

Biomarkers and inhaled corticosteroid responsiveness in asthmatic patients

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Readers of the *Journal* interested in assessment of biomarkers of eosinophilic T_H2-high airway inflammation might be confused by recent guidelines on their use in the diagnosis and management of asthma. The 2014 Global Initiative for Asthma guidelines¹ state that fraction of that exhaled nitric oxide (FENO) “has not been established as being useful for making a diagnosis of asthma” and go on to say that “it cannot be recommended at present for deciding whether to treat patients with possible asthma with inhaled corticosteroids.” The blood eosinophil count is endorsed as a means of identifying patients at risk of asthma attacks, but little guidance is provided on how one should act on this information. The American Thoracic Society/European Respiratory Society severe asthma guidelines² make a lukewarm recommendation for induced sputum eosinophil-guided management but a strong suggestion that clinicians do not use FENO to guide therapy in adults and children with severe asthma. In contrast, the 2011 American Thoracic Society clinical practice guidelines³ provide a clear and unambiguous recommendation that FENO be used to identify eosinophilic airway inflammation and an increased likelihood of corticosteroid-responsive disease, and the 2014 British guidelines⁴ see biomarker-directed diagnosis and management as “a promising approach.”

What are we to make of this conflicting guidance? One concern is that the highly influential Global Initiative for Asthma guidelines will stop any further development of biomarker-guided management in its tracks. A better response is to recognize that endorsement of biomarker-directed management is a big step for a global guideline organization to take and to begin work on new studies that develop the evidence base for the use of biomarkers and have the potential to change thinking. This is a tall order because a complete rethinking of the basic philosophy of management is required to implement biomarker-assisted clinical approaches for asthma. Moreover, additional evidence on feasibility, which biomarker to assess in different circumstances, and whether such a management approach is feasible and

cost-effective is required before use of biomarkers can be recommended in nonspecialist settings, where most key management decisions are made.

In relation to the basic philosophy of management, 3 fundamental truths are emerging. First, biomarkers assess eosinophilic T_H2-mediated inflammation rather than asthma, a diagnosis that remains based on recognition of a characteristic pattern of symptoms and disordered airway function. There is a significant disconnect between symptoms and impaired airway function on the one hand and the presence of eosinophilic T_H2-high airway inflammation on the other.^{3,5}

Second, persistent eosinophilic T_H2-high inflammation is more closely associated with the short- and long-term response to corticosteroids⁵ and other more specific inhibitors of T_H2 inflammation⁶ than the presence of symptoms or the results of traditional tests of airway dysfunction.

Finally, the main clinical consequence of persistent eosinophilic T_H2-high inflammation in patients already treated with inhaled corticosteroids is an increased risk of asthma attacks.⁶ This is particularly the case in patients with more severe disease in whom the main effect of treatment that targets inflammation is to reduce the risk of attacks.⁶

In this issue of the *Journal*, Cowan et al⁷ provided new information on the relationship between markers of eosinophilic T_H2-high inflammation and the short-term response to inhaled corticosteroids. The authors carried out additional analysis of an earlier uncontrolled trial⁸ of the introduction of 500 µg of inhaled fluticasone dipropionate twice daily in patients whose symptoms deteriorated and/or who had evidence of persistent asthma within 28 days of withdrawal of inhaled steroids. The ability of 3 tests of eosinophilic T_H2-high inflammation to predict inhaled corticosteroid responsiveness was compared: measurement of induced sputum differential eosinophil counts, FENO values, and urinary bromotyrosine levels. The study would probably not pass muster in the corridors of power at the Global Initiative for Asthma because the design is artificial and there is a high potential for improvement with treatment as a result of regression to the mean and selection of a particularly corticosteroid-responsive population. In addition, the authors mainly evaluated surrogate markers of treatment efficacy, the most responsive of which (airway responsiveness to inhaled adenosine monophosphate) is of uncertain clinical relevance. However, these deficiencies do not compromise the basic aim of the study, which was to compare the predictive ability of the different biomarkers, and we believe the new information provided by the study is important and has the potential to change current thinking.

All biomarkers were associated with a positive response to treatment, and there was little to choose between them. Their findings bolster the evidence base on the use of biomarkers of eosinophilic T_H2-high inflammation to predict corticosteroid

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response. Readers might be surprised how large the effect was given that the participants already had objective evidence of symptomatic asthma. The finding of an increased biomarker level increased the odds of a response up to 10-fold, with the odds generally increasing in parallel to the rigor of the definition of a response to inhaled corticosteroid. Thus armed with the additional information provided by assessment of a biomarker, the clinician is in a stronger position to predict response to inhaled corticosteroid treatment and market this treatment to a potentially skeptical patient. The study validated previous cut points for the more familiar biomarkers, although the skilled clinician might well choose different cut points depending on the clinical question and likely response to that question.

The study is notable in that it provides the first information on the use of urinary bromotyrosine, a less familiar biomarker of eosinophilic T_H2 -high inflammation. Bromotyrosine is a product of the effect of eosinophil peroxidase-generated hypobromous acid on protein tyrosine and is therefore likely to be a specific marker of eosinophil-mediated inflammation. It might be clinically useful because it is applicable in situations in which blood, sputum, and exhaled breath assessment are not possible.

The study also provides new information on the “which biomarker when” question. The effects of combinations of biomarkers were additive such that a patient with 2 or 3 positive test results were more likely to cross the threshold of inhaled corticosteroid response than a patient who had only 1 abnormal test result. Thus the more information the clinician has on biomarkers of eosinophilic T_H2 -high inflammation, the better. This finding parallels earlier findings showing that the ability of biomarkers to predict the occurrence of asthma attacks is additive.⁹

It seems that, as with cardiovascular risk reduction, the clinician should seek to build up as detailed a profile as possible to refine prediction of risk and likely treatment benefits.

The different biomarkers assessed by Cowan et al⁷ were not clearly related, raising the possibility that they identify different aspects of T_H2 -mediated inflammation. Could this be clinically important? This question was not addressed, but earlier work has shown that blood eosinophilia is more closely associated with the risk of severe asthma attacks than an increased FENO value.⁹ Existing data also show differences in the ability of biomarkers to predict treatment responsiveness. FENO and serum periostin values are good biomarkers of treatment response to biological agents inhibiting IL-13,¹⁰ whereas blood eosinophil counts are most closely associated with a response to anti-IL-5.⁶ Moreover, treatment with anti-IL-5 reduces the blood eosinophil count but not the FENO value,⁶ whereas the reverse is true for anti-IL-13.¹⁰ Whether these biomarkers can be used to identify subgroups of patients within the T_H2 -high population who have different risk profiles and are particularly suited to different cytokine blockade will be an important future research question.

Perhaps the biggest block to biomarker-directed management is that there is little information on the feasibility, efficacy, and cost-effectiveness of this approach in nonspecialist settings, where most key management decisions are made. This perception might change because a recent study in primary care has shown that FENO-guided management reduces the rate of asthma attacks, does not increase treatment burden, and appears to be cost-effective.¹¹ In addition, nonspecialist clinicians might be more receptive to this approach than specialists think because they are less encumbered by outdated paradigms and more familiar with the use of biomarkers to profile risk and likely treatment responsiveness as a result of their work in other fields. The British National Institute for Health and Care Excellence, the primary role of which is to assess the cost-effectiveness of new treatments and diagnostics, has recently published a guidance document for the clinical use of FENO measurement.¹² After a detailed investigation of available evidence, the National Institute for Health and Care Excellence concludes that “the use of FENO measurement for asthma management in adults is likely to be cost-effective.” This assessment might well turn out to be more influential than guidelines, particularly in health care systems that prioritize cost-effectiveness.

REFERENCES

1. Barros MJ, Zammattio SL, Rees PJ. Effect of changes in inspiratory flow rate on cough responses to inhaled capsaicin. *Clin Sci (Lond)* 1991;81:539-42.
2. Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J* 2014;43:343-73.
3. Dweik RA, Boggs PB, Erzurum SC, Irvin CG, Leigh MW, Lundberg JO, et al. An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FENO) for clinical applications. *Am J Respir Crit Care Med* 2011;184:602-15.
4. British guideline on the management of asthma. *Thorax* 2014;69(suppl 1):1-192.
5. Smith AD, Cowan JO, Brassett KP, Filsell S, McLachlan C, Monti-Sheehan G, et al. Exhaled nitric oxide: a predictor of steroid response. *Am J Respir Crit Care Med* 2005;172:453-9.
6. Pavord ID, Korn S, Howarth P, Bleecker ER, Buhl R, Keene ON, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *Lancet* 2012;380:651-9.
7. Cowan DC, Taylor DR, Peterson LE, Cowan JO, Palmay R, Williamson A, et al. Biomarker-based asthma phenotypes of corticosteroid response. *J Allergy Clin Immunol* 2015;135:877-83.
8. Cowan DC, Cowan JO, Palmay R, Williamson A, Taylor DR. Effects of steroid therapy on inflammatory cell subtypes in asthma. *Thorax* 2010;65:384-90.
9. Malinovschi A, Fonseca JA, Jacinto T, Alving K, Janson C. Exhaled nitric oxide levels and blood eosinophil counts independently associate with wheeze and asthma events in National Health and Nutrition Examination Survey subjects. *J Allergy Clin Immunol* 2013;132:821-7, 827.e1-5.
10. Corren J, Lemanske RF, Hanania NA, Korenblat PE, Parsey MV, Arron JR, et al. Lebrikizumab treatment in adults with asthma. *N Engl J Med* 2011;365:1088-98.
11. Honkoop PJ, Loijmans RJ, Termeer EH, Snoeck-Stroband JB, van den Hout WB, Bakker MJ, et al. Symptom- and fraction of exhaled nitric oxide-driven strategies for asthma control: a cluster-randomized trial in primary care. *J Allergy Clin Immunol* 2015;135:682-8.
12. Measuring fractional exhaled nitric oxide concentration in asthma: NIOX MINO, NIOX VERO and NOBreath. NICE diagnostic guidance 12 (British National Institute for Health and Care Excellence). Available at: <http://www.nice.org.uk/dg12>. Accessed January 3, 2015.