Assessment of serum periostin level as a predictor of requirement for intensive treatment for type-2 inflammation in asthmatics in future: A follow-up study of the KiHAC cohort

AUTHOR(S):

Sunadome, Hironobu; Matsumoto, Hisako; Tohda, Yuji; Horiguchi, Takahiko; Kita, Hideo; Kuwabara, Kazunobu; Tomii, Keisuke; ... Ohta, Shoichiro; Izuhara, Kenji; Hirai, Toyohiro

CITATION:

Sunadome, Hironobu ...[et al]. Assessment of serum periostin level as a predictor of requirement for intensive treatment for type-2 inflammation in asthmatics in future: A follow-up study of the KiHAC cohort. Allergology International 2021, 70(2): 252-254

ISSUE DATE:

2021-04

URL:

http://hdl.handle.net/2433/277431

Allergology International 70 (2021) 252–254

Contents lists available at ScienceDirect

Allergology International

journal homepage: http://www.elsevier.com/locate/alit

Letter to the Editor

Assessment of serum periostin level as a predictor of requirement for intensive treatment for type-2 inflammation in asthmatics in future: A follow-up study of the KiHAC cohort

Dear Editor,

The need for a systematic approach for the management of uncontrolled asthma has recently gained broad acceptance; these approaches include strategies, such as revision of diagnosis, evaluation of adherence, and assessment of comorbidities.[1] This care pathway is pragmatically useful and can be improved even further by incorporating biomarkers that include asthma endotypes and phenotypes and predict the need for future high-intensity treatment for type-2 inflammation. Periostin is an extracellular matrix protein that is detected in serum[2,3]; elevated levels of serum periostin have been associated with the Th2-type asthma phenotype/endotype,[4,5] and its stability is repeatedly reported.[6,7] Most intriguing is the possibility that serum periostin levels might predict the long-term prognosis of asthma currently managed with inhaled corticosteroid (ICS) treatment. Here we assessed the usefulness of serum periostin as a predictor of future treatment requirements, notably the need for treatment intensification for type-2 inflammation.

Our findings are part of an observational follow-up study of the Kinki Hokuriku Airway disease Conference (KiHAC) cohort.[4] Briefly, participants in the KiHAC study included asthmatics currently undergoing treatment with ICS who were recruited between September 2009 and December 2011. Ex-smokers with more than 10 pack-years or who smoked in the year prior to enrollment or subjects with other respiratory diseases such as interstitial lung disease were not included in the original KiHAC study. In this follow-up study, we enrolled 78 patients among those who had been followed for 5 years since baseline enrollment (Supplementary Fig. 1). Patients were excluded if they had been treated with ICS <500 μg/day at baseline (n = 86), who were already under treatment with omalizumab at baseline (n = 4) or who did not receive treatment with omalizumab despite frequent exacerbations due to economic reasons, being outside the permitted range, or other reasons (n = 7). Clinical data were obtained for the 5 years after enrollment, including ICS doses, the number of concomitant drugs for asthma, systemic corticosteroid (SCS) use, introduction of omalizumab for uncontrolled allergic asthma, and the number of exacerbations during this time interval that required SCS treatment. Baseline serum periostin levels were not available to physicians.

Statistical analyses were performed using JMP software, version 12 (SAS Institute, Tokyo, Japan). We stratified the participants into "highly intensive" treatment group and "others" as follows: at baseline, subjects with ≥1000 μg/day of ICS or SCS use were defined as the "highly intensive" group; after five years, those with ≥1000 μg/day of ICS, SCS use, or omalizumab treatment as "highly intensive" group. We did not consider the use of long acting β2 agonist (LABA) because 74% of the patients had already received LABA at baseline. Data were compared between the "highly intensive" group and the others at 5 years after baseline using t-test, Wilcoxon rank-sum test, or χ^2 test, as appropriate. Serum periostin at baseline was evaluated as a potential predictor of a future need for high dose ICS (equivalent to fluticasone propionate ≥ 1000 μg/day), SCS use or omalizumab at five years after enrollment, using receiver operating characteristic (ROC) method. Data are presented as means ± SDs. $P \leq 0.05$ was considered significant. This follow-up study was approved by the ethics committee of Kyoto University (Registry ID UMIN000030674).

The baseline characteristics of the 78 patients are presented in Supplementary Table 1. In all subjects, at 5 years after baseline enrollment, 25 patients required highly intensive treatment (Table 1), and 7 required omalizumab treatment (Supplementary Table 2). High baseline levels of serum periostin, ICS dose, and SCS use at baseline, but not blood eosinophil count or serum levels of total IgE were associated with highly intensive treatment after 5 years (Table 1). In ROC analysis, serum periostin levels were predictive with respect to highly intensive treatment at 5 years later, with an area under the curve (AUC) of 0.68 and a cut-off value of 115.5 ng/mL, which showed 56.0% sensitivity and 83.0% specificity. With respect to the specific requirement of omalizumab, serum periostin levels were also predictive with moderate accuracy (AUC = 0.74, and a cut-off value of 123.7 ng/mL providing 71.4% sensitivity and 81.7% specificity).

Next, we limited the analysis to patients who were on a 500 ≤ ICS <1000 μg/day regimen without SCS use at baseline (n = 51). Six patients required highly intensive treatment after 5 years. Among various indices evaluated at baseline, serum periostin alone was significantly higher in a comparison between patients requiring highly intensive treatment and those who did not after 5 years (Supplementary Table 3). In ROC analysis, serum periostin levels were predictive with moderate accuracy (AUC = 0.79, and a cut-off value of 115.5 ng/mL with 83.3% sensitivity and 86.7% specificity; Fig. 1). In this population, subjects with serum periostin ≥115.5 ng/mL tended to have more frequent exacerbations than the

Peer review under responsibility of Japanese Society of Allergology.

https://doi.org/10.1016/j.alit.2020.10.006

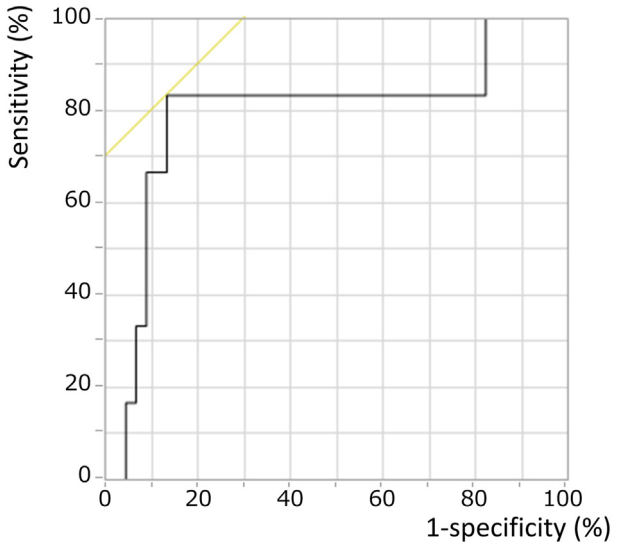
Table 1
Associations between clinical indices at baseline and requirement of high dose ICS, omalizumab (OML) or systemic corticosteroid (SCS) treatment after 5 years.

	ICS <1000, OML (−) and SCS (−) after 5 years n = 53	ICS ≥ 1000, OML (+) or SCS (+) after 5 years n = 25	*P* value
Gender (female), n (%)	36 (67.9)	20 (80.0)	0.27
Age at baseline (years)	61 ± 15	62 ± 13	0.85
Age at asthma onset (years)	41 ± 20	40 ± 16	0.89
BMI (kg/m^2)	23.2 ± 3.6	22.3 ± 3.4	0.29
ICS dose[†] (μg/day)	655 ± 215	956 ± 338	<0.01
Number of concomitant drugs, n	1.6 ± 0.2	1.9 ± 0.3	0.35
Number of LABA users, n (%)	37 (69.8)	21 (84.0)	0.18
Number of SCS users, n (%)	1 (1.9)	9 (36.0)	<0.01
Highly intensive treatment at baseline[‡], n (%)	8 (15.1)	19 (76.0)	<0.01
Patients with recent exacerbations[§], n (%)	3 (5.7)	5 (20.0)	0.06
ACT score (points)	22.5 ± 2.7	21.6 ± 4.1	0.27
Serum periostin (ng/mL)	92.5 ± 46.1	116.2 ± 46.6	0.01
Serum IgE (IU/mL)	221 (64–591)	185 (100–420)	0.89
Blood eosinophils (/μL)	305 ± 248	323 ± 487	0.45
Predicted FEV1 (%)	96.9 ± 20.7	90.3 ± 22.9	0.21
Predicted FEV1 (%) < 80%, n (%)	12 (22.6)	10 (40.0)	0.11

Data at baseline are presented as mean ± SD, except for serum IgE which is presented as the median value (range).
ICS, inhaled corticosteroid; OML, omalizumab; LABA, long acting β2 receptor agonist; SCS, systemic corticosteroid; ACT, Asthma Control Test; FEV1, forced expiratory volume in 1 s.
[†] Equivalent to fluticasone propionate (μg/day).
[‡] Defined as subjects with ICS ≥1000 μg/day or SCS use at baseline.
[§] Determined as exacerbations requiring systemic corticosteroids during the preceding 6 months before baseline.

remaining cohort during the ensuing 5 years (times during 5 years, means ± SD; 1.4 ± 1.7 vs. 0.6 ± 1.2, $p = 0.08$). Additionally, subjects without highly intensive treatment at both timings (baseline and five years later) showed significantly lower serum periostin levels than the remainings (86.1 ± 34.0 ng/mL vs 119.1 ± 56.0 ng/mL, $p = 0.01$).

Here we demonstrated that high serum periostin levels at baseline may predict future requirement for highly intensive asthma treatment for type-2 inflammation, i.e., the need for increasing high dose ICS (≥1000 μg/day), SCS use or omalizumab. Particularly, among patients undergoing ICS treatment with 500 to less than 1000 μg/day without SCS, 115.5 ng/mL represented the optimal cut-off for predicting the need for more intensive treatment in the future. Serum periostin (≥123.7 ng/mL) was also predictive the need for future treatment with omalizumab in patients undergoing treatment with ICS at ≥ 500 μg/day at baseline. Taken together, these findings indicate that high levels of serum periostin may serve as a biomarker of responsiveness to omalizumab as previously shown[8] and; moreover, may predict future need for this biologic therapy. As such, an evaluation of serum periostin levels may assist with identification of patients who may be resistant to 500–1000 μg/day of ICS or who may need referral to specialists for omalizumab treatment.



	AUC	Sensitivity (%)	Specificity (%)	Threshold (ng/mL)
Serum periostin	0.79	83.3	86.7	115.5

Fig. 1. ROC curve of serum periostin for high dose ICS treatment (>1000 μg/day), systemic corticosteroid use or omalizumab use at 5 years after enrollment, in patients who were treated with 500 ≤ ICS < 1000 μg/day and without systemic corticosteroid at baseline (n = 51). AUC, area under the curve.

One of the limitations of this observational study was the lack of action plans for changing the ICS doses and implementing omalizumab. However, asthma specialists managed the patients appropriately according to the guideline proposed by the Japanese Society of Allergology.[9]

In conclusion, the clinical efficacy of serum periostin levels as a prognostic marker in patients with asthma who may require highly intensive treatment within 5 years. These findings will help to identify patients who may ultimately require specialized treatments and may also help to prevent delayed introduction of biologic therapies.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.alit.2020.10.006.

Conflict of interest

HM received personal fees from AstraZeneca, Novartis Pharma, GlaxoSmithKline, and Kyorin Pharmaceutical outside the submitted work. YT reports personal fees from Kyorin Pharmaceutical, Teijin Pharma and research funding from Kyorin Pharmaceutical, Meiji Seika Pharma, Teijin Pharma, Boehringer-Ingelheim, Daiichi Sankyo, Astellas Pharma and Pearl Therapeutics outside the submitted work. KT reports a personal fee from AstraZeneca outside the submitted work. TI reports a personal fee from Kyorin Pharmaceutical and research funding from Kyorin Pharmaceutical, Meiji Seika Pharma, Boehringer-Ingelheim, Teijin Pharma, Daiichi Sankyo and Pearl Therapeutics outside the submitted work. SH reports personal fees from Astra Zeneca, GlaxoSmithKline, Novartis Pharma, Astellas Pharma,

Boehringer-Ingelheim, Sanofi and Kyorin Pharmaceutical. AN reports personal fees from AstraZeneca, MSD, Nippon Boehringer-Ingelheim, Kyorin Pharmaceutical, GlaxoSmithKline, Novartis Pharma and research funding from Novartis Pharma, MSD, Nippon Boehringer-Ingelheim and Boston Scientific Japan. TO reports personal fees from AstraZeneca, Nippon Boehringer-Ingelheim, Kyorin Pharmaceutical, GlaxoSmithKline, Novartis Pharma and Sanofi and research funding from Fujifilm outside the submitted work. JO is an employee of Shino-Test. KI reports personal fees and a research funding from Shino-Test. The rest of the authors have no conflict of interest.

Hironobu Sunadome [a], Hisako Matsumoto [a,b,*], Yuji Tohda [b], Takahiko Horiguchi [b], Hideo Kita [b], Kazunobu Kuwabara [b], Keisuke Tomii [b], Kojiro Otsuka [b], Masaki Fujimura [b], Noriyuki Ohkura [b], Takashi Iwanaga [b], Soichiro Hozawa [b], Akio Niimi [a,b], Yoshihiro Kanemitsu [a,b], Tadao Nagasaki [a], Noriyuki Tashima [a], Yumi Ishiyama [a], Chie Morimoto [a], Tsuyoshi Oguma [a], Tomoko Tajiri [a], Isao Ito [a], Junya Ono [c], Shoichiro Ohta [d], Kenji Izuhara [e], Toyohiro Hirai [a]

[a] *Department of Respiratory Medicine, Graduate School of Medicine, Kyoto University, Kyoto, Japan*
[b] *Kinki Hokuriku Airway Disease Conference (KiHAC), Sayama, Japan*
[c] *Shino-Test Corporation, Sagamihara, Japan*
[d] *Department of Laboratory Medicine, Saga Medical School, Saga, Japan*
[e] *Division of Medical Biochemistry, Department of Biomolecular Sciences, Saga Medical School, Saga, Japan*

* Corresponding author. Department of Respiratory Medicine, Graduate School of Medicine, Kyoto University, 53 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto 606-8507, Japan.
E-mail address: hmatsumo@kuhp.kyoto-u.ac.jp (H. Matsumoto).

References

1. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. 2019 Updated. https://ginasthma.org/reports/2019-gina-report-global-strategy-for-asthma-management-and-prevention/.
2. Izuhara K, Nunomura S, Nanri Y, Ono J, Takai M, Kawaguchi A. Periostin: an emerging biomarker for allergic diseases. *Allergy* 2019;**74**:2116–28.
3. Izuhara K, Conway SJ, Moore BB, Matsumoto H, Holweg CTJ, Matthews JG, et al. Roles of periostin in respiratory disorders. *Am J Respir Crit Care Med* 2016;**193**:949–56.
4. Kanemitsu Y, Matsumoto H, Izuhara K, Tohda Y, Kita H, Horiguchi T, et al. Increased periostin associates with greater airflow limitation in patients receiving inhaled corticosteroids. *J Allergy Clin Immunol* 2013;**132**:305–12.
5. Sunadome H, Matsumoto H, Petrova G, Kanemitsu Y, Tohda Y, Horiguchi T, et al. IL4Rα and ADAM33 as genetic markers in asthma exacerbations and type-2 inflammatory endotype. *Clin Exp Allergy* 2017;**47**:998–1006.
6. Semprini R, Caswell-Smith R, Fingleton J, Holweg C, Matthews J, Weatherall M, et al. Longitudinal variation of serum periostin levels in adults with stable asthma. *J Allergy Clin Immunol* 2017;**139**:1687–8.
7. Caswell-Smith R, Cripps T, Charles T, Hosking A, Handigol M, Holweg C, et al. Day-time variation of serum periostin in asthmatic adults treated with ICS/LABA and adults without asthma. *Allergy Asthma Clin Immunol* 2017;**13**:8.
8. Tajiri T, Matsumoto H, Gon Y, Ito R, Hashimoto S, Izuhara K, et al. Utility of serum periostin and free IgE levels in evaluating responsiveness to omalizumab in patients with severe asthma. *Allergy* 2016;**71**:1472–9.
9. Nakamura Y, Tamaoki J, Nagase H, Yamaguchi M, Horiguchi T, Hozawa S, Japanese Society of Allergology. Japanese guidelines for adult asthma 2020. *Allergol Int* 2020;**69**:519–48.

Received 16 June 2020
Received in revised form 8 October 2020
Accepted 20 October 2020
Available online 18 November 2020