http:// ijp.mums.ac.ir
Original Article (Pages: 15937-15944)

The Role of Serum Periostin Level in Different Pediatric Allergic Diseases: A Case-Control Study

Montaser M Mohamed[1], *Ramadan A Mahmoud[1], Christina K Hanna[1], Abdelhady R Abdel-Gawad[2], Sherif A Sayed[2], Eman M Fahmy[1]

[1] Department of Pediatrics, Sohag Faculty of Medicine, Sohag University, Sohag, Egypt.

[2] Department of Clinical and Chemical Pathology, Sohag Faculty of Medicine, Sohag University, Sohag, Egypt.

Abstract

Background: Allergic diseases represent one of the most common types of diseases globally and affect a large sector of population especially children. The main purpose of this study is to evaluate the relation between serum periostin and different allergic diseases and to compare them with children of non-allergic diseases as a control group.

Methods: 80 children were included in the study; 40 had allergic diseases and 40 children had no allergic diseases as controls. All participants completed the history and clinical examination, complete blood count, total serum immunoglobulin IgE (UI/ml), and serum periostin level.

Results: Among the patients with allergic diseases, bronchial asthma was the most common diagnosed disease 29/40 (72.50%). Patients with allergic diseases had significantly higher mean (±SD) serum periostin when compared to infants with no allergic diseases (271.9±263.27 ng/ml and 115.33±191.42 ng/ml, P-value 0.0001). However, highly elevated serum periostin >150 ng/ml were found exclusively in patients with allergic diseases 22/40 (55.00%) and only in 4/40 (10.0%) of the controls (p-value<0.0001). Furthermore, there were a statistically significant difference between the patients with different degrees of allergic diseases severity and serum periostin level as it was 1080±251.73 ng/ml in severe allergic diseases compared to 244.5±263.57 ng/ml in mild allergic diseases (P- value 0.01).

Conclusion: The most common type of allergic diseases in our study was bronchial asthma. Higher serum periostin levels were observed in allergic patients in comparison to the controls; and they were found to have a significant relationship with disease severity.

Key Words: Allergic diseases, Bronchial asthma, Serum immunoglobulin E, Serum periostin.

* Please cite this article as: Mohamed MM, Mahmoud RA, Hanna CK, Abdel-Gawad AR, Sayed SA, Fahmy EM. The Role of Serum Periostin Level in Different Pediatric Allergic Diseases: A Case-Control Study. Int J Pediatr 2022; 10 (5):15937-15944. DOI: **10.22038/ijp.2022.63426.4838**

Corresponding Author:

Ramadan A Mahmoud, Department of Pediatrics, Sohag Faculty of Medicine, Sohag University, Sohag, Egypt. Email: ramadan.aboelhassan@yahoo.com, ramadan_aboelhassan@med.sohag.edu.eg

Received date: Feb.04,2022; Accepted date:Mar.22,2022

1- INTRODUCTION

Allergic disease is one of the most prevalent types of diseases worldwide and refers to the body's immune reaction to foreign substances in the environment and triggers a reaction from the body's immune system called hypersensitivity (1). Globally, allergic diseases are among the most common diseases. They contribute significantly to global health burdens. Major chronic allergic diseases include rhinitis, bronchial asthma, atopic dermatitis, gastrointestinal tract diseases and food allergy (2). In the course of the pathogenesis of bronchial asthma, periostin was discovered as a novel mediator in allergic diseases (3). Periostin is expressed in fibroblasts and epithelial cells. The significance of interleukin (IL)-13, a type-2 cytokine, in the pathogenesis of bronchial asthma was established around 2000 based on analyses of model mice and of susceptible asthma associated genes (4). The bronchial epithelial cells are one of the important target cells for IL-13 to cause airway hyper-responsiveness which is the typical feature of asthma. The induction of periostin by IL-13 is more than ten-fold by quantitative PCR analysis and IL-4 has the same ability to induce periostin as IL-13 (5).

A study on severe adult asthma showed that serum periostin levels had the potential to be used as a biomarker of eosinophilic airway inflammation (6). Another study found that high serum periostin levels are correlated with a decrease in the forced expiratory volume in 1 second with age (7). Studies have also shown that serum periostin levels can be used to determine how effective the omalizumab is in treating asthma. Periostin is therefore a powerful biomarker for treating asthma (8).

Therefore in this study, we evaluated serum periostin level in children with different allergic diseases and compared them with non-allergic patients to find whether the serum periostin level is associated with the degree of severity and the degree of control of allergic diseases.

2- MATERIALS AND METHODS

2-1. Sample selection

This study was conducted at the Pediatric Allergy and Immunology Unit in the Pediatric Department, Sohag University Hospital, Egypt. We included 40 children aged from 6 months to 15 years old confirmed to have different allergic diseases (allergic rhinitis, allergic conjunctivitis, bronchial asthma, atopic dermatitis, others) attending the unit over one year from February 2020 to February 2021. Furthermore, 40 children without allergic diseases were studied as the control group. Both cases and controls belonged to the same demographic population.

2-2. Data collection

All patients in this study were subjected to history taking including age, sex, residence, consanguinity, similar allergic diseases in the family, type of allergic disease such as bronchial asthma, allergic rhinitis, allergic conjunctivitis, and atopic dermatitis, complaints related to allergic diseases including cough, fever, skin rash, difficulty of breathing, runny nose, and red eye or excessive lacrimation. The disease severity was identified using GINA guideline (9), ARIA 2016 (Allergic Rhinitis and its Impact on Asthma) in allergic rhinitis (10), DECA 2015 (Consensus document on allergic conjunctivitis) in allergic conjunctivitis (11), EASI 2019 (Eczema Area and Severity Index score) in allergic dermatitis (12). Based on the specific grading of the disease severity, the patients' diseases were divided into mild, moderate or severe.

Clinical examination included systemic examination for symptoms and signs of allergy (dyspnea, skin rash, itching marks,

running nose) and local examination for signs of allergy as chest wheezing, decrease air entry in bronchial asthma, red eye, and lacrimation in allergic conjunctivitis, skin rash, and wheels in atopic dermatitis. Investigations on both allergic and non-allergic children included complete blood count with white blood cell count (x10^9/dl), serum blood eosinophilic cell count (x10^9/dl), hemoglobin level g/dl, and platelets count (x10^9/dl); and the results were compared to the normal reference range of each age group.

Total serum IgE (UI/ml) was done in allergic patients while serum periostin level was done in both allergic and control patients using ELISA kit Human Periostin/OSF 2 of Aviscera Bioscience.

The kit contains the necessary components required for the quantitative measurement of recombinant and natural human periostin/OSF 2 in biological samples employing sandwich ELISA format. Detection range of the kit is as follows: 3ng/ml-100ng/ml Interpretation; normal: 3-100 ng/ml, elevated: 100-150 ng/ml, highly elevated >150 ng/ml.

2-3. Statistical analysis

Data were analyzed using STATA intercooled version 12.1. The descriptive results are represented as mean, standard deviation, median, and range. The quantitative data were analyzed using a Mann–Whitney test as the distribution was not normal. The qualitative data are presented as number and percentage; they were compared using either a chi-square test or Fisher's exact test. A binary logistic regression model was used to calculate the odds ratio (OR), 95% confidence interval (CI), and P value of the risk factors of allergic disorders. Results were considered significant at $P < 0.05$.

3- RESULTS

3-1. Patients' characteristics

Our study included 40 children with different types of allergic diseases with the mean age of 5.33±3.08 years; most of them were females (55.00%) with a female to male ratio of 1.2:1. In addition, 40 non-allergic children participated as a control group with a mean of age 7.35±3.91 years; most of them were females (60.00%) with a female to male ratio of 1.5:1. The other patient characteristics are described in **Table 1.**

Table-1: Comparing the demographic data and investigations between the studied groups

Variable		Cases (N=40)	Control (N=40)
Age/year	Mean ± SD	5.33±3.08	7.35±3.91
	Median (range)	5 (0.21-12)	8 (0.58-12)
Gender	Female	22 (55.00%)	24 (60.00%)
	Male	18 (45.00%)	16 (40.00%)
Residence	Rural	27 (67.50%)	24(60.00%)
	Urban	13 (32.50%)	16 (40.00%)
WBCs (x10^9/dl) Mean ± SD		12.18±4.02	7.67±5.12
Eosinophils (x10^9/dl) Mean ± SD		7.03±4.45	3.45±3.75
Hemoglobin (g/dl) Mean ± SD		10.97±1.44	11.01±2.34
Platelets (x10^9/dl) Mean ± SD		296.5±74.15	251.4±33.02
Parent consanguinity	Negative	25 (62.50%)	27 (67.50%)
	Positive	15 (37.50%)	13 (32.50%)
Family history of allergy	Negative	21 (52.50%)	23(57.50%)
	Positive	19 (47.50%)	17 (42.50%)

In this study, 40 patients were diagnosed with allergic diseases. Bronchial asthma was the most common diagnosed allergic disease 29 (72.50%), as shown in **Table 2**. With regard to the distribution of studied patients according to disease severity, prior to the study, we found that among 40 patients with different allergic disorders, 24 (60%) had mild disease, 12 (30%) had moderate disease, and 4 (40%) had severe disease **(Table 3).**

Table-2: Distribution of allergic diseases among the cases

Allergic disease	Number 40 (%)
Bronchial asthma	29 (72.50%)
Atopic dermatitis	4 (10.00%)
Allergic rhinitis	4 (10.00%)
Allergic conjunctivitis	3 (7.50%)

Table-3: Frequency of disease severity in different types of allergic disease

Disease severity	Bronchial asthma (N=29)	Atopic dermatitis (N=4)	Allergic rhinitis (N=4)	Allergic conjunctivitis (N=3)
Mild	18 (62.07%)	2(50%)	2(50%)	2(66.67%)
Moderate	9 (31.03%)	1(25%)	1(25%)	1(33.33)
Severe	2 (6.90%)	1(25%)	1(25%)	0

3-2. Serum periostin level

There was a statistically significant difference between the mean (±SD) of serum periostin in patients with allergy disorders (271.9±263.27 ng/ml) and the mean (±SD) of serum periostin in the control group (115.33±191.42 ng/ml) (P-value 0.0001). Highly elevated serum periostin >150 ng/ml was found as 22/40 (55.00%) in the case group compared to 4/40 (10.0%) in controls (P<0.0001).

3-3. The relationship between serum periostin level and other allergic markers

As shown in **Table.4**, serum periostin level was significantly different between severe allergic diseases (1080±251.73 ng/ml) in the mild diseases (244.5±263.57 ng/ml) (P- value 0.01). Furthermore, the elevated total immunoglobulin E (IU/ml) in allergic patients associated with higher serum periostin (373.71±246.31 ng/ml) when compared to children with allergic diseases with normal total immunoglobulin E (IU/ml), 179.79±91.99 ng/ml) (P=0.02). However, there was no clinical correlation between serum periostin and age of the patients in the case group (P=0.43) or in the control group (P=0.72). Moreover, the serum level of periostin was not significantly difference among the patients with different types of the allergic diseases, genders, and eosinophil levels (p->0.05).

4- DISCUSSION

This study is conducted on 40 children with different allergic diseases most of whom were females (55.00%); and on 40 patients without allergic diseases as controls, most of whom were females (60.00%). Serum periostin was significantly higher in different allergic patients when compared to the controls and correlated well with disease severity and total immunoglobulin E level. However, serum periostin level was not disease-specific and it was elevated in all allergic disorders.

Table-4: The association between serum periostin level and the variables of gender, type of disease, disease severity, and serum immunoglobulin E

Variable		Number	Mean ±SD serum periostin	P-value
Gender	Female	22	288.66±307.43,	0.83
	Male	18	251.42±203.59,	
Type of disease	Bronchial asthma	29	286.31±298.97,	0.65
	Atopic dermatitis	4	221.75±136.44,	
	Allergic rhinitis	4	289.5±163.26,	
	Allergic conjunctivitis	3	176±99.05,	
Disease severity	Mild	24	244.5±263.57,	0.01
	Moderate	12	487.28±137.45	
	Severe	4	1080±251.73,	
Total immunoglobulin E (IU/ml)	Normal	15	179.79±91.99,	0.02
	Elevated	25	373.71±246.31,	
Eosinophils (x10^9/dl)	Normal	15	297.83±353.98,	0.98
	Eosinophilia	25	256.34±197.14,	

Santos-Fernandez et al. (13) also reported the female predominance among children with bronchial asthma (55.9%). This can be explained by the predominance of the relative small diameter airway in female children (14). The prevalence of allergic diseases in this study shows that bronchial asthma was the most common (72.5%) allergic disorder followed by atopic dermatitis (10%). Beken et al. (15), however, had found that the prevalence of allergic rhinitis, asthma, atopic dermatitis, and episodic wheezing were 10.3%, 6.5%, 4.7%, and 3.7% respectively. In this study most of the cases had mild asthma (62 %) and moderate (31.03%) and severe (6.90%), while in the study by Yavuz et al. (16) asthma severity was mild in 41 (32.8%), moderate in 63 (50.4%), and severe in 21 (16.8%) children.

Our study found a highly significant difference between the patients with allergy and the control group regarding the serum periostin. This result is in line with the findings of Fujitani et al. (17) studying 432 children with allergic diseases to evaluate serum periostin and found higher periostin levels in allergic children than in the control group after the age of 3 years old. Furthermore, Inoue et al. (18) have also detected significantly higher serum periostin levels in children with bronchial asthma in comparison to those without any allergic diseases in a cross-sectional study; and they indicated the possible role of serum periostin in the diagnosis of childhood asthma. Another study by Song et al. (19) which was conducted to correlate serum periostin with airway hyper-responsiveness in children with bronchial asthma had found significantly higher serum periostin in children with asthma as compared with the controls. However, Inoue et al. (20) found no statistically significant difference in periostin level between children with allergic diseases and the controls; they explained this by high rates of bone turnovers in this group and high baseline levels of serum periostin in children.

In our study there was no statistically significant correlation between serum periostin level and age of the allergic patients. This goes in line with Yavuz et al. (16), who had found no statistically significant correlation between serum

periostin and age of asthmatic children. But in contrast to a previous study by Fujitani et al. (17) which revealed a statistically significant relationship between periostin level and age in the allergic group. They had also found that serum periostin steadily decreased until the age of 7 years and then increased slightly. Another study by Sung et al. (21) revealed that allergic children with onset times of < 2 years had significantly higher periostin levels ($P = 0.030$) compared to those having allergic disease with onset times of ≥ 2 years.

Our study revealed no significant correlation between the serum periostin level and eosinophilic count and the total immunoglobulin E level in allergic patients. This is consistent with the results of Konradsen et al. (22) who did not detect any correlation between serum periostin and blood eosinophils. This can be explained by high baseline levels of serum periostin in children (20). These results are also in agreement with Tan et al. (23) which revealed no significant correlation between the serum periostin level and serum eosinophilic count. In contrast to our study, Song et al. (19), Sung et al. (24) and El Basha et al. (25) found significant correlations between the high level of serum periostin and increased blood eosinophils.

In this study we found a significant relationship between the raised serum periostin level and allergic disease severity. Tan et al. (23) and Jonstam et al. (26) had also the same findings. Furthermore, Yavuz et al. (20), performing a multivariable logistic regression analysis, demonstrated an association between serum periostin levels and asthma severity in children (OR, 1.10; 95% CI, 1.04-1.15, $P < 0.001$).

This single control study had some limitations such as the small sample size. However, we included 80 patients (40 cases and 40 controls) selected from the same demographic population and found relevant data. Further studies are needed to clarify the ranges of serum periostin in different age groups and to determine in which age groups the serum periostin level can be a useful biomarker.

5- CONCLUSION

The most common type of allergic diseases in our study was bronchial asthma. Most of our allergic patients had mild disease forms. Higher serum periostin levels were observed in allergic patients in comparison to the controls; and they were found to have a significant relationship with disease severity. Furthermore, serum periostin was neither age specific, nor related to serum immunoglobulin E nor blood eosinophilia level.

6- ETHICAL CONSIDERATIONS

Informed written consents were taken from the caregivers of children included in the study. Our study had to be approved by the ethical scientific committee of Sohag Faculty of Medicine, Sohag University, Egypt (Approval number 345, approval time, January; 2020).

7- CONFLICT OF INTEREST

None

8- ACKNOWLEDGEMENTS

The authors thank http://proof-reading-services.com for language editing.

9- REFERENCES

1. Fischer D, Vander Leek TK, Ellis AK, Kim H. Anaphylaxis. Allergy Asthma Clin Immunol 2018; 14(2):54.

2. Pinart M, Albang R, Maier D, Duran-Tauleria E, Mena G, Gimeno-Santos E, Solà I, Garcia-Aymerich J, Guerra S, Stein RT, Benet M, Carlsen KH, Herr M, Jacquemin B, Momas I, Pin I, Rancière F, Smit HA, Varraso R, Bonfill X, Keil T, Bousquet J, Antó JM. Systematic review on the definition of allergic diseases in

children: The Medall study. Int Arch Allergy Immunol. 2015; 168(2):110-21.

3. Cobo, T, Viloria CG, Solares L, Fontanil T, González-Chamorro E, Carlos FD, Cobo J, Cal S, Obaya AJ. Role of periostin in adhesion and migration of bone remodeling cells. PLoS One. 2016; 11(1), e0147837.

4. Izuhara K, Ohta S, Ono J. Using periostin as a biomarker in the treatment of asthma. Allergy Asthma Immunol Res. 2016; 8(6):491.

5. Izuhara K, Arima K, Ohta S, Suzuki S, Inamitsu M, Yamamoto K I. Periostin in allergic inflammation. Allergol Int 2014; 63(2):143-51.

6. Jia G, Erickson RW, Choy DF, Mosesova S, Wu LC, and Solberg OD. Periostin is a systemic biomarker of eosinophilic airway inflammation in asthmatic patients. J Allergy Clin Immunol 2012; 130(3):647-54.

7. Kanemitsu Y, Matsumoto H, Izuhara K, Tohda Y, Kita H, Horiguchi T, Kuwabara K, Tomii K, Otsuka K, Fujimura M, Ohkura N, Tomita K, Yokoyama A, Ohnishi H, Nakano Y, Oguma T, Hozawa S, Nagasaki T, Ito I, Oguma T, Inoue H, Tajiri T, Iwata T, Izuhara Y, Ono J, Ohta S, Tamari M, Hirota T, Yokoyama T, Niimi A, Mishima M. Increased periostin associates with greater airflow limitation in patients receiving inhaled corticosteroids. J Allergy Clin Immunol 2013; 132(2):305-12.

8. Hanania NA, Wenzel S, Rosén K, Hsieh HJ, Mosesova S, Choy DF, Lal P, Arron JR, Harris JM, Busse W. Exploring the effects of omalizumab in allergic asthma: an analysis of biomarkers in the EXTRA study. Am J Respir Crit Care Med 2013; 187(8):804-11.

9. Von Mutius E. Presentation of new GINA guidelines for pediatrics. The Global Initiative on Asthma. Clinical and experimental allergy. Clin Exp Allergy 2000; 30(1):6-10.

10. Brożek JL, Bousquet J, Agache I, Agarwal A, Bachert C, Bosnic-Anticevich S, Brignardello-Petersen R, Canonica GW, Casale T, Chavannes NH, Sousa JC, Cruz AA, Cuello-Garcia CA, Demoly P, Dykewicz M, Etxeandia-Ikobaltzeta I, Florez ID, Fokkens W, Fonseca J, Hellings PW, Klimek L, Kowalski S, Kuna P, Laisaar KT, Larenas-Linnemann DE, Carlsen KCL, Manning PJ, Meltzer E, Mullol J, Muraro A, O'Hehir R, Ohta K, Panzner P, Papadopoulos N, Park HS, Passalacqua G, Pawankar R, Price D, Riva JJ, Roldán Y, Ryan D, Sadeghirad B, Samolinski B, Schmid-Grendelmeier P, Sheikh A, Togias A, Valero A, Valiulis A, Valovirta E, Ventresca M, Wallace D, Waserman S, Wickman M, Wiercioch W, Yepes-Nuñez JJ, Zhang L, Zhang Y, Zidarn M, Zuberbier T, Schünemann HJ. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines—2016 revision. J Allergy Clin Immunol 2017; 140(4):950-58.

11. Sánchez-Hernández M, Montero J, Rondon C, Benitez del Castillo JM, Velázquez E, Herreras JM, Fernández-Parra B, Merayo-Lloves J, Del Cuvillo A, Vega F, Valero A, Panizo C, Montoro J, Matheu V, Lluch-Bernal M, González M L, González R, Dordal MT, Dávila I, Colás C, Campo P, Antón E, Navarro A, SEAIC 2010 Rhinoconjunctivitis Committee; Spanish Group Ocular Surface-GESOC. Consensus document on allergic conjunctivitis (DECA). J Investig Allergol Clin Immunol 2015; 25(2):94-106.

12. Lara-Corrales I, Bergman JN, Landells I, Ramien ML, Lansang P. Approach to the assessment and management of pediatric patients with atopic dermatitis: a consensus document. Section I: overview of pediatric atopic dermatitis. J Cutan Med Surg 2019; 23(5):3S-11S.

13. Santos-Fernándeza WJ, Jones-Turciosa GS, Ávila-Vallea GL, Portillo-Canalesa S, Orellana-Áragona E, Mayorgabc Á, Herrera-Paz EF. Comparison of the prevalence of bronchial asthma in school-aged children and adolescents on Roatán Island and in other coastal communities in Honduras. Rev Med Hosp Gen Méx 2016; 79(3):124-35.

14. Kahwa EK, Waldron NK, Younger NO, Edwards NC, Knight-Madden JM, Bailey KA, Wint YB, Lewis-Bell KN. Asthma and allergies in Jamaican children aged 2–17 years: a cross-sectional prevalence survey. BMJ Open 2012; 2:e001132

15. Beken B, Ozturk GK, Aygun FD, Aydogmus C, Akar HH. Asthma and allergic diseases are not risk factors for hospitalization in children with coronavirus disease 2019. Ann Allergy Asthma Immunol 2021; 126(5):569-75.

16. Yavuz ST, Bagci S, Bolat A, Akin O, Ganschow R. Association of serum periostin levels with clinical features in children with asthma. Pediatr Allergy Immunol 2021; 32(5):937-44.

17. Higa Y, Fujikawa S, Ohta N, Ono J, Izuhara K, Shintaku H. Age-related changes in serum periostin level in allergic and non-allergic children. Allergol Int 2019; 68(2):285-56.

18. Inoue T, Akashi K, Watanabe M, Ikeda Y, Ashizuka S, Motoki T, Suzuki R, Sagara N, Yanagida N, Sato S, Ebisawa M, Ohta S, Ono J, Izuhara K, Katsunuma T. Periostin as a biomarker for the diagnosis of pediatric asthma. Pediatr Allergy Immunol 2016; 27(5):521-26.

19. Song JS, You JS, Jeong SI, Yang S, Hwang IT, Im YJ, Baek HS, Kim HY, Suh DI, Lee HB, Izuhara K. Serum periostin levels correlate with airway hyper-responsiveness to methacholine and mannitol in children with asthma. Allergy 2015; 70(6):674-81.

20. Inoue Y, Izuhara K, Ohta S, Ono J, Shimojo N. No increase in the serum periostin level is detected in elementary school-age children with allergic diseases. Allergol Int 2015; 64(3):289-90.

21. Sung M, Lee KS, Ha EG, Lee SJ, Kim ME, Lee SW, Jee HM, Sheen YH, Jung YH, Han MY. An association of periostin levels with the severity and chronicity of atopic dermatitis in children. Pediatr Allergy Immunol 2017; 28(6):543-50.

22. Konradsen JR, Skantz E, Nordlund B, Lidegran M, James A, Ono J, Ohta S, Izuhara K, Dahlén SE, Alving K, Hedlin G. Predicting asthma morbidity in children using proposed markers of Th2-type inflammation. Pediatr Allergy Immunol 2015; 26(8):772-79.

23. Tan H-TT, Sugita K, Akdis CA. Novel biologicals for the treatment of allergic diseases and asthma. Curr Allergy Asthma Rep. 2016; 16(10):1-14.

24. Sung M, Baek HS, Yon DK, Lee SW, Ha EK, Lee SK, Jee HM, Sheen YH, Ono J, Izuhara K, Han MY. Serum periostin level has limited usefulness as a biomarker for allergic disease in 7-year-old children. Int Arch Allergy Immunol 2019; 180(3):195-201.

25. El Basha NR, Osman HM, Abdelaal AA, Saed SM, Shaaban HH. Increased expression of serum periostin and YKL40 in children with severe asthma and asthma exacerbation. J Investig Med 2018; 66(8):1102-08.

26. Jonstam K, Westman M, Holtappels G, Holweg CT, Bachert C. Serum periostin, IgE, and SE-IgE can be used as biomarkers to identify moderate to severe chronic rhinosinusitis with nasal polyps. J Allergy Clin Immunol 2017; 140(6):1705-08.