The Clinical Relevance of Periostin in Asthma

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ABSTRACT

Periostin is a matricellular protein which is generated by airway epithelial cells in response to interleukin (IL)-4 and IL-13. Serum periostin levels have been proposed as a biomarker of type-2 inflammation with clinical utility in severe asthma. Normal reference ranges have been established in a predominant Caucasian population using the Elecsys® Periostin immunoassay. Periostin levels do not differentiate asthma from non-asthma, or mild-to-moderate asthma from severe asthma, although they are higher in adults with asthma who have raised levels of blood eosinophils and fractional exhaled nitric oxide (FeNO). Periostin status can predict response to monoclonal antibody therapy directed against IL-13 and immunoglobulin E (IgE), such that adults with severe asthma and a periostin level \( \geq 50 \text{ ng/ml} \) (designated "periostin-high") have a greater therapeutic response than "periostin-low" patients. The clinical relevance of these findings is uncertain, due to the similar predictive ability of the more commonly available biomarkers blood eosinophils and/or FeNO.

Key words: Asthma. Biomarkers. Periostin. Phenotypes.
INTRODUCTION

In asthma, biomarkers have played a pivotal role in the identification of clinical phenotypes, risk stratification of patients, prediction of treatment responsiveness to therapies, monitoring of disease and new drug development\(^1,2\). An effective biomarker must be objectively measurable and allow evaluation as an indicator of normal or pathological processes or treatment responsiveness\(^3\). Traditional biomarkers in asthma have included induced sputum and blood eosinophil levels, total and allergen specific serum immunoglobulin E (IgE), and fraction of exhaled nitric oxide (FeNO)\(^1,2\).

More recently, periostin has been identified as a biomarker with possible clinical utility in severe asthma\(^4-10\). Periostin is a matricellular protein which is generated by airway epithelial cells, partly regulated by interleukin (IL)-13 and IL-4 and is detectable in serum. Serum periostin levels may identify patients with a high risk of forced expiratory volume in one second (FEV\(_1\)) decline\(^11\) and increased risk of asthma exacerbation despite inhaled corticosteroids (ICS) therapy\(^12\). It may also identify those with eosinophilic airway inflammation and those with eosinophilic infiltration of the lung parenchyma and sputum eosinophilia\(^5\). Periostin gene expression is reduced with ICS therapy\(^4\), and serum periostin levels are reduced with inhaled\(^13\) and systemic\(^14\) glucocorticoid treatment. High serum periostin levels may also indicate responsiveness to monoclonal antibody therapies targeting the type-2 inflammatory pathway, including IL-13\(^12,15,16\) and IgE\(^17\).

There is substantive evidence that periostin is associated with and contributes to type-2 dependent inflammation in asthma. The gene coding for periostin (POSTN) is among the most highly upregulated genes in the airway of asthma patients compared to non-asthmatics\(^18\). Interleukin-4 and IL-13 cytokines are key in regulating the expression of periostin in airway epithelial cells\(^19\). Periostin is also secreted in vitro by primary lung fibroblasts and cell lines in response to IL-4 and IL-13\(^6\). In a chronic asthma mouse model, type-2 inflammatory cytokines IL-4 and IL-13 induce upregulation of the POSTN gene\(^6\) causing increased circulating periostin which in turn binds not only to bronchial smooth muscle\(^20,21\), but also to integrins on eosinophils, promoting eosinophilic localisation and adhesion to the airways\(^10\) and consequent pulmonary inflammation and fibrosis\(^22,23\). Over-expression of periostin in epithelial cells also results in the stimulation of transforming growth factor–beta (TGF-b), which in turn stimulates secretion of type-1 collagen by airway fibroblasts\(^24\). The structure of periostin is critical in the type-2 inflammatory pathway. Periostin has a splicing domain at its C-terminal, four fasciclin-1 domains in the middle and a cysteine-rich domain at its N-terminal\(^25\). The cysteine-rich domains bind integrin proteins, thereby regulating cell adhesion and mobility\(^26\) assisting with connective tissue remodelling and repair.

However, periostin is not specific to asthma or the airway epithelium. Various isomers can be found in skeletal muscle\(^27\), the myocardium\(^28\), heart valves\(^29\), skin\(^30\), bone\(^31\), and periodontal ligaments\(^32\). Periostin is increased in many patients with conditions associated with high levels of cell division and turnover, such as cancers and fibroblastic proliferation\(^33-35\). This ubiquity raises the risk that disruption...
of other human systems may affect serum periostin levels and confound interpretation in the clinical context of asthma.

Additionally, a number of periostin assays have been used in asthma research, of which only two have published data with respect to stability and variability\(^{36,37}\), and none are commercially available for clinical practice currently. To justify its development as a commercially available test, periostin must show its value as uniquely superior to other type-2 biomarkers in identifying asthma phenotypes which preferentially respond to specific asthma treatments and monitor their response to such treatments.

The purpose of this review is to discuss what is known about periostin, both in the absence and presence of asthma, and to assess the clinical utility of periostin as a biomarker in the management of asthma.

WHAT IS KNOWN ABOUT PERIOSTIN IN ADULTS WITHOUT ASTHMA?

The normal reference range of periostin has been determined in a sample of 480 predominantly European adults\(^{38}\), in accordance with the Clinical and Laboratory Standards Institute guidelines for determining reference values and reference intervals for quantitative clinical laboratory tests\(^{39}\) using the Elecsys\textsuperscript{®} Periostin immunoassay (Roche Diagnostics, Penzberg, Germany\(^{36}\)). Adults with asthma, chronic obstructive pulmonary disease (COPD) and comorbidities that might putatively result in increased periostin levels were excluded from the study. In this population the distribution of serum periostin was relatively wide, with a marked right skew distribution (Fig. 1a). The median (interquartile range [IQR]) periostin level was 50.1 (43.1 to 56.9) ng/ml, with a five-fold range of 28.1 to 136.4 ng/ml, and the 90% confidence limits were 35.0 to 71.1 ng/ml. There was no association between serum periostin levels and age, sex or common non-respiratory comorbidities, but serum periostin levels were lower in current smokers and lower in those with a high body mass index (BMI), consistent with other studies\(^{40-42}\). A related study showed a modest reduction in serum periostin levels in the evening, compared with morning testing (46.2 ng/ml at 1800 hr versus 50.5 ng/ml at 0800 hr\(^{43}\)).

Trends towards higher periostin levels in adults without asthma who identify as “Asian” have been observed\(^{38}\). This trend was confirmed in a dedicated study showing that the median (IQR) periostin level in non-asthmatic Chinese is 59.6 [50.3 to 67.9] ng/ml, which is approximately 17% higher than Caucasians (49.7 [42.8 to 56.5] ng/ml)\(^{44}\). Unlike Caucasians, periostin levels were sex-dependent in the Chinese group, with median (IQR) periostin levels of 61.3 [51.8 to 73.1] ng/ml and 55.2 [46.4 to 58.3] ng/ml in females and males respectively. Japanese women also have higher levels of periostin than their male counterparts\(^{42}\) but no comparison has been made of periostin levels in Japanese with Caucasians.

Influence of bone disease

Periostin was first identified in mouse osteoblasts and originally called osteoblastic-specific factor 2\(^{32}\). Not surprisingly, a number of consequent studies have investigated the relationship between serum periostin and states
Periostin levels are lower in those with osteoarthritis of the knee and in progressive osteoarthritis, but are elevated in post-menopausal women with non-vertebral osteoporotic fractures and in the early stages after hip fracture. In joint replacement surgery, periostin levels show a biphasic response, characterised by an initial fall, then increasing to almost double baseline levels by eight weeks, and remaining...
risen at 26 weeks post-surgery\textsuperscript{49}. In long bone fractures, a similar time course is followed, with periostin levels reaching a (less-er) maximum level at eight weeks, whereas in small bone fractures, there is a brief initial dip, with a return to stable levels at two weeks\textsuperscript{49}. Thus a history of the timing and extent of recent bone injury needs to be considered in the interpretation of serum periostin levels.

### Influence of type-2 inflammatory related conditions

Allergic rhinitis in non-asthmatics, but not in asthmatics, is associated with higher periostin levels\textsuperscript{42}. Periostin has been implicated in the inflammatory and fibrotic pathways of atopic dermatitis\textsuperscript{50}, psoriasis\textsuperscript{51} and chronic rhino-sinusitis with nasal polyps\textsuperscript{52,53}. Whether these and other type-2 related conditions result in elevated periostin levels compared to those without the disease is yet to be elucidated.

### Summary of non-asthma findings

A clinician can utilise serum periostin levels in an adult Caucasian patient without consideration of sex or age. In Chinese patients, one would expect periostin levels to be about 20% higher than those of Caucasians, and for Chinese women to have levels approximately 15% higher than Chinese men. Similarly, Japanese women have higher periostin levels than Japanese men. Periostin levels should be interpreted with caution in those with osteoarthritis, and it would be prudent to wait at least six months after joint surgery and large bone fractures to assess periostin levels. Periostin levels are lower in smokers and in those with elevated BMIs. The effect of other type-2 inflammatory conditions such as allergic rhinitis on serum periostin levels is not yet certain. The time of day a blood sample is taken is unlikely to confound interpretation of the result.

### WHAT IS KNOWN ABOUT PERIOSTIN IN ADULTS WITH ASTHMA?

#### Asthma versus non-asthma

In adults with symptomatic airflow obstruction, most of whom had a doctor’s diagnosis of asthma, the distribution of serum periostin is relatively wide (Fig. 1b)\textsuperscript{12}. In studies of predominantly Caucasian adults with asthma using the Elecsys\textsuperscript{®} Periostin immunoassay the median (IQR) periostin levels were between 47.7 (40.2 to 56.3) ng/ml and 54 (46 to 62) ng/ml (Table 1)\textsuperscript{13-15,17,38,43,44,49,54-57}. This is similar to a predominant Caucasian non-asthma population in which the median (IQR) level of 50.1 (43.1 to 56.9) ng/ml has been derived\textsuperscript{38}. In Chinese adults with asthma the median (IQR) level is 56.8 (47.8 to 70.4) ng/ml compared to 57.0 (50.3 to 67.9) ng/ml in Chinese adults without asthma\textsuperscript{44}. Thus serum periostin levels cannot distinguish between those with asthma from those without.

#### Asthma severity

In a direct comparison of periostin levels in patients with and without asthma of differing severity, the median (IQR) periostin levels were 53 (44 to 62) ng/ml and 54 (46 to 62) ng/ml
### Table 1. Serum periostin levels in study participants using the Elecsys® Periostin immunoassay

<table>
<thead>
<tr>
<th>Population</th>
<th>Median (IQR) ng/ml</th>
<th>Mean (SD) ng/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-asthmatic participants</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-asthmatic: n = 16 (Caswell-Smith et al.45)</td>
<td>49.4 (42.5 to 62.7)</td>
<td>50.5 (13.0)</td>
</tr>
<tr>
<td>Non-asthmatic: n = 27 (Simpson et al.59)</td>
<td>49 (46 to 65)</td>
<td>–</td>
</tr>
<tr>
<td>No diagnosis of respiratory disease: n = 480 (Caswell-Smith et al.30)</td>
<td>50.1 (43.1 to 56.9)</td>
<td>51.2 (11.9)</td>
</tr>
<tr>
<td>Non-asthmatic, 26 weeks post small bone fracture: n = 24 (Varughese et al.49)</td>
<td>50.0 (44.2 to 54.4)</td>
<td>53.0 (14.8)</td>
</tr>
<tr>
<td>Non-asthmatic awaiting joint surgery baseline: n = 34 (Varughese et al.49)</td>
<td>49.1 (39.3 to 62.0)</td>
<td>54.2 (18.0)</td>
</tr>
<tr>
<td>Non-asthmatic, 26 weeks post large bone fracture: n = 30 (Varughese et al.49)</td>
<td>51.4 (45.8 to 67.3)</td>
<td>56.0 (16.3)</td>
</tr>
<tr>
<td>Chinese non-asthmatic: n = 120 (Semprini et al.44)</td>
<td>–</td>
<td>59.6 (15.4)</td>
</tr>
<tr>
<td><strong>Patients with undifferentiated obstructive respiratory disease</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undifferentiated obstructive respiratory disease: n = 386 (Fingleton et al.13)</td>
<td>54.0 (45.1 to 65.6)</td>
<td>57.3 (18.6)</td>
</tr>
<tr>
<td>Subgroup: no diagnosis of asthma: n = 101</td>
<td>54.6 (44.5 to 63.9)</td>
<td>56.3 (16.1)</td>
</tr>
<tr>
<td>Subgroup: doctor-diagnosed asthma: n = 285</td>
<td>53.7 (45.2 to 65.7)</td>
<td>57.7 (19.4)</td>
</tr>
<tr>
<td>Undifferentiated obstructive respiratory disease: n = 389 (Wagener et al.58)</td>
<td>54.3 (45.2 to 65.8)</td>
<td>57.3</td>
</tr>
<tr>
<td>Subgroup: obese comorbid: n = 54</td>
<td>53.5 (45.9 to 68.2)</td>
<td>51.7 (11.5)</td>
</tr>
<tr>
<td>Subgroup: asthma-COPD overlap: n = 33</td>
<td>55.2 (47.3 to 63.0)</td>
<td>56.1 (15.7)</td>
</tr>
<tr>
<td>Subgroup: mild intermittent asthma: n = 73</td>
<td>53.5 (48.1 to 63.9)</td>
<td>56.3 (18.8)</td>
</tr>
<tr>
<td>Subgroup: mild atopic asthma: n = 145</td>
<td>55.2 (43.7 to 65.1)</td>
<td>57.6 (17.7)</td>
</tr>
<tr>
<td>Subgroup: moderate-to-severe atopic asthma: n = 53</td>
<td>54.4 (43.4 to 67.8)</td>
<td>63.8 (25.2)</td>
</tr>
<tr>
<td><strong>Asthma patients</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma: doctor-diagnosed asthma: n = 285 (Fingleton et al.13)</td>
<td>53.7 (45.2 to 65.7)</td>
<td>57.7 (19.4)</td>
</tr>
<tr>
<td>Mild-to-moderate asthma: n = 110 (Fingleton et al.56)</td>
<td>47.7 (40.2 to 56.3)</td>
<td></td>
</tr>
<tr>
<td>Unstable asthma within 48 hours of severe exacerbation and treatment: n = 34</td>
<td>48.9 (42.2 to 66.6)</td>
<td>54.6 (21.5)</td>
</tr>
<tr>
<td>Moderate-to-severe asthma: n = 37 (Fingleton et al.56)</td>
<td>50.8 (45.7 to 60.4)</td>
<td></td>
</tr>
<tr>
<td>On GINA treatment step 3 to 5: n = 83 (Fingleton et al.57)</td>
<td>51.6 (41.8 to 62.6)</td>
<td></td>
</tr>
<tr>
<td>Non-severe asthma: n = 75 (Simpson et al.59)</td>
<td>53 (44 to 62)</td>
<td></td>
</tr>
<tr>
<td>Severe asthma: n = 51 (Simpson et al.59)</td>
<td>54 (46 to 62)</td>
<td></td>
</tr>
<tr>
<td>On ICS and LABA: n = 60 (Semprini et al.14)</td>
<td>48.9 (41.6 to 60.3)</td>
<td>52.2 (16.4)</td>
</tr>
<tr>
<td>On ICS and LABA: n = 16 (Caswell-Smith et al.49)</td>
<td>51.7 (41.5 to 63.7)</td>
<td>53.5 (13.6)</td>
</tr>
<tr>
<td>Chinese, stable asthma, range of severity: n = 68 (Semprini et al.44)</td>
<td>56.8 (47.8 to 70.4)</td>
<td>59.9 (16.3)</td>
</tr>
<tr>
<td>Uncontrolled asthma on ICS (LAVOLTA I by treatment group: n = 1081, Hanania et al.16)</td>
<td>53.8 (44 to 66)</td>
<td></td>
</tr>
<tr>
<td>Uncontrolled asthma on ICS (LAVOLTA II by treatment group: n = 1067, Hanania et al.16)</td>
<td>55.3 (44 to 69)</td>
<td></td>
</tr>
</tbody>
</table>

(continued)
in those with non-severe and severe asthma respectively (Fig. 2)\textsuperscript{54}.

Similarly, patients with severe uncontrolled allergic asthma despite at least Global Initiative for Asthma (GINA) step 4 treatment have comparable serum periostin levels to adults with mild-to-moderate asthma (Table 1)\textsuperscript{55}. In a study of patients with symptomatic obstructive respiratory disease, those with a diagnosis of asthma (285 of 386) had a median (IQR) periostin of 53.7 (45.2 to 65.7) ng/ml\textsuperscript{12}. When this population was phenotypically characterised by cluster analysis\textsuperscript{56}, three distinct asthma phenotypes became apparent: mild intermittent asthma, mild atopic asthma and moderate-to-severe atopic asthma, with median (IQR) periostin levels of 53.5 (48.1 to 63.9), 55.2 (43.7 to 65.1) and 54.4 (43.4 to 67.8) ng/ml respectively. While the highest periostin levels were in the moderate-to-severe atopic asthma group, the large range of values between the groups resulted in considerable overlap with the other asthma phenotypes.

**Table 1. Serum periostin levels in study participants using the Elecsys® Periostin immunoassay (continuation)**

<table>
<thead>
<tr>
<th>Population</th>
<th>Median (IQR) ng/ml</th>
<th>Mean (SD) ng/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncontrolled severe persistent allergic asthma: omalizumab trials: n = 534 (Hanania et al.\textsuperscript{17})</td>
<td>–</td>
<td>48.0 (not reported)</td>
</tr>
<tr>
<td>Subgroup: eosinophils &lt; 260/µL: n = 383</td>
<td>–</td>
<td>48 (14)</td>
</tr>
<tr>
<td>Subgroup: eosinophils ≥ 260/µL: n = 414</td>
<td>–</td>
<td>58 (20)</td>
</tr>
<tr>
<td>Subgroup: FeNO &lt; 19.5 ppb: n = 193</td>
<td>–</td>
<td>49 (15)</td>
</tr>
<tr>
<td>Subgroup: FeNO ≥ 19.5 ppb: n = 201</td>
<td>–</td>
<td>60 (24)</td>
</tr>
<tr>
<td>Uncontrolled asthma despite the use of medium- to-high-dose inhaled glucocorticoids and a second controller: lebrikizumab trials: pooled data n = 463 (Corren et al.\textsuperscript{19})</td>
<td>46.4 to 48.7 across four groups</td>
<td></td>
</tr>
</tbody>
</table>

Footnote: The variable periostin assays used in the literature make comparative assessments of serum periostin levels between studies difficult. However, by limiting those studies in asthma patients where serum periostin levels were determined using the clinical trial version of the Elecsys® Periostin immunoassay (Roche Diagnostics, Penzberg, Germany) it is possible to make comparisons. This assay was developed according to the guidelines of the Clinical and Laboratory Institute (CLSI) and is a fully automated immunoassay operated on the e601 module of the cobas 6000 system equipped with software version 05–01 or higher\textsuperscript{36}. It has a high repeatability with coefficients of variation across multiple sites and reagent lots of 1.7 to 3.1%.

COPD: chronic obstructive pulmonary disease; FeNO: fractional exhaled nitric oxide; GINA: Global Initiative for Asthma; ICS: inhaled corticosteroids; IQR: interquartile range; LABA: long-acting beta agonist; LAVOLTA: Efficacy and safety of lebrikizumab in patients with uncontrolled asthma; ppb: parts per billion; standard deviations (SD) are referred between parentheses.

**Figure 2. Serum periostin in subjects with severe asthma, non-severe asthma and no asthma (reproduced from Johansson MW et al.\textsuperscript{54} with permission from Elsevier).**

**Associations with other type-2 biomarkers**

In asthma there are weak associations between serum periostin and other type-2 biomarkers such as FeNO, serum total IgE and blood eosinophil count (Fig. 3)\textsuperscript{13,54}. In severe asthma
populations, the serum periostin level is higher in the subgroups of patients with a strong type-2 phenotype, characterised by raised blood eosinophil and FeNO levels\textsuperscript{17}. This suggests that these biomarkers identify both similar and different aspects of type-2 inflammation in asthma. This interpretation is consistent with the observations that anti-IL-13 therapy results in a reduction in serum periostin and FeNO but not eosinophil levels\textsuperscript{15}, whereas anti-IL5 reduces eosinophils and not FeNO\textsuperscript{59}.

**Within-patient variation**

The intra-participant coefficient of variation of serum periostin levels is approximately 6% in adults with stable asthma patients on ICS/long-acting β\textsubscript{2}-agonist (LABA) treatment when measured repeatedly over an eight-week period (Fig. 4)\textsuperscript{13}. Similarly, within-patient variations of 5% and 5.3% have been reported in poorly controlled asthmatics despite treatment with ICS\textsuperscript{14} and in patients with severe asthma refractory to ICS treatment\textsuperscript{5}. This suggests...

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**Figure 3.** The association between log serum periostin and a) log FeNO, b) log IgE, c) blood eosinophil count and d) forced expiratory volume in one second (FEV\textsubscript{1}) (reproduced from Fingleton J et al.\textsuperscript{13} with permission from ©ERS 2016).

FeNO: fractional exhaled nitric oxide; IU: international unit; ppb: part per billion.
that serum periostin is a stable biomarker in adult asthma.

**Diurnal variation**

As with healthy adults, mean serum periostin levels in asthma patients reduce gradually during the day with a fall of approximately 5%, from 53.5 ng/ml at 0800 hr to 50.9 ng/ml at 1800 hr\(^43\). This daytime variation is similar to that observed in other type-2 biomarkers such as sputum and blood eosinophils\(^60\)-\(^64\), and FeNO\(^65\)-\(^67\) which are higher in the early morning compared with late afternoon or evening. This suggests that the time of day in which a blood sample is taken is unlikely to influence clinical decision-making for asthma patients.

**Seasonal variation**

Three studies have assessed whether there is any seasonal variation in periostin levels taken from asthmatic patients. There was no evidence of seasonal variation in a study of asthma patients prescribed ICS/LABA therapy conducted over a 15-month period\(^13\), in asthmatics who suffered an asthma exacerbation which was conducted over an 11-month period\(^54\), or in asthma patients prescribed long-term ICS over an eight-year period\(^11\). This contrasts with findings related to
IgE, where seasonal variation does occur, attributed to variations in allergen exposures\textsuperscript{68,69}.

**Response to steroid treatment**

Serum periostin levels decrease by 5% in steroid naïve asthma patients after the introduction of the ICS fluticasone propionate 400 mcg daily\textsuperscript{9}, and by about 10% after 12 weeks of the ICS budesonide 800 mcg daily\textsuperscript{12}. Periostin levels also fall by approximately 10% in patients on ICS therapy who are treated with systemic glucocorticoids during an asthma exacerbation\textsuperscript{13} and between 15% and 17% in asthmatic patients treated with systemic glucocorticoids after presenting a severe exacerbation\textsuperscript{13} and between 15% and 17% in asthmatic patients treated with systemic glucocorticoids after presenting a severe exacerbation\textsuperscript{13} and between 15% and 17% in asthmatic patients treated with systemic glucocorticoids after presenting a severe exacerbation\textsuperscript{13} and between 15% and 17% in asthmatic patients treated with systemic glucocorticoids after presenting a severe exacerbation\textsuperscript{13} and between 15% and 17% in asthmatic patients treated with systemic glucocorticoids after presenting a severe exacerbation\textsuperscript{13} and between 15% and 17% in asthmatic patients treated with systemic glucocorticoids after presenting a severe exacerbation\textsuperscript{13} and between 15% and 17% in asthmatic patients treated with systemic glucocorticoids after presenting a severe exacerbation\textsuperscript{13} and between 15% and 17% in asthmatic patients treated with systemic glucocorticoids after presenting a severe exacerbation\textsuperscript{13} and between 15% and 17% in asthmatic patients treated with systemic glucocorticoids after presenting a severe exacerbation\textsuperscript{13}.

Thus, both inhaled and oral glucocorticoids result in a modest reduction in serum periostin levels in asthma.

**Predicting responsiveness to monoclonal antibody therapies**

The concept that the presence of high periostin levels may identify patients who are likely to respond to monoclonal antibody treatment directed against type-2 inflammation\textsuperscript{4} was confirmed by a randomised controlled trial (RCT) of lebrikizumab (anti-IL-13 therapy) in adults with moderate-to-severe asthma and uncontrolled symptoms despite ICS therapy\textsuperscript{14}. The “periostin-high” patients (those with a periostin level ≥ 50 ng/ml, the median observed in the patient cohort being analysed) had a greater improvement in FEV\textsubscript{1} in the lebrikizumab treatment arm compared to placebo whereas the “periostin-low” patients did not (Fig. 5). This predictive ability was not limited to periostin, as in a post hoc analysis, high FeNO levels also identified patients who had greater improvements in lung function. The intra-patient variability in the two-week run-in period of the study was less for periostin than FeNO, indicating that periostin is a more stable biomarker. In the high T helper 2 (Th2) subgroup (defined by total serum IgE and blood eosinophil levels) the rate of exacerbations was 60% lower in the lebrikizumab group than in the placebo group (p = 0.03), with a trend towards a similar effect in the “periostin-high” group, with the exacerbation rate being 26% lower (p = 0.40).

These findings were extended in the subsequent replicate RCTs evaluating multiple doses of lebrikizumab in patients with uncontrolled asthma despite use of ICS and a second controller (Fig. 6a)\textsuperscript{15}. Treatment with lebrikizumab reduced the rate of severe exacerbations compared to placebo (the primary outcome variable) which was more pronounced in the “periostin-high” patients (60% reduction) than in the “periostin-low” patients (5% reduction). Lung function also improved following lebrikizumab treatment to a greater extent in “periostin-high” patients (increase in FEV\textsubscript{1} of 9.1 versus 2.6% predicted). Raised FeNO and blood eosinophils were also predictive of treatment response to lebrikizumab.

More recently, two replicate phase 3 studies Efficacy and safety of lebrikizumab in patients with uncontrolled asthma (LAVOLTA I and II) have shown limitations in the use of periostin as a predictor of responsiveness to anti-IL-13 therapy, and the efficacy of lebrikizumab therapy\textsuperscript{16}. In these replicate trials,
LA VOLTA I showed significantly reduced asthma exacerbation rates in “biomarker-high” patients (periostin ≥ 50 ng/ml or blood eosinophils ≥ 300 cells/μL) although there was not a clear distinction in efficacy between “biomarker-high” and “low” groups. In contrast, in LA VOLTA II, there was no significant reduction in exacerbation risk in “biomarker-high” patients.
patients, although lebrikizumab showed greater benefit in the “biomarker-high” group than the “biomarker-low” group. There were similar findings, regardless of whether the data were analysed separately as a “periostin-high” or composite “blood eosinophil or periostin-high” group. Although the treatment-by-biomarker interaction analysis failed to reach statistical significance, the strongest interaction was observed for blood eosinophils. In both trials there was a significant improvement in FEV\(_1\) with lebrikizumab compared with placebo in “biomarker-high” patients, suggesting that anti-IL-13 treatment may have more effect on airflow obstruction than on exacerbation risk.

Similar findings were observed in a study of the efficacy of tralokinumab, another monoclonal antibody directed against IL-13\(^7\). Although tralokinumab did not significantly reduce exacerbation rates in patients with severe uncontrolled asthma, FEV\(_1\) was improved. In a post hoc analysis of the subgroups with raised periostin (≥ median periostin level), improvements in lung function were greatest in patients with airway reversibility at baseline and not receiving long-term oral glucocorticoids. In the replicate phase 3 trials of tralokinumab in patients with severe uncontrolled asthma\(^7\), STRATOS 1 identified a baseline FeNO measure of ≥ 37 ppb as the “preferred” biomarker, with a 44% reduction in annual exacerbation rate in this group compared to placebo. In STRATOS 2, a reduction in annualised exacerbations rates in this same “FeNO-high” group was not seen raising questions as to the applicability of FeNO as a predictive biomarker for this treatment, while periostin analyses have not yet been reported.

The ability of serum periostin to predict responsiveness to monoclonal antibody therapy beyond IL-13 was demonstrated in the post hoc analysis of a large RCT of omalizumab, an anti-IgE therapy, in patients with uncontrolled severe persistent allergic asthma (Fig. 6b)\(^1\). After 48 weeks of omalizumab, reductions in exacerbations were greater in the “high” versus “low” subgroups for all three biomarkers: periostin (30 versus 3%), FeNO (53 versus 16%), and blood eosinophils (32 versus 9%). Previous investigations have shown that potential biomarkers, including allergen-specific IgE, total IgE, serum tryptase, eosinophil cationic protein and soluble CD23, were not able to predict the therapeutic response to omalizumab\(^7\).

The ability of serum periostin to predict responsiveness has also been assessed with dupilumab, a monoclonal antibody directed against IL-4 alpha chain receptor (IL-4R\(\alpha\)) thereby inhibiting both IL-4 and IL-13 signalling. Dupilumab reduced exacerbations in both “periostin-high” and “periostin-low” patient subgroups (≥ and < median periostin respectively)\(^7\). Similarly the efficacy of dupilumab in reducing exacerbations was comparable in the groups defined by blood eosinophil levels ≥ and < 300/uL respectively\(^7\). In the most recent phase 3 study\(^7\), dupilumab improved FEV\(_1\) at 12 weeks and reduced annual exacerbation rates in all patients, with a greater effect in patients with blood eosinophils ≥ 300/uL, while periostin analyses are yet to be reported.

**Asthma exacerbation risk**

Higher serum periostin levels have consistently been associated with an increased risk of asthma exacerbation in clinical trials of
monoclonal antibody therapy in adults with uncontrolled severe persistent allergic asthma. However, this has not been borne out in a cohort of asthma patients with predominantly mild asthma, in whom higher periostin levels are associated with a longer time to exacerbation. This suggests that high levels of serum periostin predict increased risk of severe exacerbations in patients with severe asthma but not in mild asthma.
Summary of asthma findings

There is a wide range in serum periostin levels in adult asthma, similar to that observed in a non-asthma population. Periostin levels are relatively stable and the time of day or the time of year in which blood sampling is done is unlikely to confound interpretation of the results. Periostin levels fall by up to 10% with the initiation of ICS therapy in ICS-naïve patients, and by up to 15% with the initiation of oral CS treatment after an asthma exacerbation. There is no discernible difference in periostin levels between those who have asthma and those who do not, nor is there a discernible pattern of increasing periostin levels with increasing asthma severity. While ICS treatment suppresses periostin levels, this is unlikely to completely explain the lack of difference in periostin levels between those with severe asthma and mild-to-moderate asthma, and those without asthma. While periostin is a predictor of exacerbations in severe asthma, this has not been borne out in a more generalised mild-to-moderate asthma population.

The ability of “periostin-high” levels to predict responsiveness to monoclonal antibody therapies targeting the type-2 inflammatory pathway, anti-cytokine IL-13 and anti-IgE has the greatest potential for the use of this measurement in clinical practice. However, the observation that the more widely available type-2 biomarkers, blood eosinophils and possibly FeNO, also have predictive ability for anti-IL-13 and anti-IgE therapies means that the place of periostin for this purpose is uncertain. Furthermore, blood eosinophils predict responsiveness to anti-IL-5 therapy77, but not anti-epithelial-cell derived cytokine thymic stromal lymphopoietin (TSLP) therapy78. Together, this means that specific biomarkers cannot help guiding which of the existing therapies should be used. This is disappointing as it would have been ideal to have one specific biomarker for each monoclonal antibody therapy with a corresponding biomarker “readout” indicating the therapy to which the patient is most likely to respond.

CONCLUSIONS

Periostin levels do not distinguish those with asthma from those without, nor do they allow evaluation of disease severity. Periostin levels may be helpful in categorising the type-2 status of patients with severe asthma and may also predict treatment responsiveness to monoclonal antibody treatment directed against IL-13 and IgE in patients with severe persistent allergic asthma, although blood eosinophils and FeNO have similar predictive capability. From the current evidence available, serum periostin should be interpreted with caution when incorporating into decision-making about treatment for asthma patients, as levels may differ according to the assay used, will change with bony injury, and may vary between ethnicities making interpretation of levels problematic.

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