

Original Article



Siglec-8 as a Biomarker for Predicting Anti-IL-5 Response in Severe Asthma

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OPEN ACCESS

Received: Apr 5, 2025

Revised: Jul 11, 2025

Accepted: Jul 17, 2025

Published online: Nov 11, 2025

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ABSTRACT

Purpose: Biologic therapies have revolutionized the management of severe asthma (SA), yet the variability in patient responses necessitates identification/verification of predictive biomarkers. Siglec-8, a sialic acid-binding immunoglobulin-like lectin 8 selectively that is expressed on eosinophils, could serve as a biomarker for predicting responsiveness to biologics in patients with SA. It is necessary to evaluate the predictive value of baseline serum Siglec-8 levels compared to other parameters, including blood eosinophil counts, in determining clinical responses to anti-interleukin 5 (IL-5) therapies in patients with SA.

Methods: This study included 68 patients with SA from the Precision Medicine Intervention in Severe Asthma study, who had initiated anti-IL-5 therapies and whose baseline serum Siglec-8 levels were measured. Clinical outcomes were assessed at 6 and 12 months following treatment. Excellent responders were defined as patients with zero exacerbations during follow-up. Multivariable logistic regression and receiver operating characteristic curve

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Trial Registration

ClinicalTrials.gov Identifier: [NCT05164939](https://clinicaltrials.gov/ct2/show/study/NCT05164939)

Disclosure

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

analyses were performed to compare the predictive performance of serum Siglec-8 levels versus that of other parameters.

Results: Data from 29 patients treated with mepolizumab and 39 patients treated with reslizumab were analyzed. Baseline serum Siglec-8 levels showed a trend toward better diagnostic performance compared to blood eosinophil counts for predicting 6- and 12-month clinical responses (area under the curve, 0.931 vs. 0.836; $P = 0.08$ for 6-month responders; and 0.811 vs. 0.628, $P = 0.05$ for 12-month excellent responders). Additionally, the ratio of serum Siglec-8 levels to blood eosinophil counts significantly increased after 6 months of anti-IL-5 therapy ($P < 0.001$).

Conclusions: Baseline serum Siglec-8 levels showed a trend toward better predictive performance than other parameters for predicting 6- and 12-month responses to anti-IL-5 therapies in patients with SA. These findings suggest that Siglec-8 may have the potential as a biomarker for guiding treatment decisions, although further validation in larger, prospective studies is warranted.

Trial Registration: ClinicalTrials.gov Identifier: [NCT05164939](https://clinicaltrials.gov/ct2/show/study/NCT05164939)

Keywords: Asthma; biological therapy; IL-5; receptors, immunologic; eosinophils; biomarkers; treatment

INTRODUCTION

Biologic therapies have revolutionized the treatment of severe asthma (SA) by targeting the underlying mechanisms of airway inflammation and hyperresponsiveness.^{1,2} Unlike conventional treatments, which primarily manage symptoms through anti-inflammatory corticosteroids (CSs) and bronchodilators, biological therapies such as anti-immunoglobulin E (IgE), anti-interleukin (IL)-5, and anti-IL-4 α target specific molecules or pathways involved in the pathophysiology of SA. This shift not only has improved symptom control and reduced asthma exacerbations (AEs) in patients with SA but also decreased dependency on oral CSs (OCSs), enhancing the overall quality of life for patients and reducing the long-term side effects associated with the use of high-dose CS.

Previous studies have shown that some patients who do not respond to biologic therapies exhibit clinical phenotypes and endotypes similar to those of responders, necessitating a biomarker to better predict responses to biologic therapies. Eosinophils have been utilized as biomarkers to predict clinical responses to biologics in SA owing to their roles in the underlying inflammatory processes.³ However, relying solely on blood or sputum eosinophils to predict eosinophilic or type 2 airway inflammation in SA can be problematic owing to their variability and the influence of external factors.⁴⁻⁶ Eosinophil levels can be suppressed by systemic CS use and affected by other variables such as acute respiratory infections or sampling techniques.⁵ While eosinophils and fractional exhaled nitric oxide (FeNO) are effective indicators of type 2 airway inflammation, they do not always capture the full complexity of the disease or accurately predict the severity of inflammation in all patients with SA. Variations in individual immune responses, genetic factors, and the influences of environmental triggers mean that some patients may have type 2 airway inflammation that is not adequately detected by these markers. Discovering new biomarkers could allow for the identification of additional inflammatory mediators or genetic markers that provide a more comprehensive understanding of type 2 airway inflammation.

This would enable more precise patient stratification and facilitate targeted therapies tailored to the specific characteristics of each individual's disease, thus improving therapeutic efficacy and patient outcomes.

Sialic acid-binding immunoglobulin-like lectin 8 (Siglec-8) is an inhibitory receptor selectively expressed on blood and tissue eosinophils, mast cells, and basophils, with low expression on basophils.^{7,8} Siglec-8 exhibits anti-eosinophil activity, as its crosslinking with a monoclonal antibody on blood eosinophils induces apoptosis via a caspase-dependent pathway.^{7,9}

The discovery of the biological functions of Siglec-8 led to the development of a humanized monoclonal antibody targeting Siglec-8 (AK002, also known as liletrinemab) for treating eosinophilic diseases. This antibody effectively depletes blood eosinophils and has exhibited clinical efficacy in eosinophilic and mast cell-driven diseases such as chronic urticaria, eosinophilic gastrointestinal disorders, and severe allergic conjunctivitis.^{10,12} Previous studies have evaluated the clinical utility of Siglec-8 as a therapeutic target for the treatment of eosinophil and mast cell-driven diseases; however, no research has yet explored its usefulness as a biomarker for predicting responses to biological therapies in patients with SA. In this study, we aimed to demonstrate the predictive value of serum Siglec-8 levels as a biomarker for predicting responses to anti-IL-5 therapies in patients with SA.

MATERIALS AND METHODS

Study subjects

We initiated the Precision Medicine Intervention in Severe Asthma (PRISM) study, a nationwide multicenter prospective observational investigation, from May 2020 to December 2022. This study involved 23 hospitals and included patients aged 18–80 years with SA who received either biologics or conventional treatment. This study protocols, including inclusion and exclusion criteria, have been previously described in detail.¹³ In brief, the study enrolled adult patients with uncontrolled SA or those who achieved only suboptimal control despite using medications corresponding to steps 4–5 of the Global Initiative for Asthma guidelines.¹⁴ Exclusion criteria included recent use of biologic therapies in the previous 3 months or significant use of OCS for a prolonged period (> 90 mg prednisolone in total) or prednisolone use owing to recent exacerbations in the 4 weeks before enrollment. Patients with blood eosinophil count ≥ 150 cells/mL received anti-IL-5 therapies as add-on treatments.¹⁵ The other patients continued conventional treatments, with their clinical outcomes monitored for at least 6 months. In this study, we included a subgroup of patients from the PRISM cohort (between May 2020 and October 2022) with SA who underwent anti-IL-5 therapies (mepolizumab and reslizumab) and had their serum Siglec-8 levels measured at baseline. The study protocol is registered at ClinicalTrials.gov (NCT05164939). The Institutional Review Board (IRB) of all participating centers approved the study, and all participants provided written informed consent (IRB No. 2019-1676).

Measurement of serum Siglec-8 levels

Serum Siglec-8 levels were measured by using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (Cusabio®, Houston, TX, USA). Serum samples were processed according to the manufacturer's instructions, applied to ELISA plates, and incubated with a primary antibody specific to Siglec-8. After binding, a secondary antibody conjugated with an enzyme was added to amplify the signal. The reaction was visualized using a substrate, and the resulting color change was measured at 450 nm using a plate

reader. The concentration of serum Siglec-8 was determined by comparing the absorbance values to a standard curve. The range of detection of serum Siglec-8 was 0.156–10.0 ng/mL.⁸

Definition of treatment response

Our analysis included only patients who completed a 6-month follow-up to evaluate clinical responses to anti-IL-5 therapies. After 24 weeks of treatment, patients were categorized as responders or non-responders based on their treatment responses. Response was defined as a 50% reduction in the annualized exacerbation rate or a 50% reduction in the daily maintenance OCS dose. Patients who required a 5-mg maintenance OCS dose for adrenal insufficiency were not classified as requiring maintenance OCS for SA. A subset analysis focused on the following categories of responders: super-responders, defined as patients who no longer required maintenance OCS therapy and were free of exacerbations; excellent responders, who showed zero exacerbations during the 6-month follow-up period; and responders who achieved a 50% reduction in the annualized exacerbation rate. Demographic information and clinical data of all included patients were retrieved from electronic medical records.

Statistical analyses

To assess the association between baseline serum Siglec-8 levels and clinical features of SA at baseline and 6 months, we categorized continuous variables for each clinical feature into 2 or 3 groups and compared serum Siglec-8 levels, either at baseline or follow-up. The *t*-test was used for comparisons between 2 groups, and analysis of variance was used for comparisons among 3 groups. Spearman correlation analysis was employed to evaluate the relationship between baseline serum Siglec-8 levels and clinical outcomes of SA, including the number of exacerbations, Asthma Control Test score, lung function, and laboratory findings.

To assess the added diagnostic value of individual and composite biomarkers in predicting clinical responses to anti-IL-5 therapies, we used a multivariable logistic regression model adjusted for age, sex, type of biologics, body mass index, and OCS use. This model calculated the area under the curve (AUC) for the main exposure at 6 and 12 months after anti-IL-5 therapies to identify the most accurate predictor of treatment outcomes. Log transformations were used to create a normal distribution for variables with skewed distributions, which were then standardized to compare main exposure values across different ranges.

Changes in serum Siglec-8 levels from baseline to the 6-month follow-up and serum Siglec-8 level/blood eosinophil count ratios were compared using paired *t*-tests within each subgroup of anti-IL-5 therapies. All statistical analyses were performed using SAS (version 9.4; SAS Institute Inc., Cary, NC, USA). A *P* value < 0.05 was considered statistically significant.

RESULTS

Baseline characteristics

A total of 68 patients with SA were included. The overall mean age was 51.54 ± 11.26 years, 49.34 ± 11.40 years in those treated with mepolizumab, and 53.18 ± 11.02 years in those treated with reslizumab (*P* = 0.167). The mean asthma duration was 10.00 ± 7.74 months, with 10.30 ± 8.77 months in the mepolizumab group and 9.79 ± 7.04 months in the reslizumab group (*P* = 0.797). The proportion of male patients was 41.2% overall,

with 31.0% in the mepolizumab group and 48.7% in the reslizumab group ($P = 0.143$). In the previous 12 months, 61.8% of all patients had experienced at least one AE, with 65.5% in the mepolizumab group and 59.0% in the reslizumab group ($P = 0.583$); the mean number of AEs was 3.66 ± 4.79 overall, 4.10 ± 5.51 in the mepolizumab group, and 3.33 ± 4.21 in the reslizumab group ($P = 0.516$). The mean blood eosinophil count was 834.00 ± 606.62 cells/ μ L for all patients, with 952.62 ± 647.22 cells/ μ L in the mepolizumab group and 745.80 ± 566.95 cells/ μ L in the reslizumab group ($P = 0.333$). The mean FeNO level was 69.27 ± 52.82 ppb, with 78.24 ± 57.76 ppb in the mepolizumab group and 62.42 ± 48.38 ppb in the reslizumab group ($P = 0.360$). Induced sputum eosinophil percentages, available for 49 patients, showed a mean of $23.08 \pm 28.33\%$, with $29.09 \pm 27.59\%$ in the mepolizumab group and $18.19 \pm 28.49\%$ in the reslizumab group ($P = 0.101$). The mean predicted FEV1% at baseline was $63.75 \pm 18.20\%$ overall, $58.97 \pm 15.07\%$ in the mepolizumab group, and $67.39 \pm 19.68\%$ in the reslizumab group ($P = 0.059$). There were no statistically significant differences in most clinical or laboratory characteristics between patients treated with mepolizumab, and those treated with reslizumab (all $P > 0.05$), except for smoking history ($P = 0.038$), with a higher proportion of never-smokers in the mepolizumab group. **Table 1** summarizes the baseline characteristics of study patients treated with anti-IL-5 therapies.

Table 1. Baseline characteristics of study subjects (n = 68)

Variables	All (n = 68)	Mepolizumab (n = 29)	Reslizumab (n = 39)	P value*
Age (yr)	51.54 $\pm$ 11.26	49.34 $\pm$ 11.40	53.18 $\pm$ 11.02	0.167
Age of symptom onset (yr)	40.58 $\pm$ 13.45	37.59 $\pm$ 13.04	42.71 $\pm$ 13.50	0.132
Age of diagnosis with asthma (yr)	41.28 $\pm$ 13.43	38.19 $\pm$ 12.91	43.47 $\pm$ 13.52	0.118
Duration of asthma (yr)	10.00 $\pm$ 7.74	10.30 $\pm$ 8.77	9.79 $\pm$ 7.04	0.797
Male	28 (41.2)	9 (31.0)	19 (48.7)	0.143
BMI (kg/m ²)	24.87 $\pm$ 3.58	25.26 $\pm$ 4.30	24.59 $\pm$ 2.97	0.476
Ever experienced AE (in the previous 12 mon)	42 (61.8)	19 (65.5)	23 (59.0)	0.583
Number of AE (in the previous 12 mon)	3.66 $\pm$ 4.79	4.10 $\pm$ 5.51	3.33 $\pm$ 4.21	0.516
OCS maintenance	18 (26.5)	7 (24.1)	11 (28.2)	0.707
Smoking history				0.038
Never-smokers	39 (57.4)	21 (72.4)	18 (46.2)	
Ex-smokers	24 (35.3)	8 (27.6)	16 (41.0)	
Current smokers	5 (7.4)	0 (0.0)	5 (12.8)	
History of asthma exacerbation (in the previous 12 mon)				
Unscheduled visits to the outpatient clinic	24 (35.3)	10 (34.5)	14 (35.9)	0.904
Unscheduled visits to the emergency department	12 (17.7)	4 (13.8)	8 (20.5)	0.472
Hospitalizations owing to asthma exacerbation	11 (16.2)	4 (13.8)	7 (18.0)	0.645
ICU admissions owing to asthma exacerbation	0 (0.0)	0 (0.0)	0 (0.0)	N/A
Laboratory parameters				
White blood cells ($\times 10^3$ / μ L)	8.04 $\pm$ 2.07	8.48 $\pm$ 2.33	7.71 $\pm$ 1.81	0.114
Eosinophils (cells/ μ L)	834.00 $\pm$ 606.62	952.62 $\pm$ 647.22	745.80 $\pm$ 566.95	0.333
Eosinophils (%)	10.66 $\pm$ 6.98	11.86 $\pm$ 7.70	9.76 $\pm$ 6.34	0.290
Neutrophils (%)	53.42 $\pm$ 11.72	51.11 $\pm$ 12.37	55.13 $\pm$ 11.06	0.363
Total IgE (kU/L) (n = 52)	404.08 $\pm$ 491.39	356.37 $\pm$ 305.13	431.55 $\pm$ 574.75	0.093
FeNO (ppb)	69.27 $\pm$ 52.82	78.24 $\pm$ 57.76	62.42 $\pm$ 48.38	0.360
Sputum eosinophils (%) (n = 49)	23.08 $\pm$ 28.33	29.09 $\pm$ 27.59	18.19 $\pm$ 28.49	0.101
Sputum neutrophils (%) (n = 45)	54.73 $\pm$ 33.78	50.67 $\pm$ 30.50	58.29 $\pm$ 36.68	0.686
Pre-BD FEV1 (%)	63.75 $\pm$ 18.20	58.97 $\pm$ 15.07	67.39 $\pm$ 19.68	0.059
Pre-BD FEV1/FVC	0.66 $\pm$ 0.12	0.64 $\pm$ 0.13	0.67 $\pm$ 0.11	0.332
Post-BD FEV1 (%)	67.80 $\pm$ 19.22	63.58 $\pm$ 16.79	70.94 $\pm$ 20.51	0.140
Post-BD FEV1/FVC	0.67 $\pm$ 0.12	0.65 $\pm$ 0.13	0.69 $\pm$ 0.12	0.577
ACT scores	15.04 $\pm$ 5.41	15.48 $\pm$ 5.91	14.72 $\pm$ 5.06	0.763

Values are presented as mean $\pm$ standard deviation or number (%). BMI, body mass index; AE, asthma exacerbation; OCS, oral corticosteroid; ICU, intensive care unit; N/A, not available; IgE, immunoglobulin E; FeNO, fractional exhaled nitric oxide; BD, bronchodilator; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; ACT, asthma control test.

*Data are numbers with percentages in parentheses.

Association between serum Siglec-8 levels and demographic and clinical characteristics

Baseline and 6-month serum Siglec-8 levels were analyzed across various demographic and clinical characteristics (**Table 2**). At baseline, patients with symptom onset at age ≥ 40 years had significantly higher serum Siglec-8 levels compared to those with onset at < 40 years (1.18 ± 0.55 ng/mL vs. 0.90 ± 0.47 ng/mL, $P = 0.032$). Additionally, patients receiving maintenance OCS tended to have higher baseline serum Siglec-8 levels compared to those not receiving OCS (1.10 ± 0.52 ng/mL vs. 0.85 ± 0.52 ng/mL, $P = 0.081$). At the 6-month follow-up, no significant differences were observed in serum Siglec-8 levels across any demographic or clinical subgroups. In addition, we performed Spearman correlation analysis to evaluate the relationship between baseline serum Siglec-8 levels and various clinical parameters at baseline. No significant correlations were observed between Siglec-8 levels and asthma control status, lung function parameters, or type 2 inflammation markers such as blood eosinophils, FeNO, and total IgE (all $P > 0.05$). Detailed correlation coefficients and P values are provided in **Supplementary Table S1**.

Table 2. Association between serum Siglec-8 levels, and demographic and clinical characteristics

Variables	No. (%)	Siglec-8 at baseline	<i>P</i> value	Siglec-8 at 6 mon	<i>P</i> value
Age (yr)			0.687		0.848
≥ 60	13 (19.1)	0.98 ± 0.41		1.00 ± 0.34	
< 60	55 (80.9)	1.05 ± 0.55		1.03 ± 0.54	
Sex			0.389		0.462
Male	28 (41.2)	0.97 ± 0.44		0.97 ± 0.42	
Female	40 (58.8)	1.08 ± 0.58		1.06 ± 0.56	
BMI (kg/m ²)			0.664		0.744
≥ 25	32 (47.1)	1.01 ± 0.47		1.00 ± 0.42	
< 25	36 (58.8)	1.06 ± 0.58		1.04 ± 0.58	
Smoking status			0.514*		0.231*
Never smokers	39 (57.4)	1.09 ± 0.57		1.11 ± 0.58	
Former smokers	24 (35.3)	0.94 ± 0.42		0.89 ± 0.36	
Current smokers	5 (7.4)	1.11 ± 0.64		0.97 ± 0.41	
Age of symptom onset (yr)			0.032		0.266
≥ 40	33 (48.5)	1.18 ± 0.55		1.09 ± 0.44	
< 40	35 (51.5)	0.90 ± 0.47		0.96 ± 0.56	
OCS maintenance			0.081		0.065
Yes	50 (73.5)	1.10 ± 0.52		1.08 ± 0.55	
No	18 (26.5)	0.85 ± 0.52		0.87 ± 0.34	
Asthma control status			0.083*		0.205*
Controlled	9 (13.2)	1.09 ± 0.95		1.09 ± 0.95	
Partly controlled	25 (36.8)	0.88 ± 0.40		0.88 ± 0.40	
Uncontrolled	34 (50.0)	1.11 ± 0.40		1.11 ± 0.40	
Pre-BD FEV1			0.317		0.421
$\geq 60\%$	40 (58.8)	0.98 ± 0.45		0.98 ± 0.57	
$< 60\%$	28 (41.2)	1.12 ± 0.62		1.08 ± 0.40	
Post-BD FEV1			0.171		0.134
$\geq 60\%$	42 (61.8)	0.96 ± 0.44		0.95 ± 0.56	
$< 60\%$	26 (38.2)	1.16 ± 0.63		1.14 ± 0.40	
Pre-BD FEV1/FVC			0.184		0.860
≥ 0.7	26 (38.2)	0.93 ± 0.47		1.01 ± 0.60	
< 0.7	42 (61.8)	1.10 ± 0.55		1.03 ± 0.45	
Post-BD FEV1/FVC			0.154		0.367
≥ 0.7	28 (41.2)	0.93 ± 0.45		0.96 ± 0.60	
< 0.7	40 (58.8)	1.11 ± 0.57		1.07 ± 0.44	

Data are represented as mean $\pm$ standard deviation.

Unless otherwise indicated, all P values were calculated by the t -test for 2 groups of variables.

Siglec-8, sialic acid-binding immunoglobulin-like lectin 8; BMI, body mass index; OCS, oral corticosteroid; BD, bronchodilator; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity.

* P values were calculated by the analysis of variance test.

Predictability of serum Siglec-8 levels for treatment response to anti-IL-5 therapies

Baseline serum Siglec-8 levels showed higher diagnostic value for predicting responders, excellent responders, and exacerbation during 6 months of treatment than all the conventional parameters, including baseline blood eosinophil counts. The AUC for predicting responders was 0.931 for Siglec-8 levels compared to 0.836 for blood eosinophil counts ($P = 0.082$). For predicting excellent responders, the AUC was 0.712 for Siglec-8 levels compared to 0.662 for blood eosinophil counts ($P = 0.413$), and for predicting exacerbations, the AUC was 0.819 for Siglec-8 levels compared to 0.668 for blood eosinophil counts ($P = 0.210$). The improvement in diagnostic performance showed a trend toward significance only for predicting 6-month responders ($P = 0.082$; **Table 3**).

For predicting 12-month clinical responses, baseline serum Siglec-8 levels showed higher diagnostic performance for identifying excellent responders, showing a trend toward significance when compared to blood eosinophil counts (AUC for excellent responders, 0.811 vs. 0.628; $P = 0.047$). For responders, the change in the ratio of serum Siglec-8 levels to blood eosinophil counts from baseline to 6 months (Δ Siglec-8/ Δ Blood eosinophil at 6 months) showed the highest AUC among variables (AUC, 0.831; $P = 0.359$), followed by baseline serum Siglec-8 levels (AUC, 0.826; $P = 0.551$) and baseline FeNO levels (AUC, 0.823; $P = 0.518$). The diagnostic performance of baseline blood eosinophil counts for predicting responders yielded an AUC of 0.802. The ratio of serum Siglec-8 levels to blood eosinophil counts

Table 3. Predictive value of baseline biomarkers for clinical responses to anti-interleukin 5 therapies at the 6-month follow-up

Variables	Responders		Super-responders		Excellent responders		Exacerbation	
	AUC	P value	AUC	P value	AUC	P value	AUC	P value
Baseline blood eosinophils (/ μ L)	0.836	Ref	0.751	Ref	0.662	Ref	0.668	Ref
Baseline serum Siglec-8 (ng/mL)	0.931	0.082	0.778	0.510	0.712	0.413	0.819	0.210
Baseline serum Siglec-8/blood eosinophils	0.866	0.292	0.761	0.64	0.669	0.859	0.774	0.155
Baseline FeNO	0.862	0.422	0.781	0.438	0.692	0.592	0.655	0.849

Logistic regression was adjusted by age, sex, biologics, body mass index, and mOCS. Not all variables listed in the table achieved statistical significance. Treatment response definitions: responder, $\geq 50\%$ reduction in annualized exacerbation rate or daily mOCS dose (63/68, 92.7%); super responders, no exacerbations and no mOCS use (46/68, 67.7%); excellent responders, zero exacerbations during 6 months (50/68, 73.5%); exacerbation, $\geq 50\%$ reduction (60/68, 88.2%).

AUC, area under the curve; Siglec-8, sialic acid-binding immunoglobulin-like lectin 8; FeNO, fractional exhaled nitric oxide; mOCS, maintenance oral corticosteroid.

Table 4. Predictive value of baseline biomarkers for clinical responses to anti-interleukin 5 therapies at the 12-month follow-up

Variables	Responders		Super-responders		Excellent responders		Exacerbation	
	AUC	P value	AUC	P value	AUC	P value	AUC	P value
Baseline blood eosinophils (/ μ L)	0.802	Ref	0.697	Ref	0.628	Ref	0.645	Ref
Baseline serum Siglec-8 (ng/mL)	0.826	0.551	0.752	0.491	0.811	0.047	0.686	0.519
Serum Siglec-8 at 6 mon/baseline serum Siglec-8	0.810	0.736	0.694	0.971	0.651	0.749	0.638	0.883
Baseline serum Siglec-8/baseline blood eosinophils	0.810	0.803	0.727	0.442	0.704	0.215	0.665	0.512
Serum Siglec-8/blood eosinophils at 6 mon	0.807	0.801	0.769	0.386	0.747	0.205	0.675	0.566
Δ serum Siglec-8/ Δ blood eosinophils at 6 mon	0.831	0.359	0.690	0.902	0.643	0.735	0.651	0.858
Baseline FeNO	0.823	0.518	0.705	0.861	0.643	0.832	0.693	0.413

Logistic regression was adjusted by age, sex, biologics, body mass index, and regular oral corticosteroid. Not all variables listed in the table achieved statistical significance.

Treatment response definitions: responder: $\geq 50\%$ reduction in annualized exacerbation rate or daily mOCS dose (50/52, 96.2%); super responders: no exacerbations and no mOCS use (30/52, 57.7%); excellent responders: zero exacerbations during 6 months (31/52, 59.6%); exacerbation: $\geq 50\%$ reduction (49/52, 94.2%).

AUC, area under the curve; Siglec-8, sialic acid-binding immunoglobulin-like lectin 8; FeNO, fractional exhaled nitric oxide; mOCS, maintenance oral corticosteroid.

at 6 months demonstrated the highest diagnostic performance for predicting 12-month treatment super-responders (AUC, 0.769; $P = 0.386$), followed by baseline Siglec-8 (AUC, 0.752; $P = 0.491$; **Table 4**).

Changes in serum Siglec-8 levels after anti-IL-5 therapies

There were no significant changes in serum Siglec-8 levels from baseline to the 6-month follow-up after anti-IL-5 therapies (1.01 ± 0.52 ng/mL and 1.02 ± 0.51 ng/mL, respectively; $P = 0.810$; **Fig. A**) across all patients, as well as when stratified by the type of therapy: mepolizumab (1.07 ± 0.54 ng/mL and 1.12 ± 0.46 ng/mL, respectively; $P = 0.592$) and reslizumab (1.01 ± 0.53 and 0.95 ± 0.53 , respectively; $P = 0.542$; **Fig. B**). In contrast, there was a significant increase in the serum Siglec-8/blood eosinophil ratios from baseline to the 6-month follow-up across all patients treated with anti-IL-5 therapies (0.0026 ± 0.005 and 0.0259 ± 0.0226 , respectively; $P < 0.001$; **Fig. C**), as well as when stratified by the type of therapy: mepolizumab (0.0019 ± 0.0025 and 0.0178 ± 0.0178 , respectively; $P < 0.001$) and reslizumab (0.0035 ± 0.0070 and 0.0310 ± 0.0239 , respectively; $P < 0.001$; **Fig. D**).

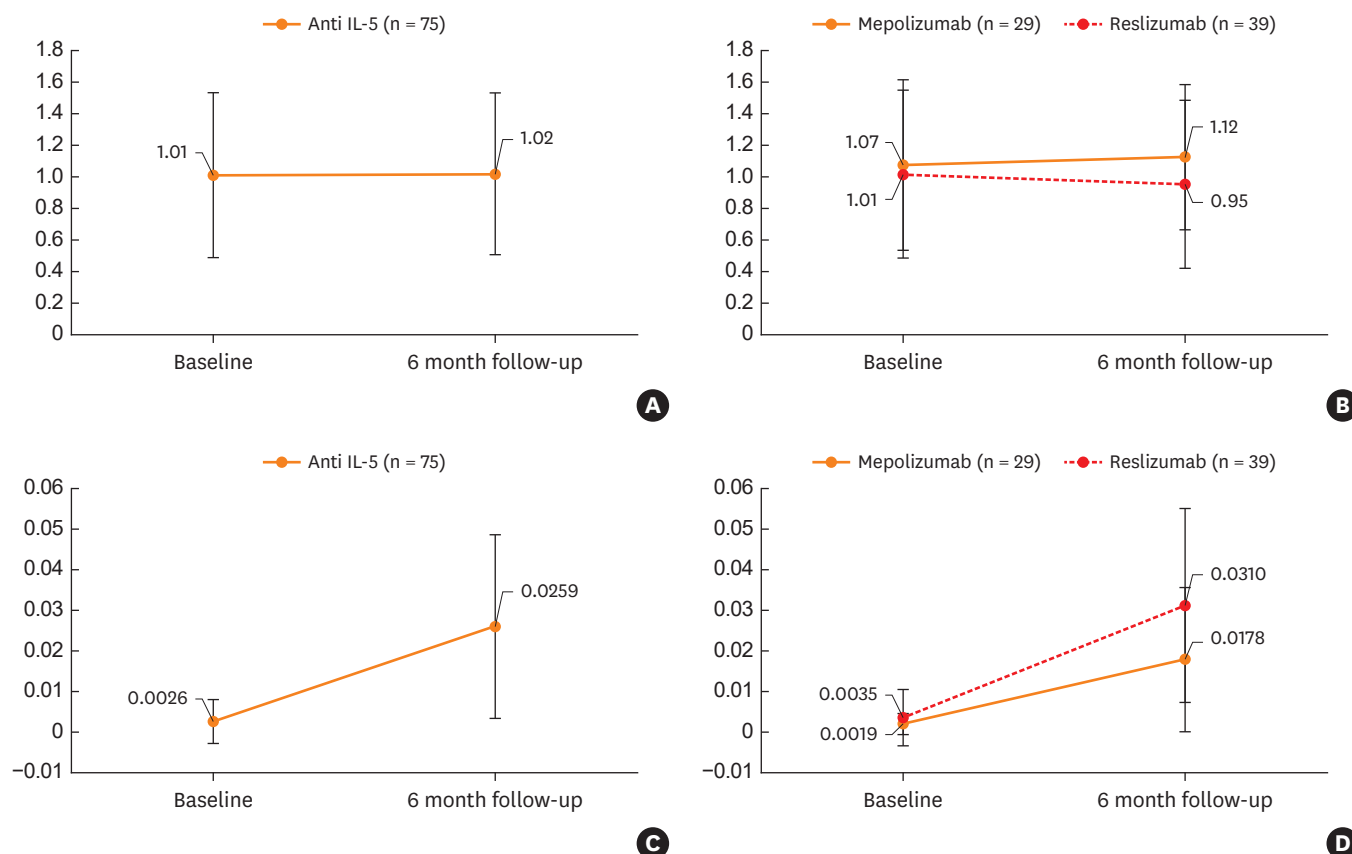


Figure. Changes in serum Siglec-8 levels and serum Siglec-8/blood eosinophil ratios from baseline to 6-month follow-up after anti-IL-5 therapies. Changes in serum Siglec-8 levels (A) across all patients treated with anti-IL-5 therapies and (B) stratified by anti-IL-5 therapies (mepolizumab and reslizumab). Changes in serum Siglec-8/blood eosinophil ratios (C) across all patients treated with anti-IL-5 therapies and (D) stratified by anti-IL-5 therapies (mepolizumab and reslizumab).

The increase in the serum Siglec-8/blood eosinophil ratio may largely reflect blood eosinophil suppression rather than a dynamic change in serum Siglec-8 levels. Siglec-8, sialic acid-binding immunoglobulin-like lectin 8; IL-5, interleukin 5.

DISCUSSION

In this study, we evaluated serum Siglec-8 levels as a potential biomarker for predicting treatment responses to anti-IL-5 therapies in patients with SA. Baseline Siglec-8 levels demonstrated the highest diagnostic performance compared to other conventional parameters, including baseline blood eosinophil counts, and showed a trend toward significance compared to blood eosinophil counts in predicting 6-month responders and 12-month excellent responders. In addition, the ratio of serum Siglec-8 levels to blood eosinophil counts significantly increased after 6 months of anti-IL-5 therapies. These findings indicate that baseline serum Siglec-8 levels show promising diagnostic performance for predicting treatment responses to anti-IL-5 therapies in patients with SA, suggesting that serum Siglec-8 levels could serve as a valuable biomarker for improving the prediction of biologic treatment responses in SA.

Previous studies have established blood eosinophil counts as a reliable predictor of clinical response to biological therapies targeting eosinophilic inflammation. For instance, higher baseline blood eosinophil counts were associated with better clinical outcomes in patients treated with anti-IL-5 therapies such as mepolizumab and reslizumab.¹⁶ Consistent with these findings, our study showed that baseline blood eosinophil counts strongly predicted responders at both 6-month and 12-month follow-ups. However, baseline blood eosinophil counts demonstrated lower performance in predicting other clinical outcomes, such as super-responders, excellent responders, and exacerbations. In contrast, we found that baseline serum Siglec-8 levels showed a trend toward better predictive performance (AUC, 0.931), compared to blood eosinophil counts, suggesting potential utility as a biomarker, although statistical significance was not reached. In addition, previous research has suggested that anti-Siglec-8 could reduce eosinophilic inflammation, a key pathophysiological component of SA.¹⁷ Our study expands on previous findings by evaluating the predictive value of serum Siglec-8 levels for treatment response to anti-IL-5 therapies. While blood eosinophil counts are important, they do not reflect the activation state of individual eosinophils. However, serum Siglec-8 levels may provide more specific information on eosinophil activation, potentially offering improved prediction of treatment response to anti-IL-5 therapies in which eosinophilic activation is considered important. In addition, by comparing serum Siglec-8 levels with other biomarkers, we observed that the ratio of serum Siglec-8 levels to blood eosinophil counts at baseline showed relatively high AUC values, suggesting potential utility as a composite biomarker. Composite biomarkers are generally designed to enhance predictive accuracy by integrating distinct biological signals—for example, combining markers of eosinophil burden with those reflecting eosinophil activation or regulation.¹⁸ In this context, the ratio may capture both the quantitative and functional aspects of type 2 inflammation. However, the improvement in predictive accuracy was not statistically significant compared to baseline serum Siglec-8 levels or FeNO, and the clinical relevance of this ratio remains uncertain.

Our study also evaluated the predictive value of serum Siglec-8 levels at the 12-month follow-up. Baseline serum Siglec-8 levels demonstrated significant predictive values for identifying excellent responders, with an AUC of 0.811, suggesting that higher baseline serum Siglec-8 levels may be associated with better long-term outcomes. In contrast, changes in serum Siglec-8 levels from baseline to the 6-month follow-up showed lower predictive performance compared to baseline levels. This reduced predictability could be attributed to the mechanism of anti-IL-5 therapies, which significantly deplete eosinophils and suppress

eosinophilic inflammation. Consequently, serum Siglec-8 levels after anti-IL-5 therapies may be less predictive than baseline levels. However, further research is warranted to evaluate the dynamic changes in serum Siglec-8 levels over time and their clinical implications in the management of SA. In our study, patients with later symptom onset (≥ 40 years) showed significantly higher baseline serum Siglec-8 levels than those with earlier onset. Although the underlying mechanism is not fully understood, this finding may reflect a distinct inflammatory phenotype in late-onset asthma, potentially involving different patterns of eosinophil activation or regulation. Further studies are needed to explore the clinical implications of this association.

One important consideration is that Siglec-8 is primarily a membrane-bound protein on eosinophils. However, in this study, we measured soluble Siglec-8 levels in serum. The presence of a soluble form of Siglec-8 in serum may result from several mechanisms, including proteolytic cleavage from the cell surface or secretion by activated cells. Previous research has reported that the soluble form might reflect the activation status and turnover of eosinophils and mast cells in the context of inflammation.¹⁹ However, further studies are needed to understand the precise roles and mechanisms of membrane-bound Siglec-8 and soluble Siglec-8. Despite its membrane-bound origin, measuring serum Siglec-8 levels could provide valuable insights into the dynamics of eosinophil activity. A previous study showed that serum Siglec-8 levels were downregulated by IL-5 and restored by mepolizumab *in vitro*, and suggested that serum Siglec-8 might act as an inhibitory receptor. This receptor could block Siglec-8 ligands, thus inhibiting the function of membrane-bound Siglec-8.²⁰ In our study, serum Siglec-8 levels did not show statistically significant differences before and after anti-IL-5 therapies. However, the ratio of serum Siglec-8 levels to blood eosinophil counts significantly increased after 6 months of anti-IL-5 therapies. However, this increase was primarily driven by the expected reduction in blood eosinophil counts rather than a change in serum Siglec-8 itself. Therefore, the change in the ratio may not directly reflect the diagnostic utility of serum Siglec-8. Rather, its potential value appears to lie in its baseline level as a predictor of treatment response, which warrants further investigation.

Although this is a prospective multi-center study that enhances generalizability and reduces selective bias, certain limitations should be acknowledged. First, the relatively small sample size and the use of 2 different anti-IL-5 therapies in each subgroup may have limited the statistical power for some comparisons, despite observable trends. Second, there may be variability in the techniques used to measure serum Siglec-8. While we used a validated ELISA kit, differences in laboratory protocols and measurement standards could affect the reproducibility. Third, this study did not explore mechanistic differences between soluble versus membrane-bound forms of Siglec-8, which may have different biological implications. Standardization of measurement methods and mechanistic studies will be important for future clinical applications. Future research should focus on longitudinal studies to assess the stability of serum Siglec-8 levels over time and their correlation with long-term clinical outcomes. In addition, exploring the interaction between serum Siglec-8 and other biomarkers could provide a more comprehensive understanding of the molecular pathways involved in SA. Moreover, investigating the roles of serum Siglec-8 in other inflammatory diseases could expand its clinical utility beyond asthma.¹¹ Furthermore, integrating serum Siglec-8 measurement with omics technologies such as genomics, proteomics, and metabolomics could provide a multi-dimensional perspective on the pathophysiology of asthma and facilitate the identification of new therapeutic targets.²¹

In conclusion, baseline serum Siglec-8 level has the highest predictive performance among other parameters for assessing 6-month and 12-month responses to anti-IL-5 therapies in SA, suggesting its potential as a biomarker for optimizing treatment strategies in this patient population.

ACKNOWLEDGMENTS

This research was supported by a grant from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (grant number: RS-2024-00403700).

SUPPLEMENTARY MATERIAL

Supplementary Table S1

Correlation between baseline serum sialic acid-binding immunoglobulin-like lectin 8 levels and baseline clinical parameters

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