Clinical Communications

The association between serum periostin and a type 2 helper airway composite index in optimally treated asthmatics

Elissavet Konstantellou, MD[a], Stelios Loukides, MD, PhD[b], Polyxeni Ntontsi, MD[b], Evgenia Papathanasiou, MD[b], Konstantinos Kostikas, MD, PhD[b], Georgios Paptheodorou, PhD[c], Georgios Hillas, MD, PhD[d], Spyros Papiris, MD, PhD[b], Nikolaos G. Koulouris, MD, PhD[a], and Petros Bakakos, MD, PhD[a]

Clinical Implications

- In a population of optimally treated asthmatics, serum periostin has a weak performance in predicting a Th2 airway response regardless of underlying severity.

TO THE EDITOR:

Serum periostin is an extracellular matrix protein secreted by bronchial epithelial cells and lung fibroblasts and serves as a basic component of subepithelial fibrosis observed in the asthmatic airways. Its expression is upregulated by type 2 cytokines IL-4 and IL-13, and it has been recognized as a surrogate marker of Th2 response.[1]

Contradictory data exist regarding the predictive role of periostin for airway eosinophilia.[2,3] Data support an association between serum periostin with a type 2 immunity score consisting of blood eosinophils (%), sputum eosinophils (%), fraction of exhaled nitric oxide (FeNO), and IgE.[4] In the present study, we evaluated the diagnostic performance of serum periostin in the assessment of a type 2 airway composite index in optimally treated asthmatics and the potential role of the underlying disease severity. As a secondary outcome, we evaluated the association of periostin with various inflammatory study variables (sputum eosinophils, sputum IL-13, and blood eosinophils).

Patients with asthma were recruited from an ongoing cohort of asthmatic patients who were followed up in 2 university asthma clinics (1st and 2nd Respiratory Medicine Departments of the University of Athens) between June 2012 and September 2014. The diagnosis of asthma was established according to GINA guidelines,[5] whereas the diagnosis of severe refractory asthma (SRA) was established according to ERS/ATS guidelines.[6] We recruited 145 patients (56 with SRA and 89 with mild-to-moderate asthma), nonsmokers all optimally treated for at least 6 months. All patients were treated by an asthma specialist to achieve the best level of asthma control, were adherent to therapy, and had at least 6-month follow-up. We excluded patients younger than 18 or older than 70 years, pregnant women, and patients with any other respiratory disease or concomitant malignant, heart, renal, liver, or collagen disease. Patients with a respiratory tract infection or asthma exacerbation in the 8 weeks before the study entry were also excluded. The study was approved by the ethics committees of both hospitals, and all subjects provided written informed consent. All patients underwent dynamic spirometry for the determination of forced expiratory volume in 1 second and forced vital capacity, FeNO measurement, and sputum induction (details are provided in Supplement E1 available in this article's Online Repository at www.jaci-inpractice.org). Sputum cell counts and measurement of IL-13 in sputum supernatant were performed. Blood was drawn for the measurement of periostin and blood eosinophils (% and absolute counts). A composite Th2 airway index was determined by using the following variables: (1) sputum eosinophils $\geq$3%, (2) FeNO $\geq$25 ppb, and (3) sputum IL-13 $\geq$66 pg/mL (defined as the lowest confidence interval [CI] as previously defined).[7] We calculated the index as follows: high Th2—one or more of the 3 with the exception of sputum eosinophils as a sole criterion; low Th2—none of the 3 variables or sputum eosinophils $\geq$3% only. There is recent evidence supporting that airway eosinophilia may be present irrespective of the classical Th2-mediated process. Stimulation of type 2 innate lymphoid cells by both thymic stromal lymphopoietin (TCLP) and IL-33 produces Th2-related mediators independently of what we call the allergen-specific Th2-mediated process. To ensure that we avoid possible bias due to eosinophil production through the above pathway, we decided not to include sputum eosinophils as a standalone criterion, but only in the context of the composite index.[8] Serum periostin was measured by an enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, Minn, duoset Elisa development system, cat. DY3548). The lowest detection level of periostin is 0.975 ng/mL in diluted samples (1:25). The limit of detection was determined by adding 3 standard deviations to the mean value of 30 zero standard measurements. IL-13 was measured using an enzyme-linked immunosorbent assay kit (R&D Systems, with a detection limit of 13.2 pg/mL, cat. D1300B). Statistical analysis is provided in Supplement E1 available in this article's Online Repository at www.jaci-inpractice.org.

Subject characteristics are presented in Table I. Inflammatory variables were elevated in patients with severe asthma compared with those with mild to moderate (Table I). Values of the 3 components of the Th2 index are provided in a graph in Figure E1 available in this article's Online Repository at www.jaci-inpractice.org. We have performed receiver operating characteristic (ROC) curve analysis to evaluate the performance of periostin for the prediction of a high Th2 airway composite index. In the whole population, periostin showed a weak predictive performance with an area under the curve (AUC) of 0.59 (CI 0.5-0.67), $P = .045$ (Figure 1, *A*), with the optimal cutoff value of 47.4 ng/mL presenting sensitivity 25%, specificity 92%, positive predictive value (PPV) 80%, and negative predictive value (NPV) 49%. Periostin failed to predict the Th2 airway composite index in patients with SRA, presenting an AUC of 0.5 (CI 0.38-0.66), $P = .76$ (Figure 1, *B*). However, in patients with mild-to-moderate asthma, periostin showed a weak performance for the identification of a high airway Th2 composite score, with an AUC of 0.58 (CI 0.49-0.68), $P = .043$, with the optimal cutoff value 17.89 ng/mL presenting sensitivity 90%, specificity 30%, PPV 54%, and NPV 76% (Figure 1, *C*). We also performed ROC analyses for the individual components of

TABLE I. Subject characteristics of study participants

Variables	Total (n = 145)	Mild-moderate (n = 89)	SRA (n = 56)
Age	54 (39-62)	58 (39-68)	54 (43-59)
Sex (female/male)	87/58	53/36	34/22
Atopy	83/145	54/89	29/56
BMI (kg/m^2)	27 (25-31)	28 (26-31)	27 (25-31)
FEV_1 % pred.	78 ± 20	88 ± 19	65 ± 17*
FEV_1/FVC %	70 ± 11	75 ± 7	64 ± 10*
Sputum eosinophils (%)	2 (0-4)	1 (0-3)	3 (2-6)*
FeNO (ppb)	22 (17-29)	19 (16-23)	22 (20-34)
IL-13 (pg/mL)	66 (59-86)	61 (57-69)	78 (60-109)*
Periostin (ng/mL)	28 (21-42)	25 (17-37)	36 (27-50)*
Blood eosinophils (%)	2 (0-3)	1 (0-2)	2 (1-7)*
Blood eosinophils absolute count	90 (0-186.5)	81 (0-130)	160 (60-430)*
Treatment regimens			
ICS	145	89†	56‡
LABA	132	81	54
CS per os	23	0	23§
LTRA	33	13	20
Omalizumab	16	0	16

BMI, Body mass index; FeNO, fraction of exhaled nitric oxide; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; ICS, inhaled corticosteroids; LABA, long-acting β_2-agonists; LTRA, leukotriene receptor antagonists; SRA, severe refractory asthma.
Normally distributed data are presented as mean ± SD; skewed data are presented as median (interquartile ranges); and categorical data as n (%).
*Statistically significant difference compared with mild-to-moderate asthma, all differences for $P < .05$.
†≤800 μg budesonide/d or equivalent.
‡≥1200 μg budesonide/d or equivalent.
§Sixteen were receiving 5 mg prednisolone/d, whereas 4 were receiving 7.5 mg prednisolone/d, 2 were receiving 10 mg prednisolone/d, and 1 was receiving 20 mg prednisolone/d.

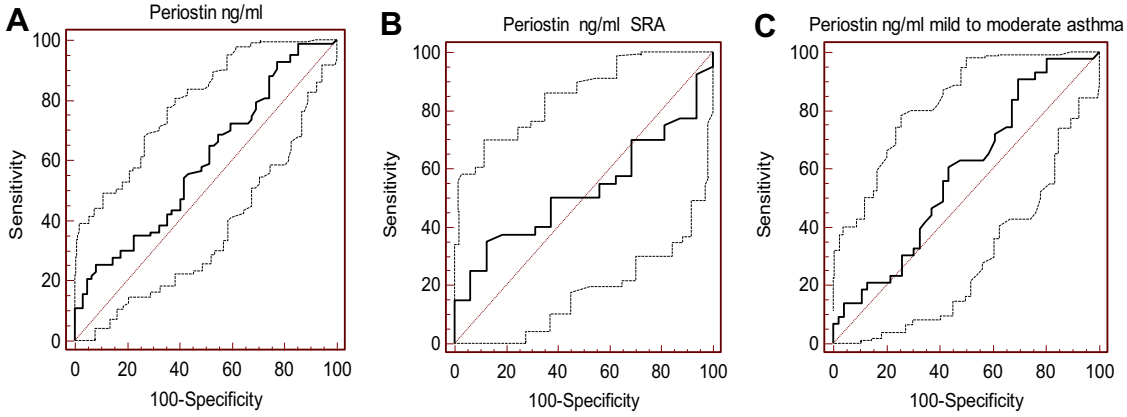

FIGURE 1. Receiver operating characteristic curves for serum periostin for the identification of a Th2 airway composite index in patients with asthma. **A**, All; **B**, severe refractory asthma (SRA); **C**, mild to moderate. For data see text.

the Th2 index. Periostin failed to show a statistically significant performance for all the individual components and the AUCs were comparable, all not exceeding the 0.6 value. Regression analysis evaluating the associations of serum periostin with inflammatory markers revealed that the only significant association was with both the absolute count and the percentage of blood eosinophils (B coefficient 3.76, $P < .001$, and B coefficient 5.13, $P = .045$, respectively).

In this prospective study, we showed that in optimally treated patients with asthma with different levels of severity, serum periostin had a weak performance in predicting a Th2 airway composite index. Using a regression analysis model the only significant associations of periostin were those with blood eosinophils. The poor ROC performance of periostin was further supported by the similarly poor performance for the individual components. Previous data regarding the predictive role of serum periostin for an airway Th2 response were controversial.[1] We created an airway Th2 composite index consisting of 3 markers of Th2 response. We chose to evaluate this composite index for 3 reasons. First, it consists of airway biomarkers only, thus reflecting airway inflammation better compared with systemic biomarkers. Second, periostin is easily measured in serum, thus