

What is an “eosinophilic phenotype” of asthma?

Parameswaran Nair, MD, PhD, FRCP, FRCPC *Hamilton, Ontario, Canada*

Key words: Sputum eosinophils, blood eosinophils, fraction of exhaled nitric oxide, asthma, phenotype

The role of eosinophils as a key player in the pathophysiology of asthma has been debated, despite evidence that the cells are present and activated in the airway lumen and tissue¹ of patients with current asthma, that the cells are increased in number when asthma is uncontrolled or severe² and decreased in number when asthma is controlled,³ and that treatment strategies that aim to control airway eosinophilia are significantly more effective and less expensive in improving asthma control⁴ and decreasing asthma exacerbations compared with guideline-based clinical strategies. Cynicism was fuelled by observations that in murine models of allergic sensitization airway hyperresponsiveness could be induced without eosinophils.⁵ Skepticism grew stronger when therapy with mAbs against IL-5, which has no known clinically relevant biologic activity other than on eosinophils, did not result in improvement in asthma outcomes despite decreasing airway and blood eosinophil numbers.^{6,7}

A major reason for the failure of the early anti-IL-5 clinical trials was that the patients recruited into the studies were not identified to have a predominantly eosinophil-driven disease.⁸ Traditionally, treatment decisions are made on the basis of patient-reported symptoms or measures of airflow or airway hyperresponsiveness. The cellular nature of inflammation is not often identified, although quantitative cell counts in sputum provide a reliable and relatively noninvasive method to assess bronchitis. Sputum examination has identified cellular heterogeneity in asthmatic patients in routine clinical practice⁹ and in patients recruited into clinical trials.¹⁰ The importance of careful phenotyping and the relevance of eosinophils in asthmatic patients were confirmed by the demonstration of the efficacy of anti-IL-5 mAb therapy in patients with asthma who had consistently increased eosinophil counts in sputum of greater than 2.5% to 3% on at least 2 occasions.¹¹

However, there is a perceived difficulty in implementing sputum cell counts in routine clinical practice because it requires access to a laboratory. Therefore alternative methods to identify the “eosinophil phenotype” have been explored. Measurements of fraction of exhaled nitric oxide levels, blood eosinophil counts,

and periotin levels in serum are the most widely used methods. Measurement of eosinophil counts in blood has the advantage of being inexpensive and widely available. However, these measurements are nonspecific for asthma, and all asthmatic patients do not have increased blood eosinophil counts.¹² However, when increased, a direct correlation exists between blood eosinophil counts and symptom scores,¹³ whereas there is an inverse correlation with FEV₁ in both children and adults.¹³ In asthmatic patients blood eosinophil counts start to decrease within 24 hours after intravenous administration of anti-IL-5 antibody, followed by much greater decreases several days later.^{11,14} When used along with other clinical variables, particularly consistent response to prednisone, increased blood eosinophil counts have been shown to be a predictor of response to mepolizumab therapy¹⁵ and more recently, to dupilumab therapy.¹⁶

In this issue of the *Journal*, Hastie et al¹⁷ have examined the ability of multiple clinical variables, fraction of exhaled nitric oxide levels, and blood eosinophil counts to identify an eosinophil phenotype of asthma. The sensitivity and specificity of blood eosinophil counts of greater than 300/ μ L to detect an “eosinophil phenotype” based on sputum eosinophil counts of greater than 2% were 59% and 65%, respectively, over a range of asthma severity. The accuracy was 63%, and the positive predictive value was 50%. Factor analysis and stepwise selection found fraction of exhaled nitric oxide and serum IgE levels and FEV₁ percent predicted values, but not blood eosinophil counts, correctly predicted 69% of sputum eosinophil counts of less than or greater than 2%. The ability of clinical variables, such as age, FEV₁, asthma duration, and blood neutrophil counts, to predict a “neutrophilic phenotype” defined as a sputum neutrophil count of greater than 40% was just as poor. The poor correlations between blood eosinophil and sputum eosinophil counts are consistent with our observations in patients with severe asthma (Fig 1)¹¹ and those with mild-to-moderate asthma.¹⁸ Furthermore, because the nature of bronchitis can change over time in an individual patient,^{9,19} the correlations between blood and airway eosinophil counts and neutrophil counts are likely to be even lower in longitudinal studies. However, it remains to be seen whether higher cutoff levels of blood eosinophil counts would improve the positive predictive value of identifying the eosinophilic phenotype. Recent studies with reslizumab, another anti-IL-5 mAb, seem to suggest that blood eosinophil counts of greater than 400/ μ L might be able to improve the prediction of sputum eosinophil counts of greater than 3%.²⁰

These observations have very important clinical implications. Increased blood eosinophil or neutrophil counts are not specific for asthma, and they do not accurately identify airway eosinophilia or neutrophilia in prednisone-dependent asthmatic patients. Thus it might be prudent not to use these to guide therapy with biologic agents in patients who might have an eosinophil- or neutrophil-driven disease, particularly when the efficacy of using sputum eosinophil^{11,20,21} and neutrophil²² counts to guide such

From the Department of Medicine, Division of Respiriology, McMaster University.
Supported by a Canada Research Chair in Airway Inflammometry.

Disclosure of potential conflict of interest: P. Nair has consultant arrangements with Teva; has received grants from GlaxoSmithKline, Novartis, and AstraZeneca; has received payment for lectures from Merck; has a patent for a biological filtration device; and has received travel support from Novartis.

Received for publication May 6, 2013; accepted for publication May 7, 2013.

Corresponding author: Parameswaran Nair, MD, PhD, FRCP, FRCPC, McMaster University, Firestone Institute for Respiratory Health, 50 Charlton Ave E, St Joseph's Healthcare, Hamilton, Ontario L8N 4A6, Canada. E-mail: parames@mcmaster.ca.

J Allergy Clin Immunol 2013;■■■:■■■-■■■.
0091-6749/\$36.00

© 2013 American Academy of Allergy, Asthma & Immunology
<http://dx.doi.org/10.1016/j.jaci.2013.05.007>

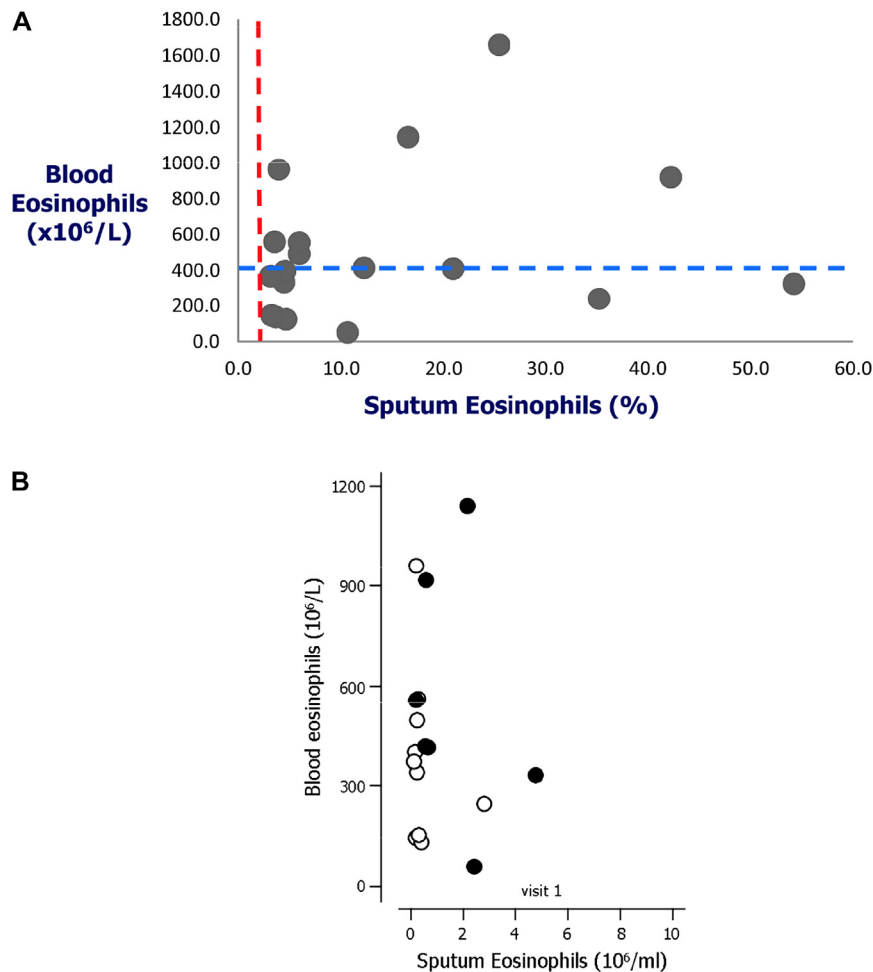


FIG 1. Poor correlation between blood eosinophils ($\times 10^6/L$) and sputum eosinophils (percentages; **A**) and between blood eosinophils ($\times 10^6/L$) and sputum eosinophils ($10^6/ml$; **B**) at baseline in patients who entered a clinical trial of mepolizumab for severe eosinophilic asthma.¹¹

therapies has been demonstrated. This becomes even more important in downtitrating the dose of steroids or anti-inflammatory therapy because sputum eosinophil counts have been shown to be much more sensitive to change than blood eosinophil counts as early as 3 months before an exacerbation.²³ In summary, until further studies are available, identification of an eosinophil phenotype based on tissue or luminal eosinophilia in sputum seems to be the most accurate and clinically relevant method, and a point-of-care test to identify eosinophil activity would overcome the perceived difficulty of measuring cell counts in sputum.

REFERENCES

- Bousquet J, Chanez P, Lacoste JY, Barnéon G, Ghavanian N, Enander I, et al. Eosinophilic inflammation in asthma. *N Engl J Med* 1990;323:1033-9.
- van Veen IH, Ten Brinke A, Gauw SA, Sterk PJ, Rabe KF, Bel EH. Consistency of sputum eosinophilia in difficult-to-treat asthma: a 5-year follow-up study. *J Allergy Clin Immunol* 2009;124:615-7.
- Jayaram L, Pizzichini MM, Cook RJ, Boulet LP, Lemi re C, Pizzichini E, et al. Determining asthma treatment by monitoring sputum cell counts: effect on exacerbations. *Eur Respir J* 2006;27:483-94.
- Petsky HL, Cates CJ, Lasserson TJ, Li AM, Turner C, Kynaston JA, et al. A systematic review and meta-analysis: tailoring asthma treatment on eosinophilic markers (exhaled nitric oxide or sputum eosinophils). *Thorax* 2012;67:199-208.
- Wills-Karp M, Karp CL. Eosinophils in asthma: remodeling a tangled tale. *Science* 2004;305:1726-9.
- Leckie MJ, ten Brinke A, Khan J, Diamant Z, O'Connor BJ, Walls CM, et al. Effects of an interleukin-5 blocking monoclonal antibody on eosinophils, airway hyper-responsiveness, and the late asthmatic response. *Lancet* 2000;356:2144-8.
- Flood-Page PT, Menzies-Gow AN, Kay AB, Robinson DS. Eosinophil's role remains uncertain as anti-interleukin-5 only partially depletes numbers in asthmatic airway. *Am J Respir Crit Care Med* 2003;167:199-204.
- O'Byrne PM, Inman MD, Nair P. The trials and tribulations of IL-5, eosinophils, and allergic asthma. *J Allergy Clin Immunol* 2001;108:503-8.
- D'Silva L, Hassan N, Wang HY, Kjarsgaard M, Efthimiadis A, Hargreave FE, et al. Heterogeneity of bronchitis in airway diseases in tertiary care clinical practice. *Can Respir J* 2011;18:144-8.
- Hastie AT, Moore WC, Meyers DA, Vestal PL, Li H, Peters SP, et al. Analyses of asthma severity phenotypes and inflammatory proteins in subjects stratified by sputum granulocytes. *J Allergy Clin Immunol* 2010;125:1028-36.e13.
- Nair P, Pizzichini MM, Kjarsgaard M, Inman MD, Efthimiadis A, Pizzichini E, et al. Mepolizumab for prednisone-dependent asthma with sputum eosinophilia. *N Engl J Med* 2009;360:985-93.
- Frick WE, Sedgwick JB, Busse WW. The appearance of hypodense eosinophils in antigen-dependent late phase asthma. *Am Rev Respir Dis* 1989;139:1401-6.
- Ulrik CS. Peripheral eosinophil counts as a marker of disease activity in intrinsic and extrinsic asthma. *Clin Exp Allergy* 1995;25:820-7.
- Kips JC, O'Connor BJ, Langley SJ, Woodcock A, Kerstjens HA, Postma DS, et al. Effect of SCH55700, a humanized anti-human interleukin-5 antibody, in severe persistent asthma: a pilot study. *Am J Respir Crit Care Med* 2003;167:1655-9.
- Pavord I, Korn S, Howarth P, Bleecker ER, Buhl R, Chanez P. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *Lancet* 2012;380:651-9.

16. Wenzel S, Ford L, Pearlman D, Spector S, Sher L, Skobieranda F, et al. Dupilumab in persistent asthma with elevated eosinophil levels. *N Engl J Med* 2013; May 21 [Epub ahead of print].
17. Hastie AT, Moore WC, Li H, Rector BM, Pascual RM, Peters SP, et al. Biomarker surrogates do not accurately predict sputum eosinophils and neutrophils in asthma. *J Allergy Clin Immunol* 2013. ■■■;■■■.
18. Pizzichini E, Pizzichini MM, Efthimiadis A, Dolovich J, Hargreave FE. Measuring airway inflammation in asthma: eosinophils and eosinophilic cationic protein in induced sputum compared with peripheral blood. *J Allergy Clin Immunol* 1997; 99:539-44.
19. D'silva L, Cook RJ, Allen CJ, Hargreave FE, Nair P. Changing pattern of sputum cell counts during successive exacerbations of airway disease. *Respir Med* 2007; 101:2217-20.
20. Castro M, Mathur S, Hargreave F, Boulet LP, Xie F, Young J, et al. Reslizumab for poorly controlled, eosinophilic asthma: a randomized, placebo-controlled study. *Am J Respir Crit Care Med* 2011;184:1125-32.
21. Haldar P, Brightling CE, Hargadon B, Gupta S, Monteiro W, Sousa A, et al. Mepolizumab and exacerbations of refractory eosinophilic asthma. *N Engl J Med* 2009;360:973-84.
22. Nair P, Gaga M, Zervas E, Alagha K, Hargreave FE, O'Byrne PM, et al. Safety and efficacy of a CXCR2 antagonist in patients with severe asthma and sputum neutrophils: a randomized, placebo-controlled clinical trial. *Clin Exp Allergy* 2012;42:1097-103.
23. Pizzichini MM, Pizzichini E, Clelland L, Efthimiadis A, Mahony J, Dolovich J, et al. Sputum in severe exacerbations of asthma: kinetics of inflammatory indices after prednisone treatment. *Am J Respir Crit Care Med* 1997;155:1501-8.