

Editorial

Asthma biomarkers and drug trials

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An article in this month's issue of The JACI describes a clinical trial of the leukotriene receptor antagonist (LTRA) montelukast in children with asthma.¹ The paper focuses on changes in biomarkers of allergic inflammation, treating these as the primary outcome measures, but it also provides data on asthma symptom scores and lung function measures as secondary endpoints. The work is well performed and adds to our knowledge, but it also raises some interesting questions about choice of endpoints and the appropriate interpretation of biomarker studies.

In clinical trials, there is a general principle that clinical effectiveness is the overriding consideration in evaluating new drugs or new indications. Effects on allergic inflammation, though interesting, are usually considered to be subsidiary endpoints unless one is trying to use the study to dissect out mechanisms of asthma. It is now an article of faith that asthma involves allergic inflammation and that this inflammation is responsible both for bronchial irritability and for the changes in airway physiology that drive the symptoms and disability of asthma. Reducing allergic inflammation must therefore be a good idea, but there is no clear consensus about which aspects of the inflammation really matter. We now have an enormous body of information about allergic inflammation, and almost every presentation at allergy meetings now includes some variation on the standard cartoons (Figs 1-3).

A detailed review of all of the processes, cells, and molecules involved is beyond the scope of this editorial; such discussion can be found elsewhere.² However, it is clear that different authorities use the term *allergic inflammation* to mean different things. For example, there is the inflammation of acute allergic responses involving the acute release of histamine, leukotrienes, and so forth from mast cells, which causes tissue edema and mucus secretion as well as smooth muscle contraction (Fig 1). Then there is the T cell-regulated inflammatory process of granulocyte recruitment and tissue damage (Fig 2). Finally, there are the more chronic

Abbreviations used

ECP: Eosinophil cationic protein
eNO: Exhaled nitric oxide
ICS: Inhaled corticosteroid
LTRA: Leukotriene receptor antagonist

inflammatory processes, such as collagen deposition, smooth muscle proliferation, and mucus hyperplasia, loosely termed *airways remodeling* (Fig 3), though this term might more accurately be used to describe the chronic alterations to airway physiology that occur in longstanding asthma.

Assessment of clinical improvement is essential in biomarker studies. A drug trial that reported a dramatic effect on a biomarker but found no impact on symptoms or lung function would suggest either that this biomarker was irrelevant or that at best it might be an indicator of some longer-term benefit that was not reflected in standard clinical assessments. The burden of proof would lie with investigators to define the long-term benefit and confirm that it was achieved in proportion to changes in the biomarker being studied.

More interesting are studies that show a heterogeneity of response in clinical parameters and biomarkers. Let us assume that we have enough subjects to make a meaningful analysis. Several different patterns can be imagined: (a) closely correlated improvements in clinical measures and biomarkers; (b) variable clinical response and uniform change in biomarkers; (c) uniform clinical response and variable change in biomarkers; (d) complete dissociation between changes in clinical measures and changes in biomarkers. Each of these scenarios could occur as a general case or as a response in a selected subset of asthmatic patients. Among these patterns, a closely correlated response is the least interesting, because we are not looking for a biomarker to replace peak flow rates. Moreover, a close correlation cannot confirm a causal relationship. For example, if serum eosinophil cationic protein (ECP) is inversely related to lung function, this suggests that clinical improvement is linked to ECP release but it does not mean that the fall in ECP is responsible for the improvement. It might simply reflect a direct action of the drug on ECP release, whereas the true mode of action of the drug lies elsewhere. Uniform change in a biomarker with heterogeneous clinical response suggests that the biomarker is directly affected by the drug but does not represent a critical target in allergic inflammation. Conversely, variable changes in biomarker with a uniform response to the drug raise

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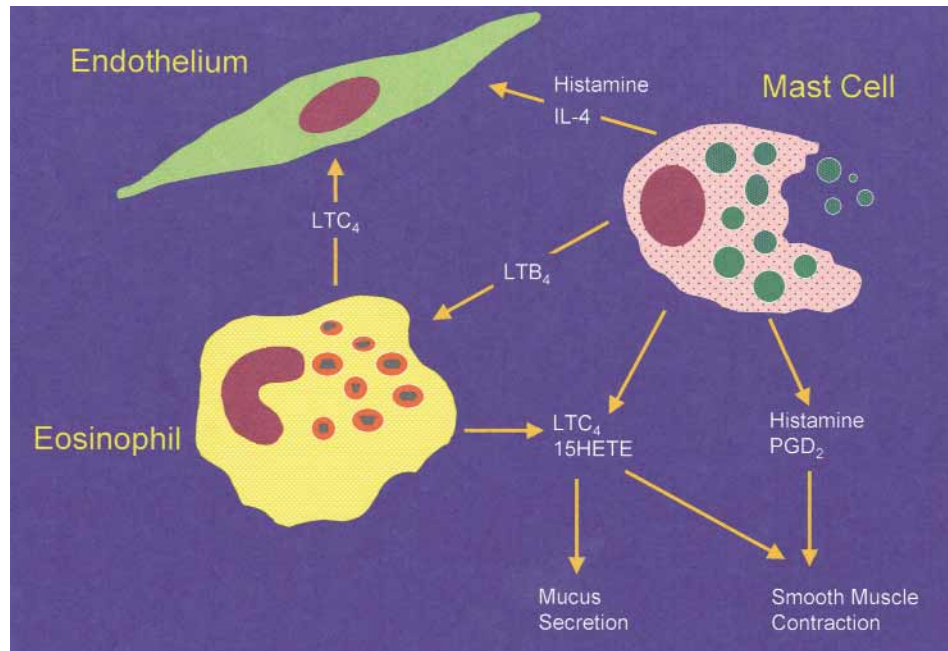


FIG 1. Mediators of acute allergic inflammation.

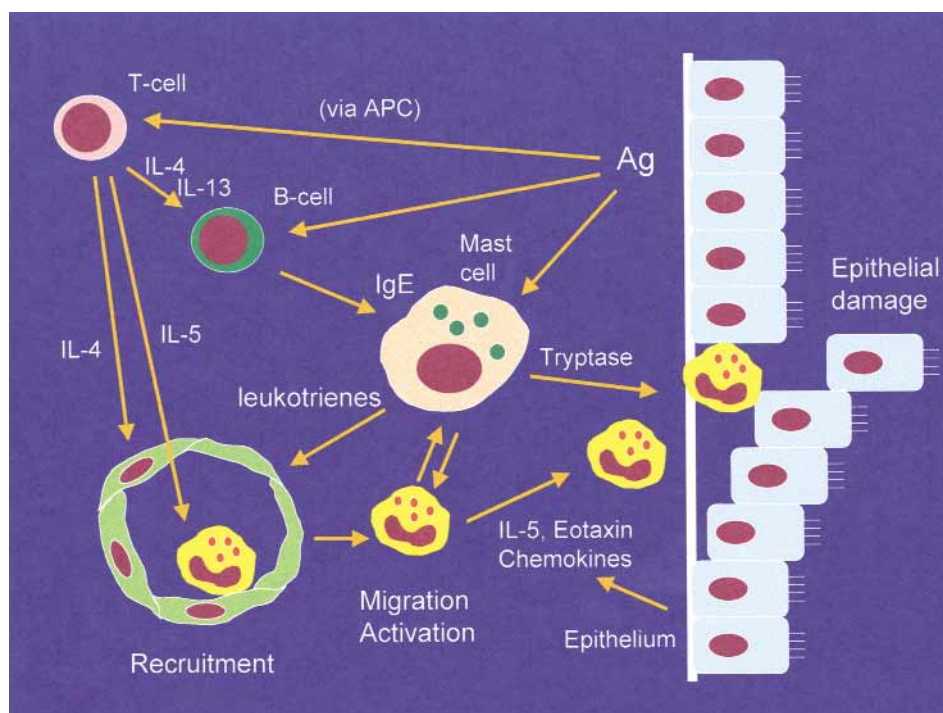


FIG 2. Mediators and cytokines involved in chronic allergic inflammation.

questions about the relevance of the biomarker to the processes targeted by the drug. Discrepancies between biomarker measurements and clinical responses are likely to add much more to our understanding, both by denying that particular markers are relevant and by highlighting the nature and extent of heterogeneity among patients with asthma.

On the basis of the known role of leukotrienes in allergic inflammation, one can see how treatment with an LTRA might do more than simply reduce bronchospasm. As well as being potent bronchoconstrictors, the sulfidopeptide leukotrienes activate inflammatory cells, induce mucus production, and have marked effects on vascular permeability. Most obviously, because eosinophils pro-

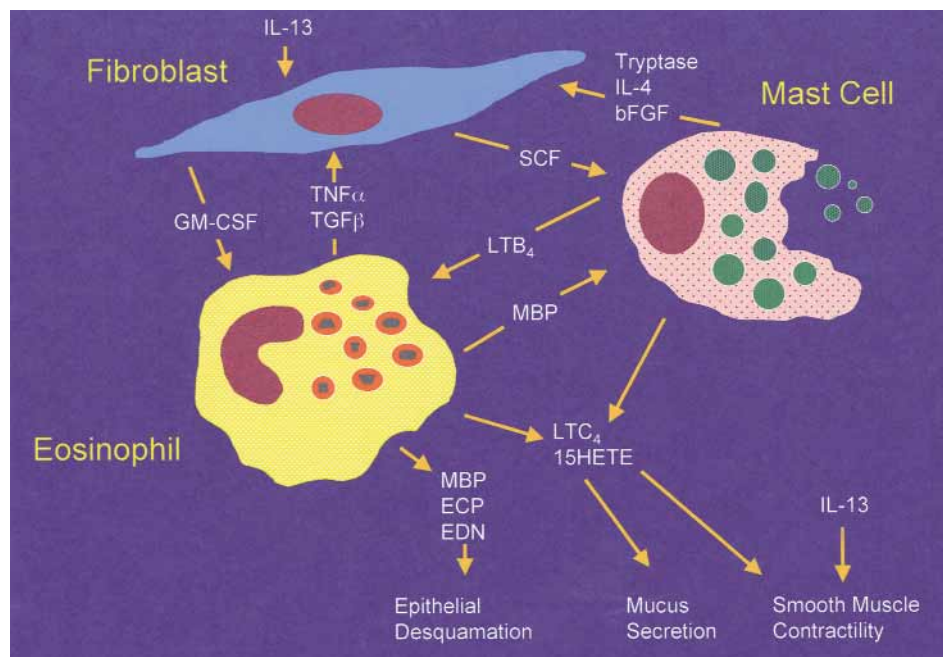


FIG 3. Mediators and cytokines involved in airways remodeling.

duce large amounts of LTC_4 , reducing eosinophil accumulation will lead directly to a reduction in leukotriene production—in a form of virtuous spiral.

A previous study has assessed the effect of montelukast on sputum eosinophilia in adults undergoing inhalation allergen challenge. Although montelukast blocked the early and late-phase physiologic responses to allergen, there was no demonstrable effect on sputum eosinophils or sputum ECP concentrations.³ In contrast, 4 weeks of treatment with montelukast reduced sputum and blood eosinophils to 50% of baseline values in a group of adults with asthma.⁴

Exhaled nitric oxide (eNO) measurements have been proposed as an alternative noninvasive measure of airway inflammation, but they are very sensitive to steroid therapy and can become dissociated from sputum eosinophil counts when patients start on inhaled corticosteroids (ICS).⁵ Consequently eNO is probably most reliable as an index of disease activity in steroid-naïve subjects. However, a short-term study of montelukast in 26 children with asthma reported a 20% reduction in eNO with montelukast compared to placebo, though montelukast did not restore eNO levels to normal.⁶ Interestingly, in the latter study, 11 of the children were already on ICS, but the effect of montelukast on eNO was similar in those receiving and those not receiving ICS.

So what are we to make of the study by Stelmach et al? We already know that LTRAs are effective agents for the treatment of asthma when added to low-dose or high-dose ICS,^{7,8} and they have been shown to have an ICS-sparing effect.⁹⁻¹² Moreover, LTRAs have been tested in children and have shown beneficial effects on lung function and peripheral blood eosinophil counts.¹³

The biomarkers chosen by Stelmach et al, though reasonable, are not exhaustive. Soluble IL-2 receptors have been studied for several years in asthma. In bronchoalveolar lavage, associations have been reported with worse lung function and with the presence of asthma symptoms.¹⁴ This marker has also been studied in blood, and a correlation with disease severity has been reported in asthmatic children aged less than 10 years, higher concentrations being seen in those with nonatopic asthma.¹⁵ Serum ECP is primarily a marker of eosinophil releasability, whereas IL-4 might arise from cells of several different types, not only from T cells.¹⁶ Although IL-4 is critical to IgE class-switching, it has multiple effects that are relevant to allergic inflammation, including direct effects on vascular endothelial cells and mucus glands. This is probably why strategies targeting IL-4 have proved more effective than a number of other immunomodulatory approaches to controlling asthma.¹⁷ Soluble ICAM-1 is thought to be a marker of endothelial activation and has been reported as elevated both in stable asthma¹⁸ and in asthma exacerbations in adults and children.^{19,20}

Thus the study by Stelmach et al confirms that montelukast is clinically effective in children, and it shows that as a consequence of LTRA therapy, several aspects of allergic inflammation are reduced, either directly or indirectly. This result confirms and extends previous work showing that LTRAs can affect biomarkers of asthma. The extent to which these changes in biomarkers are causally related to the clinical effects remains unclear, but the implication is that as well as antagonizing the actions of leukotrienes, LTRAs might also debulk the inflammatory process. It is presumed that this is due to a

combination of (a) direct effects on cells that are no longer able to respond to leukotrienes at the inflammatory site and (b) indirect effects that reduce the recruitment and activation of inflammatory effector cells. Ultimately, the clinical positioning of antiasthma drugs should be based primarily on their effects on symptoms and lung function rather than on their action against indirect markers of airway inflammation. However, this type of biomarker study can certainly help us to achieve a better understanding of the interrelationships among the various inflammatory processes that occur in asthma.

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