

Biomarkers of Type 2 Airway Inflammation in Airway Disease: And Then There Were Two



Ian D. Pavord, MD, DM FMedSci^a, and Jonathan Corren, MD^b Oxford, UK; and Los Angeles, Calif

There is growing interest in a new approach to the management of airway disease where the target of treatment is a measurable biological process (ie, a treatable trait) rather than potentially unrelated symptoms and impaired lung function.^{1,2} The blood eosinophil count and the fraction of exhaled nitric oxide (FeNO) are of acknowledged value in identifying patients with severe asthma who are likely to respond to biological agents targeting the type 2 cytokines IL-5, IL-4, and IL-13,³⁻⁶ and the blood eosinophil count has emerged as a reliable and robust predictor of the response to inhaled corticosteroids in patients with chronic obstructive pulmonary disease.^{7,8} A particular attraction of these biomarkers is their ease of measurement and the availability of a rapid result, features that make them eminently suitable for use in nonspecialist and emergency settings.

A third biomarker, serum periostin has attracted attention as a potential prognostic and predictive biomarker of type 2 inflammation that could be developed as a near-patient test. This biomarker was identified after researchers showed that one of the 3 most differentially expressed bronchial epithelial genes between asthmatic patients and healthy control subjects was

periostin and that expression of this gene was downregulated by inhaled corticosteroid treatment and induced by recombinant IL-13 treatment *in vitro*.^{9,10} Serum periostin was subsequently shown to perform well as a predictive biomarker of the response to the anti-IL-13 monoclonal antibody lebrikizumab in a phase 2b study¹¹ and as a prognostic and predictive biomarker of a beneficial response to omalizumab⁶ in patients with allergic asthma. There is also evidence that classification of a patient's type 2 status based on a composite score of FeNO, blood eosinophils, and periostin provides better prognostic information on exacerbation risk than that provided by individual biomarkers.¹²

The potential value of periostin as a predictive biomarker was assessed in a large observational study reported in this issue of the *Journal of Allergy and Clinical Immunology: In Practice*.¹³ ARIETTA was a 52-week, prospective, single-arm, longitudinal, international, noninterventional, multicenter study in adult patients with severe asthma. The study was designed to capture data on biomarker phenotypes and treatment patterns in real-world patients with severe asthma and to examine the role of key type-2 biomarkers in routine clinical practice. The primary objective of the study was to compare the asthma exacerbation rate over 52 weeks in patients with high (≥ 50 ng/mL) versus low (< 50 ng/mL) serum levels of periostin at baseline. The findings were disappointing in that higher serum levels of periostin were not associated with an increased risk of severe exacerbations. Periostin correlated only weakly with FeNO and blood eosinophil counts, perhaps because these different biomarkers assess different aspects of type 2 airway inflammation¹⁴ and there was no evidence for additive prognostic value when considered in combination with the other 2 biomarkers. The disappointing findings with serum periostin should be considered alongside the failure of periostin as a predictive biomarker in the phase 3 LAVOLTA studies of lebrikizumab in moderate-severe asthma,¹⁵ the findings of which led to the early termination of the ARIETTA study.

Why then has serum periostin not lived up to its initial promise? Serum levels are higher in children¹⁶ and in those of Chinese descent,¹⁷ particularly women. There is therefore the potential for racial, age, and gender related factors to limit the predictive and prognostic value of periostin. However, most of these factors were investigated in a multivariable model, and the results still indicated limited prognostic value for periostin. Periostin is a nonstructural extracellular matrix protein highly expressed at sites of injury, growth, or inflammation including in bone and teeth. Investigating whether perturbations of bone or teeth might have confounded the relationship is a less straightforward matter.

The ARIETTA study did show that the blood eosinophil count and FeNO performed well, with raised values of both

^aRespiratory Medicine Unit and Oxford Respiratory NIHR Biomedical Research Centre, Nuffield Department of Medicine, University of Oxford, Oxford, United Kingdom

^bAllergy, Asthma & Immunology, David Geffen School of Medicine at UCLA, Los Angeles, Calif

No funding was received for this work.

Conflicts of interest: I. D. Pavord received speaker's honoraria for speaking at sponsored meetings from AstraZeneca, Boehringer Ingelheim, Aerocrine, Almirall, Novartis, Teva, Chiesi, Sanofi/Regeneron, Menarini, and GlaxoSmithKline; received payments for organizing educational events from AstraZeneca, GlaxoSmithKline, Sanofi/Regeneron, and Teva; received honoraria for attending advisory panels with Genentech, Sanofi/Regeneron, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis, Teva, Merck, Circassia, Chiesi, and Knopp; received payments to support Food and Drug Administration approval meetings from GlaxoSmithKline; received sponsorship to attend international scientific meetings from Boehringer Ingelheim, GlaxoSmithKline, AstraZeneca, Teva, and Chiesi; received a grant from Chiesi to support a phase 2 clinical trial; is copatent holder of the rights to the Leicester Cough Questionnaire; and received payments for its use in clinical trials from Merck, Bayer, and Insmid; and in 2014, he was an expert witness for a patent dispute involving AstraZeneca and Teva. J. Corren reports research support from AstraZeneca, Genentech/Roch, Novartis, Optinose, Regeneron, and Sanofi; reports Speaker fees from and advisory board membership to AstraZeneca, Genentech/Roch, Novartis, Regeneron, and Sanofi; and reports receiving consultancy fees from AstraZeneca, Genentech/Roch, Novartis, Regeneron, Sanofi, and TEVA.

Received for publication April 17, 2020; accepted for publication April 17, 2020.

Corresponding author: Ian D. Pavord, MD, DM FMedSci, Respiratory Medicine Unit, Nuffield Department of Medicine, NDM Research Building, Old Road Campus, University of Oxford, Oxford OX3 7FZ, United Kingdom. E-mail: ian.pavord@ndm.ox.ac.uk.

J Allergy Clin Immunol Pract 2020;8:2640-2.
2213-2198

© 2020 American Academy of Allergy, Asthma & Immunology
<https://doi.org/10.1016/j.jaip.2020.04.047>

TABLE I. Summary of studies investigating the prognostic and predictive ability of the combination of blood eosinophil count and exhaled nitric oxide (FeNO)

Study	Population	Intervention	Definition of type 2 low*	No. of patients type 2 low and high/total number in placebo group	Severe exacerbations in type 2 low in placebo group (/patient/year)†	Severe exacerbation rate type 2 high (/patient/year) in placebo group	% reduction in exacerbation rate achieved with active treatment in type 2 high patients
DREAM ³	Severe asthma	Mepolizumab 75, 250, and 750 mg IV monthly for 12 mo (combined)	FeNO <25 ppb; blood eosinophils <0.15 × 10 ⁹ /L	Low: 23/150 High: 72/150	1.98	3.14	62
QUEST ⁴	Moderate and severe asthma	Dupilumab 200 mg SC every 2 wk for 52 wk	FeNO <25 ppb; blood eosinophils <0.15 × 10 ⁹ /L	Low: 55/311 High: 134/311	0.58	1.16	68
		Dupilumab 300 mg SC every 2 wk for 52 wk		Low: 52/315 High: 142/315	0.61	1.18	65
LAVOLTA I and II ¹⁴	Moderate and severe asthma	Lebrikizumab 37.5 and 125 mg SC every month for 12 m	FeNO <30 ppb; blood eosinophils <0.3 × 10 ⁹ /L	Unknown	0.61	1.19	Unknown
NOVEL-start ^{18,19}	Mild asthma	Budesonide 200 mcg inhaled twice daily via a Turbohaler for 52 wk; as needed budesonide/formoterol 100/6 mcg for 52 wk	FeNO <25 ppb; blood eosinophils <0.15 × 10 ⁹ /L	Low: 16/217 High: 51/217	12.5%†	25.5%†	Regular budesonide: 78% As needed budesonide/formoterol: 81%

All except NOVEL start showed better prognostic and predictive ability of the combination compared with either biomarker in isolation.

SC, Subcutaneously.

*Type 2 high is the reverse of type 2 low.

†Percentage with severe exacerbation.

associated with a doubling of the risk of exacerbations. This finding is in keeping with growing evidence from clinical trials of biological and inhaled treatments in asthma that both biomarkers are independently associated with an increased risk of asthma exacerbations. This increased risk increases as the biomarker level increases^{3,4} and tends to be greater in patients who have raised levels of both biomarkers (Table I).¹⁴ Importantly, these biomarkers identify a treatment opportunity, because the beneficial effects of inhaled corticosteroids¹⁸ and biologics^{3,4,14} increase progressively with increased levels of biomarkers (Table I). We think that it is now clear that the additional information provided by the assessment of blood eosinophils and FeNO would help clinicians and patients make good decisions about the need for long-term preventative treatment.² What is not clear is why guideline groups continue to make weak and equivocal recommendations on the question of whether type 2 biomarkers should be used to guide asthma treatment.^{20,21} It is time to take a leaf out of the cardiologists' book and recommend unequivocally that a biomarker-directed, precision medicine approach to the management of asthma of all severities is here and ready for prime time. If we can do this, then perhaps we will see the extraordinary improvements in the outcome seen in ischemic heart disease over the last 10 to 20 years as a result of targeted, biomarker-directed preventative treatment.

REFERENCES

- Pavord ID, Shaw DE, Gibson PG, Taylor DR. Inflammometry to assess airway diseases. *Lancet* 2008;372:1017-9.
- Pavord ID, Beasley R, Agusti A, Anderson GP, Bel E, Brusselle G, et al. After asthma: redefining airways diseases. *Lancet* 2018;391:350-400.
- 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.
- Castro M, Corren J, Pavord ID, Maspero J, Wenzel S, Rabe KF, et al. Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. *N Engl J Med* 2018;378:2486-96.
- Corren J, Parnes JR, Wang L, Mo M, Roseti SL, Griffiths JM, et al. Tezepelumab in adults with uncontrolled asthma. *N Engl J Med* 2017;377:936-46.
- Hanania NA, Wenzel S, Rosen K, Hsieh HJ, Mosesova S, Choy DF, et al. Exploring the effects of omalizumab in allergic asthma: an analysis of biomarkers in the EXTRA study. *Am J Respir Crit Care Med* 2013;187:804-11.
- Pascoe S, Locantore N, Dransfield MT, Barnes NC, Pavord ID. Blood eosinophil counts, exacerbations, and response to the addition of inhaled fluticasone furoate to vilanterol in patients with chronic obstructive pulmonary disease: a secondary analysis of data from two parallel randomised controlled trials. *Lancet Respir Med* 2015;3:435-42.
- Bafadhel M, Peterson S, De Blas MA, Calverley PM, Rennard SI, Richter K, et al. Predictors of exacerbation risk and response to budesonide in patients with chronic obstructive pulmonary disease: a post-hoc analysis of three randomised trials. *Lancet Respir Med* 2018;6:117-26.
- Woodruff PG, Modrek B, Choy DF, Jia G, Abbas AR, Ellwanger A, et al. T-helper type 2-driven inflammation defines major subphenotypes of asthma. *Am J Respir Crit Care Med* 2009;180:388-95.
- Woodruff PG, Boushey HA, Dolganov GM, Barker CS, Yang YH, Donnelly S, et al. Genome-wide profiling identifies epithelial cell genes associated with asthma and with treatment response to corticosteroids. *Proc Natl Acad Sci USA* 2007;104:15858-63.
- 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.
- Heaney LG, Djukanovic R, Woodcock A, Walker S, Matthews JG, Pavord ID, et al. Research in progress: Medical Research Council United Kingdom Refractory Asthma Stratification Programme (RASP-UK). *Thorax* 2016;71:187-9.
- Buhl RKS, Menzies-Gow A, Aubier M, Chapman KR, Canonica GW, Picado C, et al. Prospective, single-arm, longitudinal study of biomarkers in real-world patients with severe asthma. *J Allergy Clin Immunol Pract* 2020;8:2630-9.
- Shrimanker R, Keene O, Hynes G, Wenzel S, Yancey S, Pavord ID. Prognostic and predictive value of blood eosinophil count, fractional exhaled nitric oxide, and their combination in severe asthma: a post hoc analysis. *Am J Respir Crit Care Med* 2019;200:1308-12.
- Hanania NA, Korenblat P, Chapman KR, Bateman ED, Kopecky P, Paggiaro P, et al. Efficacy and safety of lebrikizumab in patients with uncontrolled asthma (LAVOLTA I and LAVOLTA II): replicate, phase 3, randomised, double-blind, placebo-controlled trials. *Lancet Respir Med* 2016;4:781-96.
- O'Connell P, Gaston B, Bonfield T, Grabski T, Fletcher D, Shein SL. Periostin levels in children without respiratory disease. *Pediatr Pulmonol* 2019;54:200-4.
- Tan E, Varughese R, Semprini R, Montgomery B, Holweg C, Olsson J, et al. Serum periostin levels in adults of Chinese descent: an observational study. *Allergy, Asthma Clin Immunol* 2018;14:87.
- Pavord ID, Holliday M, Reddel HK, Braithwaite I, Ebmeier S, Hancox RJ, et al. Predictive value of blood eosinophils and exhaled nitric oxide in adults with mild asthma: a prespecified subgroup analysis of an open-label, parallel-group, randomised controlled trial. *Lancet Respir Med* 2020.
- Beasley R, Holliday M, Reddel HK, Braithwaite I, Ebmeier S, Hancox RJ, et al. Controlled trial of budesonide-formoterol as needed for mild asthma. *N Engl J Med* 2019;380:2020-30.
- Global Initiative for Asthma (GINA). GINA 2019 main report. Available from: <https://ginasthma.org/gina-reports/>. Accessed May 1, 2020.
- British Thoracic Society. BTS/SIGN British Guideline on the Management of Asthma. Available from: <https://brit-thoracic.org.uk/quality-improvement/guidelines/asthma/>. Accessed May 1, 2020.