allergic sensitization and asthma severity, anti-IgE therapy was developed and used to treat patients with more severe disease.⁶⁶ Omalizumab (Genentech/Novartis, South San Francisco, Calif) is an injectable humanized mAb against the Cε3 domain of IgE and prevents its interaction with the high-affinity receptor FcεRI on mast cells, eosinophils, basophils, and dendritic cells.⁶⁷ The clinical requirements for omalizumab use include the presence of allergic sensitization to a perennial allergen and a feasibility dosing, which is based on the serum IgE level and patient's weight. The beneficial effects of anti-IgE therapy have been most apparent in patients with severe disease; however, the benefits of omalizumab are not necessarily predicted by the IgE level,⁶⁸ and the primary outcome associated with omalizumab, like anti-IL-5 treatment, is a prevention of asthma exacerbations.⁶⁹

Although omalizumab is approved to age 12 years in the US, most clinical trials have been conducted in adults, with very consistent 25% to 50% reductions in exacerbations.⁷⁰ To extend these findings and identify patients most likely to benefit from anti-IgE, Hanania et al²⁸ evaluated the predictive associations of biomarkers on the response to omalizumab. Three biomarkers were evaluated in relationship to risks for an exacerbation and responsiveness to omalizumab treatment: FENO values, peripheral blood eosinophil counts, and periostin levels, representing a T2 profile. The increased levels of any of these 3 biomarkers were associated with a greater risk for asthma exacerbation (Fig 7).²⁸ Also, if patients had increased FENO values, eosinophil counts,

or periostin levels, they were more likely to benefit from omalizumab, as noted by fewer exacerbations. Interestingly, there was no overlap with these biomarkers to predict either the risk for exacerbations or the benefit from omalizumab. Each of these 3 biomarkers appeared to act independently in predicting a risk for an exacerbation or benefit from omalizumab. Thus increases in biomarkers for T2 inflammation indicate that omalizumab is more likely to be of benefit and that omalizumab's benefit in preventing exacerbation might be directed toward modification of T2 inflammatory processes.

NON-T2 BIOMARKERS

A significant proportion of asthmatic patients, particularly those with severe disease, do not have a T2-enhanced phenotype.⁷¹ These patients have been classified as having a T2-low, T1-high, and T1/T_H17-high profile. These cellular markers of inflammation include neutrophilia or a paucigranulocytic pattern. At the present time, despite the importance of these patterns of inflammation to phenotypes of severe asthma, few biomarkers have emerged to define this subgroup. This absence of biomarkers for these patterns of inflammation has made it difficult to "preidentify" subjects who might respond to biologics that target this pathway, like the anti-IL-17 product brodalumab.⁷² This is an area of needed investigation to expand a biomarker recognition capability to a broader base of asthmatic patients.

CONCLUSIONS

The biomarkers most extensively studied at present in asthma are T_H2 or more generally, T2 related. Their clinical benefit might be used to phenotype features of the underlying nature of inflammation in asthmatic patients and, from these findings, select patients most likely to respond to the addition of biologics. Not all asthmatic patients, particularly those with severe disease, are characterized by a T2 profile or dominated by this pattern of inflammation. What has yet to be established is the characterization of the T2-low patient. They have asthma, often do not respond to ICSs, and do not benefit from current biologics. Nonetheless, T2-low patients have airflow obstruction, symptoms, and exacerbations. In other patients the pattern of inflammation is neutrophilic. At present, biomarkers identifying or reflecting the underlying mechanisms or aspects of disease in this setting are not available, nor are treatments available to target this pathway.

Progress has been made in the discovery, application, and implementation of biomarkers in asthmatic patients. The journey is just beginning, and the biomarkers now available, although of considerable benefit, are still too broad, too limited, and too nonspecific to identify who is at risk for asthma, what will be their pattern of disease, and what specific treatments, particularly biologics, will be most helpful. The needs for biomarkers are great and the interest high; the future for their use has yet to be fully achieved. However, we predict that within the next decade, biomarker assessment in asthmatic patients will be like HbA1c assessment in patients with diabetes and become a prerequisite criterion for selection of biological treatments. The role of biomarkers in achieving precision medicine will be critical.

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