Allergy Asthma Immunol Res. 2021 Mar;13(2):330-338
https://doi.org/10.4168/aair.2021.13.2.330
pISSN 2092-7355·eISSN 2092-7363

Allergy, Asthma & Immunology Research AAIR

Original Article

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Changes in Type 2 Biomarkers After Anti-IL5 Treatment in Patients With Severe Eosinophilic Asthma

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OPEN ACCESS

Received: Jul 2, 2020
Revised: Sep 23, 2020
Accepted: Sep 25, 2020

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ABSTRACT

Patients with severe eosinophilic asthma (SEA) suffer from frequent asthma exacerbations, where eosinophils are major effector cells in airway inflammation, and anti-interleukin (IL)-5 becomes an effective treatment modality to control eosinophilic inflammation of SEA. Fifteen patients with SEA who had been treated with anti-IL5 (reslizumab, 100 mg monthly intravenously) for 6 months at Ajou University Hospital (Suwon, Korea) were enrolled in this study. Clinical parameters, including total blood eosinophil count (TEC), FEV1%, fractional exhaled nitric oxide (FeNO) levels, and serum biomarkers such as eosinophil-derived neurotoxin (EDN), periostin (PON), and transforming growth factor-β1 (TGF-β1), were analyzed. EDN levels and TEC decreased significantly after 1 month of treatment ($P < 0.05$ for both), while no changes were noted in FeNO/PON/TGF-β1 levels. FEV1% increased after 2 months of treatment ($P < 0.05$). A positive correlation was observed between TEC and EDN levels ($r = 0.60$, $P = 0.02$). Significant negative correlations were noted between age and TEC/EDN levels ($r = -0.57$, $P = 0.02$ and $r = -0.56$, $P = 0.03$, respectively). Baseline TEC was higher in the EDN-responder group (≥75% decrease) than in the non-responder group ($P = 0.06$) with a positive correlation between %reduction in EDN and TEC ($r = 0.67$, $P = 0.01$). The onset age was younger and asthma duration was longer in the FEV1%-non-responder group (<12% increase) than in the FEV1%-responder group ($P = 0.07$ and $P = 0.007$, respectively). In conclusion, changes in the serum EDN level may be a potential biomarker for monitoring eosinophilic inflammation after anti-IL5 treatment in SEA, which is affected by onset age and asthma duration.

Keywords: Asthma; eosinophils; interleukin-5; antibodies, monoclonal; inflammation; asthma exacerbation

INTRODUCTON

Asthma is a chronic airway inflammatory disease characterized by type 2 eosinophilic inflammation. Both environmental factors and the degree of eosinophilic inflammation affect disease severity, which can be improved by classic anti-inflammatory drugs, but some patients with unusually severe eosinophilic asthma (SEA) show limited responses to the drugs and suffer from asthma exacerbation (AE).[1] Eosinophils are well known as effector cells associated with AE, and patients with SEA have frequently used systemic steroids to suppress

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Disclosure

There are no financial or other issues that might lead to conflict of interest.

eosinophilic inflammation for symptom control. Some SEA patients require daily systemic steroids to control symptoms, where alternative treatments are required to spare systemic steroid use.

Considering that interleukin (IL) 5 is known to be involved in eosinophilic proliferation and activation, antibodies to IL5 and IL5 receptors are effective in reducing AEs in SEA.[2,3] A few type 2 biomarkers, such as peripheral total eosinophil count (TEC) and fraction of exhaled nitric oxide (FeNO), have been used in practice; however, their relevance has not yet been completely elucidated. Regarding serum biomarkers, periostin (PON) is considered a biomarker of type 2 airway inflammation in asthmatics; the serum eosinophil-derived neurotoxin (EDN) is reported as a potential biomarker of eosinophil activation status and asthma severity.[4,5] Transforming growth factor (TGF)-β1 is a major cytokine acting on airway structural cells involved in airway inflammation/remodeling.[6] They may be candidate biomarkers associated with anti-IL5.[4,7] This study examined changes in clinical parameters and serum biomarkers during anti-IL5 treatment to evaluate their clinical relevance in SEA.

MATERIALS AND METHODS

Patients

This study enrolled 15 patients who had been diagnosed with SEA in the Department of Allergy and Clinical Immunology at Ajou University Hospital, Suwon, South Korea. SEA was defined if patients had peripheral eosinophilia (≥ 300 cells/μL) before anti-IL5 treatment; severe asthma was defined according to the Global Initiative for Asthma and the European Respiratory Society guidelines.[1,8] One patient was excluded from the study due to poor compliance. All patients had maintained anti-asthmatic medications, including medium- to high-dose inhaled corticosteroids (ICS), long-acting β_2-agonists (LABAs), and leukotriene receptor antagonists (LTRAs); however, they were in an uncontrolled state and had experienced recurrent AEs requiring systemic corticosteroids (over 15 mg prednisolone daily for > 3 days) > 2 times per year during the previous 2 years. The demographic characteristics were analyzed. Atopy was defined as a positive reaction when the ratio of mean diameter of specific wheal to histamine was more than 1 after skin prick test with 55 common inhalant allergens (Bencard, Bradford, UK). Serum total/specific immunoglobulin E was measured by using the ImmunoCAP® system (ThermoFisher Scientific, Waltham, MA, USA). Chronic rhinosinusitis (CRS) was confirmed clinically by history and radiological imaging studies, including paranasal sinus radiography or computed tomography. This study was approved by the Ajou University Institutional Review Board, and all of informed consent forms were obtained from all participants (AJIRB-Med-SMP-18-415).

Methods

A fixed dose of 100 mg reslizumab (Cinqair®; Teva, North Wales, PA, USA) was intravenously administered for 6 months at monthly intervals. All anti-asthmatic medications were maintained. TEC and pulmonary function tests, including FEV1% and FeNO, were performed before the treatment (V1) and repeated at each visit for the initial 3 months (V2–V4), and then the final visit was done after 6 months of treatment (V5) in order to monitor treatment responses, AEs, and adverse reactions. Sera collected at each visit to evaluate the 3 biomarkers, were frozen at –70°C, and were thawed before use. A spirometer (Jaeger, Würzburg, Germany) was used for pulmonary function tests. Airway hyperresponsiveness was confirmed by methacholine provocation tests. FeNO was measured by using Niox®

(Circassia, Sollentuna, Sweden). Serum EDN/PON/TGF-β1 levels were measured by using ELISA (K-EDN® kit; SKIMS-BIO, Seoul, Korea; SHINO-Test Corporation, Sagamihara, Japan; and DuoSet, Minneapolis, MN, USA, respectively) according to their respective manufacturers' protocols.

Demographic characteristics are presented as mean and distribution. One dropped-out patient was excluded from the analysis of treatment responses. The Wilcoxon-signed rank test was applied to compare values before and after the treatment, and the Mann-Whitney *U* test was applied to compare between responders and non-responders after the treatment, depending on changes in FEV1%, FeNO, and EDN.

The FEV1%-responder group was defined if FEV1% increased ≥ 12%; the FeNO-responder group was defined if the FeNO level decreased more than 20% (in patients with > 50 ppb of FeNO) or 10 ppb (in those with < 50 ppb); the EDN-responder group was defined if the serum EDN level decreased over 75%.[9-11] Spearman correlation coefficients were used for correlation analysis. All statistical analyses were performed and graphics were created by using GraphPad Prism for Windows version 8.0 (GraphPad Software, Inc., La Jolla, CA, USA). A *P* value of < 0.05 was considered significant.

RESULTS

Demographic and laboratory findings of the study patients

The clinical features of all enrolled subjects are summarized in **Supplementary Table S1**. Of the 15 patients, 10 were female (66.67%), and 1 dropped out. The mean age was 53.00 ± 13.92 years; the mean asthma duration was 11.67 ± 8.77 years; and the mean onset age was 41.40 ± 15.12 years. Twelve patients (80%) had CRS. The baseline FeNO was 87.33 ± 61.40 ppb; the baseline TEC was 713.60 ± 427.10 cells/μL. The baseline levels of 3 biomarkers (EDN, PON, and TGF-β1) are shown in **Supplementary Table S1**. During the study, all patients were kept in controlled state based on the GINA guideline.[1] No treatment-related adverse reactions were noted during the study.

Comparison of atopic status and correlations among clinical and serum biomarkers

The baseline levels of 3 biomarkers were not significantly different between atopics and non-atopics. No significant correlation was found between TEC and the FeNO level ($P = 0.40$), but a positive correlation was observed between TEC and EDN levels ($r = 0.60$, $P = 0.02$; **Supplementary Fig. S1A and B**). Negative correlations were noted between age and TEC/EDN levels ($r = -0.57$, $P = 0.02$; $r = -0.56$, $P = 0.03$), while no significant correlations were noted between age/TEC and PON/TGF-β1 levels ($P > 0.05$ for each; **Supplementary Table S2**).

Changes in clinical parameters and serum biomarkers after anti-IL5 treatment

Serial changes in FEV1%, FeNO, and TEC showed that there was a significant difference in FEV1% for the initial 2 months between V1 and V3 ($P = 0.02$; **Fig. 1A**), while FeNO tended to decrease, but no significant difference was noted ($P > 0.05$; **Fig. 1B**). TECs decreased notably after 1 month with statistical significance (V1 vs. V2, 757.10 ± 410.8 vs. 42.86 ± 51.36 cells/μL, $P < 0.0001$; **Fig. 1C**) which was maintained for 6 months. EDN levels decreased significantly at V2 compared to V1 ($P = 0.0001$), which remained lower, but showed variable levels during the following months ($P > 0.05$; **Fig. 1D**). Serum PON or TGF-β1 levels showed no significant changes during the study period ($P > 0.05$).

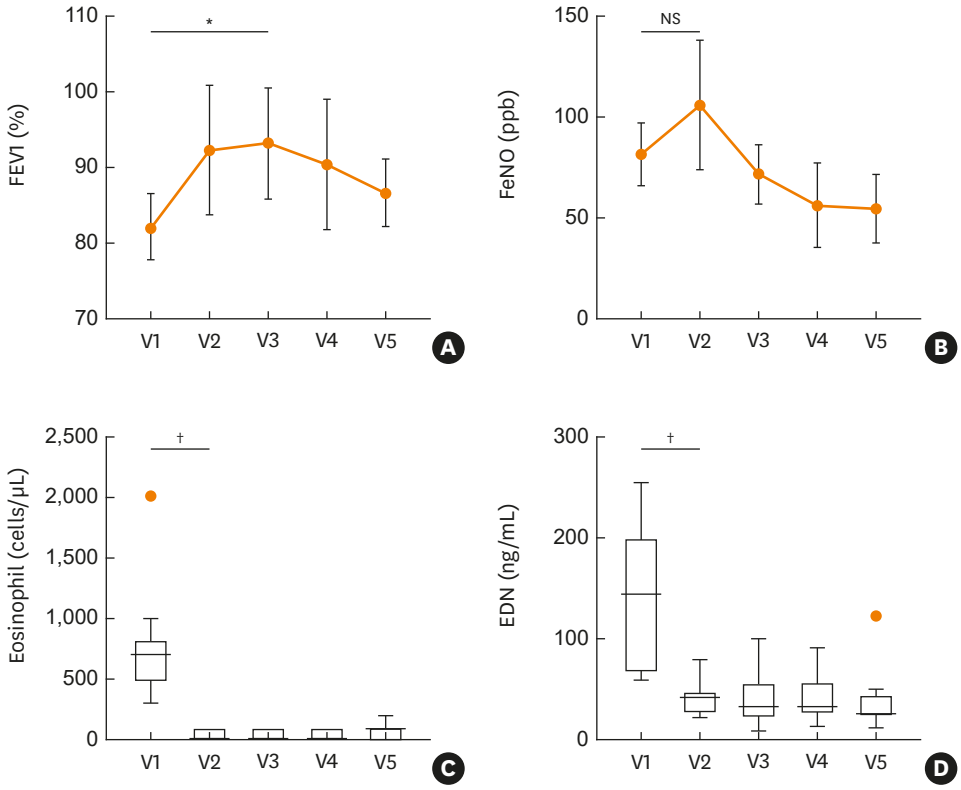

Fig. 1. Changes in FEV1 (%pred value, A), FeNO (B), TECs (C), and EDN (D) levels during anti-IL5 treatment in patients with severe eosinophilic asthma. (A and B) show mean with standard error of mean. (C and D) show boxplot with median and interquartile by Tukey method.
FEV1, forced expiratory volume in 1 second; FeNO, fractional exhaled nitric oxide; TEC, total eosinophil count; EDN, eosinophil-derived neurotoxin; V, visit; NS, not significant.
$^{*}P < 0.05$, $^{\dagger}P < 0.001$.

Comparison of clinical and laboratory parameters between responders and non-responders

Baseline TEC and EDN levels were significantly higher in the EDN-responders than in the non-responders (888.9 ± 442.8 vs. 520.0 ± 216.8 cells/μL, $P = 0.06$; 171.9 ± 60.9 vs. 94.44 ± 42.79 ng/mL, $P = 0.03$, respectively; **Fig. 2A**, **Supplementary Table S3**). Positive correlations were noted between maximum% decreases in EDN and baseline levels of TEC and FeNO ($r = 0.67$, $P = 0.01$; $r = 0.39$, $P = 0.17$), with a negative correlation with age ($r = -0.49$, $P = 0.08$; **Supplementary Fig. S2**). Asthma duration was longer in the FeNO-nonresponder group than in the FeNO-responder group (23.00 ± 8.00 vs. 7.44 ± 4.80 years, $P = 0.0028$; **Fig. 2B**); no significant differences were noted in age or body mass index. Asthma onset age was older in the FEV1%-responder group than in the FEV1-nonresponder group (48.43 ± 15.54 vs. 35.17 ± 9.89 years, $P = 0.07$; **Fig. 2C**); asthma duration was longer in the non-responder group than in the responder group (19.17 ± 8.64 vs. 6.29 ± 4.79 years, $P = 0.007$; **Supplementary Table S3**).

DISCUSSION

This is a prospectively designed real-world trial of anti-IL5 treatment for 6 months, demonstrating that all the patients were in controlled state without AEs or adverse reactions. FEV1% could increase with a significant reduction in TEC and EDN levels (without any

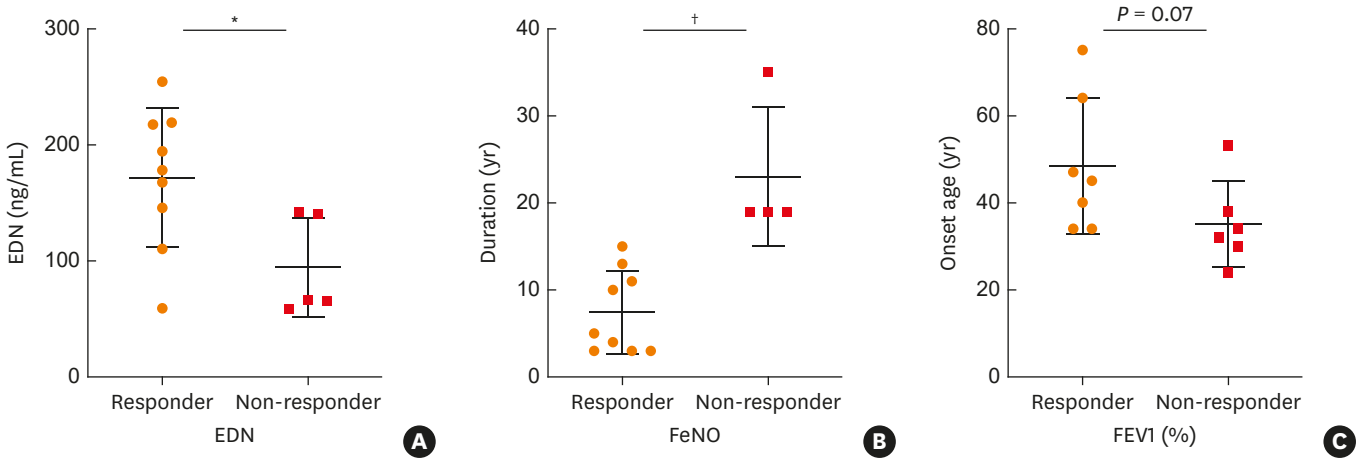

Fig. 2. Comparison of responders and non-responders according to changes in EDN/FeNO/FEV1% levels.
EDN, eosinophil-derived neurotoxin; FeNO, fractional exhaled nitric oxide; FEV1, forced expiratory volume in 1 second.
*$P < 0.05$, †$P < 0.01$.

changes in FeNO and serum PON/TGF-β1 levels), which were affected by onset age and asthma duration in SEA.

Patients with SEA are usually in an uncontrolled state, where persistent type 2 inflammation is noted in the airways. They have persistent blood/airway eosinophilia, associated with AE, progressive airway remodeling, and lung function decline.[12,13] In such cases, type 2 biologics have been recommended for suppressing uncontrolled eosinophilic airway inflammation by conventional anti-inflammatory treatment. Recent clinical trials have demonstrated that 3 currently available biologics targeting the IL5/IL5 receptor (mepolizumab, reslizumab, and benralizumab) are effective in preventing AEs and in reducing OCS use, where reslizumab has been approved in patients with SEA having higher TEC (> 400 cells/μL).[14-16] Although TEC may decrease after anti-IL5 treatment, better biomarkers for monitoring or predicting the treatment response are required. It is reported that benralizuamb (an anti-IL5 receptor antibody) could reduce serum EDN levels.[11]

The present study validated clinical and laboratory biomarkers during 6 months of reslizumab treatment (a fixed dose of 100 mg/month for all the subjects), although weight-based dose 3 mg/kg is officially recommended.[17] After 1–2 months of treatment, TEC and EDN levels were significantly reduced with a significant increase in FEV1%, which could be maintained during the study period. TEC is a well-known biomarker for SEA, and higher EDN levels have been reported to indicate the severity and control status of adult asthma.[7,18] Taken together, these findings suggest that EDN may be a useful biomarker for monitoring anti-IL5 treatment in SEA, where the fixed dose of reslizumab could be cost-effective in controlling eosinophilic inflammation in real-world practice, considering the high cost of biologics.

To evaluate asthma severity, various approaches using clinical and laboratory biomarkers are required.[1] Measurement of sputum eosinophils is considered a type 2 marker for representing airway eosinophilia; however, sputum samples are still difficult to collect from sputum-free patients and require related facilities. Several studies suggested that TEC, FeNO, and PON can be applied as type 2 inflammatory biomarkers. TEC cannot sufficiently identify specific changes in symptoms and the degree of persistent airway inflammation. In this study, even after one injection of reslizumab, TEC decreased to nearly 0 and maintained throughout the

study period; therefore, TEC is not appropriate for strictly monitoring treatment responses as reported in other studies.[19,20] Regarding the roles of PON and TGF-β1 as biomarkers, PON was reported as a type 2 biomarker in asthma associated with TGF-β1.[21-23] TGF-β1 is a profibrotic mediator expressed in the asthmatic airways which promotes the differentiation of myofibroblasts and proliferation of airway smooth muscle cells to affect airway remodeling and bronchodilator hyporesponsiveness.[24] The present study demonstrated no significant changes in serum PON or TGF-β1 levels even after 6 months' treatment with anti-IL5, implying that they may not be useful biomarkers for monitoring anti-IL5 treatment responses, although further long-term studies are needed.

It is suggested that the serum EDN level is relevant to eosinophilic airway inflammation in childhood asthma and in adult SEA.[18,25] The present study demonstrated a positive correlation between TEC and serum EDN at baseline; patients with a higher TEC/FeNO level had a greater reduction in the serum EDN level. During the anti-IL5 treatment, the serum EDN level significantly decreased with fluctuations, indicating that serum EDN level may be a potential biomarker for monitoring the degree of eosinophilic inflammation in patients with SEA.

FEV1% is a widely used clinical parameter to evaluate the degree and severity of airway obstruction in asthmatics.[26] The present study showed an increase in FEV1% up to 2 months after treatment, similar to results of previous studies.[27,28] The FEV1%-non-responders had longer duration and younger onset age of asthma, which is consistent with results of previous studies reporting that a longer duration of asthma is a risk factor for poor control. Repeated airflow obstruction and respiratory infections lead to disease progression and lung function decline in asthmatics with longer duration.[29-32]

A high FeNO level has been regarded as a clinical biomarker for type 2 asthma.[33] Asthmatics showing a higher FeNO level had a better response to ICSs, albeit with a higher incidence of AE.[33-35] The present study revealed that the FeNO-non-responder group had a longer asthma duration and FeNO level did not decrease after anti-IL5 treatment, suggesting that FeNO is not a useful clinical biomarker for anti-IL5 treatment.

There are some limitations to the present study. First, the number of subjects and the duration of study are not enough to validate these biomarkers. Assessment of changes in PON or TGF-β1 levels may require more months or years of treatment in patients with a longer duration. Secondly, a fixed dose of anti-IL5 antibody was administered, so the response may have differed according to body weight or body mass index (BMI) of each subject. Thirdly, some patients showed an increased EDN level during the treatment, which may have been attributed to the fixed dose of anti-IL5. However, this study design is helpful in comparing changes in variable clinical and serum biomarkers on exposure to the same dose of anti-IL5. Finally, objective evaluation of symptoms and quality of life were not included in the present study.

In conclusion, anti-IL5 could increase lung function as well as reduce TEC/EDN levels, indicating that the serum EDN level could be a potential biomarker for monitoring eosinophilic inflammation during the anti-IL5 treatment in which patient age and asthma duration may affect clinical outcomes.

ACKNOWLEDGMENTS

This study was supported by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute, funded by the Ministry of Health & Welfare, Republic of Korea (H116C0992). SKIMS-BIO (Seoul, Korea) provided an ELISA kit for the EDN level in this study.

SUPPLEMENTARY MATERIALS

Supplementary Table S1

Demographics and baseline clinical characteristics of the study subjects (n = 15)

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Supplementary Table S2

Correlation analysis between serum biomarkers and eosinophil/age

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Supplementary Table S3

Comparison of clinical characteristics between responders and non-responders for EDN/FeNO/FEV1(%) levels

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Supplementary Fig. S1

Correlations between total eosinophil counts and (A) FeNO/(B) EDN values at baseline.

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Supplementary Fig. S2

Correlations between changes in EDN (%) and (A) TECs/(B) FeNO/(C) age.

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REFERENCES

1. Global Initiative for Asthma. Global strategy for asthma management and prevention. Global Initiative for Asthma; 2020. Available from: www.ginasthma.org.
2. Gour N, Wills-Karp M. IL-4 and IL-13 signaling in allergic airway disease. Cytokine 2015;75:68-78.
   PUBMED | CROSSREF
3. Wu AY, Sur S, Grant JA, Tripple JW. Interleukin-4/interleukin-13 versus interleukin-5: a comparison of molecular targets in biologic therapy for the treatment of severe asthma. Curr Opin Allergy Clin Immunol 2019;19:30-7.
   PUBMED | CROSSREF
4. Johansson MW, Annis DS, Mosher DF. $\alpha_M\beta_2$ integrin-mediated adhesion and motility of IL-5-stimulated eosinophils on periostin. Am J Respir Cell Mol Biol 2013;48:503-10.
   PUBMED | CROSSREF

5. Izuhara K, Nunomura S, Nanri Y, Ogawa M, Ono J, Mitamura Y, et al. Periostin in inflammation and allergy. Cell Mol Life Sci 2017;74:4293-303.
PUBMED | CROSSREF
6. Hur GY, Broide DH. Genes and pathways regulating decline in lung function and airway remodeling in asthma. Allergy Asthma Immunol Res 2019;11:604-21.
PUBMED | CROSSREF
7. An J, Lee JH, Sim JH, Song WJ, Kwon HS, Cho YS, et al. Serum eosinophil-derived neurotoxin better reflect asthma control status than blood eosinophil counts. J Allergy Clin Immunol Pract 2020;8:2681-2688.e1.
PUBMED | CROSSREF
8. Holguin F, Cardet JC, Chung KF, Diver S, Ferreira DS, Fitzpatrick A, et al. Management of severe asthma: a European Respiratory Society/American Thoracic Society guideline. Eur Respir J 2020;55:1900588.
PUBMED | CROSSREF
9. Drick N, Seeliger B, Welte T, Fuge J, Suhling H. Anti-IL-5 therapy in patients with severe eosinophilic asthma - clinical efficacy and possible criteria for treatment response. BMC Pulm Med 2018;18:119.
PUBMED | CROSSREF
10. Dweik RA, Boggs PB, Erzurum SC, Irvin CG, Leigh MW, Lundberg JO, et al. An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FENO) for clinical applications. Am J Respir Crit Care Med 2011;184:602-15.
PUBMED | CROSSREF
11. Pham TH, Damera G, Newbold P, Ranade K. Reductions in eosinophil biomarkers by benralizumab in patients with asthma. Respir Med 2016;111:21-9.
PUBMED | CROSSREF
12. Payne DN, Rogers AV, Adelroth E, Bandi V, Guntupalli KK, Bush A, et al. Early thickening of the reticular basement membrane in children with difficult asthma. Am J Respir Crit Care Med 2003;167:78-82.
PUBMED | CROSSREF
13. Mogensen I, Alving K, Dahlen SE, James A, Forsberg B, Ono J, et al. Fixed airflow obstruction relates to eosinophil activation in asthmatics. Clin Exp Allergy 2019;49:155-62.
PUBMED | CROSSREF
14. Nussbaum JC, Van Dyken SJ, von Moltke J, Cheng LE, Mohapatra A, Molofsky AB, et al. Type 2 innate lymphoid cells control eosinophil homeostasis. Nature 2013;502:245-8.
PUBMED | CROSSREF
15. Ramonell RP, Iftikhar IH. Effect of anti-IL5, anti-IL5R, anti-IL13 therapy on asthma exacerbations: a network meta-analysis. Lung 2020;198:95-103.
PUBMED | CROSSREF
16. Hom S, Pisano M. Reslizumab (Cinqair): an interleukin-5 antagonist for severe asthma of the eosinophilic phenotype. P&T 2017;42:564-8.
PUBMED
17. Castro M, Zangrilli J, Wechsler ME, Bateman ED, Brusselle GG, Bardin P, et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. Lancet Respir Med 2015;3:355-66.
PUBMED | CROSSREF
18. Lee Y, Lee JH, Yang EM, Kwon E, Jung CG, Kim SC, et al. Serum levels of eosinophil-derived neurotoxin: a biomarker for asthma severity in adult asthmatics. Allergy Asthma Immunol Res 2019;11:394-405.
PUBMED | CROSSREF
19. Morris DW, Stucke EM, Martin LJ, Abonia JP, Mukkada VA, Putnam PE, et al. Eosinophil progenitor levels are increased in patients with active pediatric eosinophilic esophagitis. J Allergy Clin Immunol 2016;138:915-918.e5.
PUBMED | CROSSREF
20. Choi Y, Le Pham D, Lee DH, Lee SH, Kim SH, Park HS. Biological function of eosinophil extracellular traps in patients with severe eosinophilic asthma. Exp Mol Med 2018;50:104.
PUBMED | CROSSREF
21. Takayama G, Arima K, Kanaji T, Toda S, Tanaka H, Shoji S, et al. Periostin: a novel component of subepithelial fibrosis of bronchial asthma downstream of IL-4 and IL-13 signals. J Allergy Clin Immunol 2006;118:98-104.
PUBMED | CROSSREF
22. Izuhara K, Conway SJ, Moore BB, Matsumoto H, Holweg CT, Matthews JG, et al. Roles of periostin in respiratory disorders. Am J Respir Crit Care Med 2016;193:949-56.
PUBMED | CROSSREF

23. Yuyama N, Davies DE, Akaiwa M, Matsui K, Hamasaki Y, Suminami Y, et al. Analysis of novel disease-related genes in bronchial asthma. Cytokine 2002;19:287-96.
PUBMED | CROSSREF

24. Ojiaku CA, Chung E, Parikh V, Williams JK, Schwab A, Fuentes AL, et al. Transforming growth factor-beta1 decreases beta2-agonist-induced relaxation in human airway smooth muscle. Am J Respir Cell Mol Biol 2019;61:209-18.
PUBMED | CROSSREF

25. Kim CK. Eosinophil-derived neurotoxin: a novel biomarker for diagnosis and monitoring of asthma. Korean J Pediatr 2013;56:8-12.
PUBMED | CROSSREF

26. Ye Q, Liao A, D'Urzo A. FEV_1 reversibility for asthma diagnosis: a critical evaluation. Expert Rev Respir Med 2018;12:265-7.
PUBMED | CROSSREF

27. Bernstein JA, Virchow JC, Murphy K, Maspero JF, Jacobs J, Adir Y, et al. Effect of fixed-dose subcutaneous reslizumab on asthma exacerbations in patients with severe uncontrolled asthma and corticosteroid sparing in patients with oral corticosteroid-dependent asthma: results from two phase 3, randomised, double-blind, placebo-controlled trials. Lancet Respir Med 2020;8:461-74.
PUBMED | CROSSREF

28. Ibrahim H, O'Sullivan R, Casey D, Murphy J, MacSharry J, Plant BJ, et al. The effectiveness of reslizumab in severe asthma treatment: a real-world experience. Respir Res 2019;20:289.
PUBMED | CROSSREF

29. Zeiger RS, Dawson C, Weiss S. Relationships between duration of asthma and asthma severity among children in the Childhood Asthma Management Program (CAMP). J Allergy Clin Immunol 1999;103:376-87.
PUBMED | CROSSREF

30. Chetta A, Foresi A, Del Donno M, Bertorelli G, Pesci A, Olivieri D. Airways remodeling is a distinctive feature of asthma and is related to severity of disease. Chest 1997;111:852-7.
PUBMED | CROSSREF

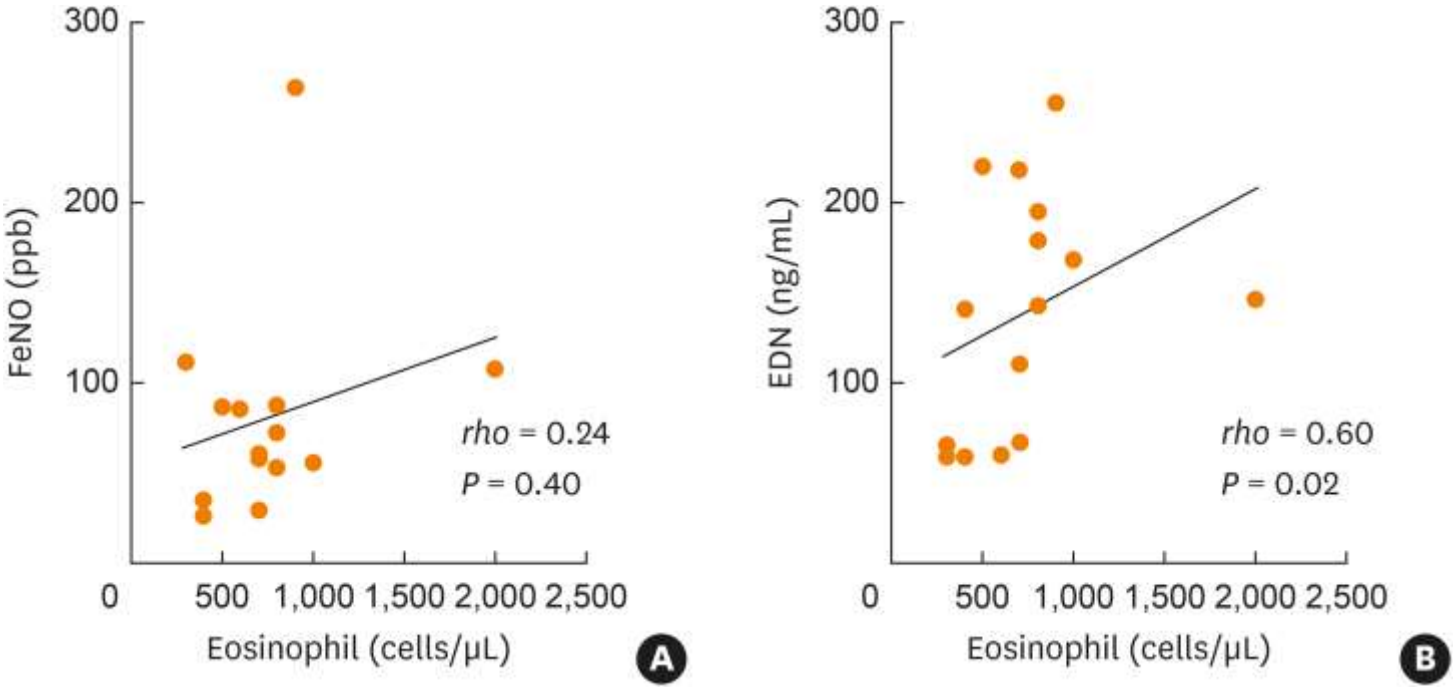
31. Máspero J. Reslizumab in the treatment of inadequately controlled asthma in adults and adolescents with elevated blood eosinophils: clinical trial evidence and future prospects. Ther Adv Respir Dis 2017;11:311-25.
PUBMED | CROSSREF

32. To M, Tsuzuki R, Katsube O, Yamawaki S, Soeda S, Kono Y, et al. Persistent asthma from childhood to adulthood presents a distinct phenotype of adult asthma. J Allergy Clin Immunol Pract 2020;8:1921-1927.e2.
PUBMED | CROSSREF

33. Silkoff PE, Lent AM, Busacker AA, Katial RK, Balzar S, Strand M, et al. Exhaled nitric oxide identifies the persistent eosinophilic phenotype in severe refractory asthma. J Allergy Clin Immunol 2005;116:1249-55.
PUBMED | CROSSREF

34. Beck-Ripp J, Griese M, Arenz S, Köring C, Pasqualoni B, Bufler P. Changes of exhaled nitric oxide during steroid treatment of childhood asthma. Eur Respir J 2002;19:1015-9.
PUBMED | CROSSREF

35. Taylor DR, Pijnenburg MW, Smith AD, De Jongste JC. Exhaled nitric oxide measurements: clinical application and interpretation. Thorax 2006;61:817-27.
PUBMED | CROSSREF



Supplementary Fig. S1. Correlations between total eosinophil counts and (A) FeNO/(B) EDN values at baseline. FeNO, fractional exhaled nitric oxide; EDN, eosinophil-derived neurotoxin.

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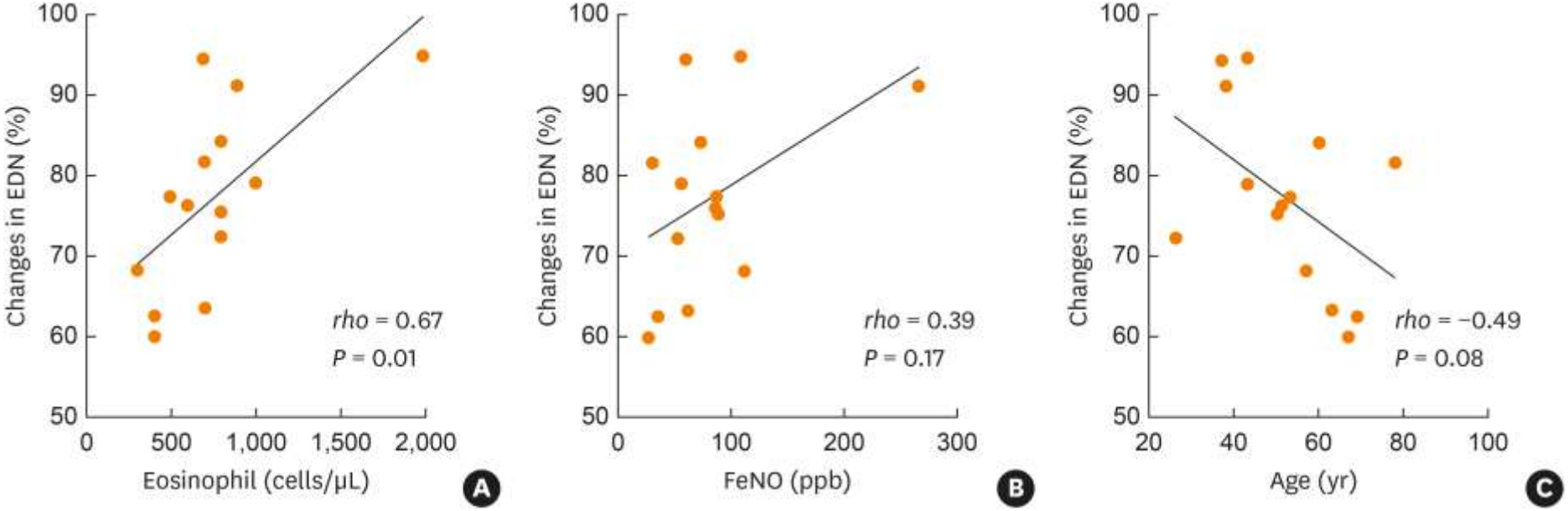
https://doi.org/10.4168/aair.2021.13.2.330



Supplementary Fig. S2. Correlations between changes in EDN (%) and (A) TECs/(B) FeNO/(C) age.

EDN, eosinophil-derived neurotoxin; TEC, total eosinophil count; FeNO, fractional exhaled nitric oxide.

Allergy Asthma Immunol Res. 2021 Mar;13(2):330-338.
https://doi.org/10.4168/aair.2021.13.2.330