

Subphenotypes of type 2 severe asthma in adults



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Clinical Implications

- More than 80% of the patients with severe asthma in a Japanese adult cohort can be classified into 1 or more of the subphenotypes of type 2 asthma with significant overlaps: eosinophilic asthma, periostin-high asthma, and atopic asthma.

TO THE EDITOR:

Asthma is a heterogeneous disease, and its treatment, especially in severe cases, should be tailored on the basis of the molecular mechanism(s) in each case. Atopic asthma is the specific target of anti-IgE antibody treatment, whereas type 2 asthma, encompassing atopic as well as nonatopic disease associated with T_H2 cytokines, is considered the candidate for various biological therapies targeting T_H2 cytokines. Biomarkers such as peripheral blood or sputum eosinophil counts, fractional exhaled nitric oxide (FeNO), and serum periostin concentration are useful for identifying patients treatable with T_H2-targeted biologics.¹ Anti-IL-5 antibodies such as mepolizumab and reslizumab, as well as the anti-IL-4 receptor- α antibody, dupilumab, reduce the risk of asthma exacerbations in patients with eosinophilic asthma exhibiting elevated peripheral blood eosinophil counts.² Serum periostin levels may predict the efficacy of anti-IL-4/13 therapies.³ Peripheral blood eosinophil counts, serum periostin levels, and FeNO are also correlated with responses to the anti-IgE antibody, omalizumab.⁴ We asked 2 clinical questions: (1) how are eosinophilic and periostin-high asthma, subphenotypes of type 2 asthma, different from each other, and (2) what proportion of patients with severe asthma are treatable with each T_H2-targeted therapy.

To answer these questions, we recruited adult patients with difficult-to-treat asthma, defined as a disease that requires Global Initiative for Asthma step 4 or 5 treatment under the management of certified pulmonologists or allergists, enrolled at 18 hospitals in Japan, as previously reported.⁵ The study protocol, registered in the UMIN Clinical Trials Registry (no. 000002980), was approved by the Institutional Review Board of each participating institution and implemented in compliance with the Declaration of Helsinki. All participants provided written informed consent.

Following the exclusion of 4 patients due to incomplete data sets, data for 144 patients were finally analyzed (Table 1). There was no patient who had asthma exacerbation within 1 month of enrolment. Serum concentrations of periostin were measured using an ELISA (Shino-Test Corp, Tokyo, Japan). Categorical data were analyzed with the chi-square test adjusted by Bonferroni correction, and numerical data were examined using

ANOVA or Kruskal-Wallis test followed by post hoc analysis. Spearman rank correlation coefficient was determined between serum levels of periostin and blood eosinophil counts. A statistically significant difference was defined as a 2-tailed *P* value of less than .05. Statistical analysis was performed using SPSS for Windows (version 20.0, IBM Corp, Armonk, NY).

Our study showed, despite a modest correlation between peripheral blood eosinophil counts and serum periostin levels ($\rho = 0.35$; $P < .001$) compatible with a previous report,⁶ that these values did not interrelate in some patients. Therefore, patients with severe asthma were divided into quadri-sections using the tentative cutoff values of 300 cells/ μ L for peripheral blood eosinophil counts² and 95 ng/mL for serum periostin levels⁶: low eosinophils-low periostin (LE-LP, *n* = 59), high eosinophils-low periostin (HE-LP, *n* = 45), low eosinophils-high periostin (LE-HP, *n* = 10), and high eosinophils-high periostin (HE-HP, *n* = 30) (Table 1). Periostin-high asthma in the LE-HP and HE-HP sections shared similar clinical characteristics including a higher prevalence of late-onset asthma, self-reported olfactory dysfunction, and leaner body mass as previously reported,⁵ regardless of the levels of peripheral blood eosinophilia. The major difference between LE-HP and HE-HP sections was the higher rate of regular oral corticosteroid use (60%) in the LE-HP category. In contrast, there was no difference in the rate of oral corticosteroid use between LE-LP and HE-LP groups, which included more patients with early-onset, atopic asthma. There were no differences in the dose of inhaled corticosteroids, asthma control status, or asthma-related quality of life among the 4 categories.

We examined the proportion of patients treatable with T_H2-targeted therapy based on the levels of biomarkers: total/allergen-specific IgE, peripheral blood eosinophil counts, and serum periostin levels (Figure 1). Eighty-six patients (60%) were atopic, defined as 1 or more perennial inhaled allergen-specific IgE concentrations of more than 0.70 UA/mL, and 70 patients (49%) among them exhibited total serum IgE levels in the treatable range (30-1500 IU/mL) with omalizumab. Approximately one-half (52%) or one-third (33%) of the patients showed peripheral blood eosinophil counts of more than 300 or more than 500 cells/ μ L, respectively, and may therefore be favorable targets for anti-IL-5 antibodies or dupilumab.² Serum periostin levels were more than 95 ng/mL in 28% of the patients. Moreover, a substantial proportion of the patients with severe asthma were candidates for 2 (28%) or 3 (9%) different T_H2-targeted therapies.

The present study showed that (1) compared with eosinophilic asthma, periostin-high asthma represents a more consistent subphenotype regardless of the type of treatment, (2) peripheral blood eosinophil counts or serum periostin levels are not the indicator of asthma control or activity, and (3) more than 80% of patients with severe asthma in a Japanese cohort can be classified into 1 or more of the type 2 asthma subphenotypes: eosinophilic asthma, periostin-high asthma, and atopic asthma. Importantly, only 17% of the patients with severe asthma had no indications for any of the T_H2-targeted drugs even under the relatively strict cutoff values for the biomarkers. The high ratio of type 2 asthma may be due to a lower prevalence of obesity in our cohort, where

TABLE I. Characteristics of the participants, stratified by peripheral blood eosinophil counts and serum periostin levels

Characteristic	LE-LP (n = 59)	HE-LP (n = 45)	LE-HP (n = 10)	HE-HP (n = 30)	P
Demographic data					
Men (%)	40.7	53.3	50.0	50.0	.61*
Age (y)	58.0 ± 15.4	59.3 ± 15.6	61.7 ± 17.6	64.4 ± 10.8	.15†
Age at asthma onset (y)	26.0 ± 23.9	33.7 ± 23.9	42.0 ± 17.1	42.4 ± 15.6‡	.004†
<12 y (%)	41.8	29.5	10.0	6.7§	.003*
≥40 y (%)	29.1	47.7	70.0§	66.7§	.003*
Disease duration (y)	32.4 ± 19.1	26.2 ± 18.3	19.7 ± 17.7	24.1 ± 17.8	.08†
Body mass index (kg/m ²)	25.6 ± 6.1	23.7 ± 3.2	22.4 ± 3.8	22.6 ± 2.6‡	.02†
History of smoking (%)	10.3	22.2	30.0	16.7	.27*
Pack-years	5.8 ± 11.6	11.2 ± 22.8	19.9 ± 28.6	11.5 ± 20.0	.17†
Atopy (%)	66.1	64.4	40.0	50.0	.24*
Mite	58.6	53.3	40.0	33.3	.13*
Animal dander	17.5	28.9	10.0	10.0	.17*
Fungi	30.5	33.3	10.0	30.0	.54*
Insects	34.7	27.5	20.0	26.9	.75*
Exacerbation in the previous year					
Usage of short-term OCS (%)	67.8	71.1	70.0	70.0	.99*
Unscheduled visit (%)	57.6	57.8	70.0	60.0	.90*
Admission (%)	30.5	22.2	20.0	20.0	.64*
Comorbidities (%)					
Atopic dermatitis	23.6	32.6	10.0	26.9	.48*
Allergic rhinitis	63.6	68.2	70.0	76.9	.69*
Olfactory dysfunction	12.7	27.9	40.0	57.7‡	<.001*
Aspirin intolerance	14.3	22.7	20.0	26.9	.55*
Laboratory data					
Eosinophils/μL of blood	131 ± 91	702 ± 579‡	142 ± 99	872 ± 609‡	<.001†
Range	0-295	302-3393	0-252	371-2400	
Total serum IgE (IU/mL)	250 (54-451)	396 (219-925)‡	503 (155-795)	355 (163-680)	.02¶
Serum periostin (ng/mL)	56 (46-67)	70 (60-81)‡	124 (109-147)‡	115 (103-136)‡	<.001¶
Pulmonary functions					
FEV ₁ (% predicted#)	76.6 ± 24.1	87.0 ± 22.6	80.8 ± 23.7	73.8 ± 20.7	.09†
FEV ₁ /FVC (%)	64.3 ± 15.3	66.1 ± 14.1	65.0 ± 14.3	59.5 ± 11.5	.31†
Treatment					
Daily dose of ICS** (μg)	725 ± 292	767 ± 288	770 ± 189	750 ± 334	.88†
OCS (%)	35.6	37.8	60.0	36.7	.70*
Omalizumab (%)	18.6	4.4	30.0	6.7	.04*
GINA step 5 (%)	45.8	37.8	70.0	40.0	.29*
Asthma severity and quality-of-life scores					
Asthma Control Test	18.8 ± 4.6	18.6 ± 5.5	19.0 ± 6.4	19.4 ± 4.0	.94†
AQLQ	4.8 ± 1.3	4.9 ± 1.2	4.8 ± 1.0	5.0 ± 1.0	.92†

AQLQ, Asthma quality of life questionnaire; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroid; FVC, forced vital capacity; OCS, oral corticosteroid; VC, vital capacity.

Values are proportions of patients in each study group, means ± SDs, or median (interquartile range).

*Chi-square test.

†ANOVA.

‡P < .05 compared with the LE-LP group.

§P < .016 compared with the LE-LP group.

||20 pack-years or more.

¶Kruskal-Wallis test.

#The predicted values were calculated on the reference equation proposed by the Japanese Respiratory Society.

**Dose of ICS is shown as fluticasone propionate equivalent.

only 7% of the patients had a body mass index of more than 30 m²/kg. Another study from Japan also reported a low prevalence of obesity (5%) among subjects with difficult-to-treat asthma.⁷ In contrast, 37% of the patients with severe asthma enrolled in the Severe Asthma Research Programme in the United States exhibited a body mass index higher than

30 m²/kg.⁸ Therefore, the proportion of cases treatable with T_H2-targeted therapies may be different depending on the rate of the late-onset/non-type 2 obese phenotype of severe asthma among the population of interest.

There are a few limitations of the present study. Some biomarkers, especially eosinophil counts, were vulnerable to the

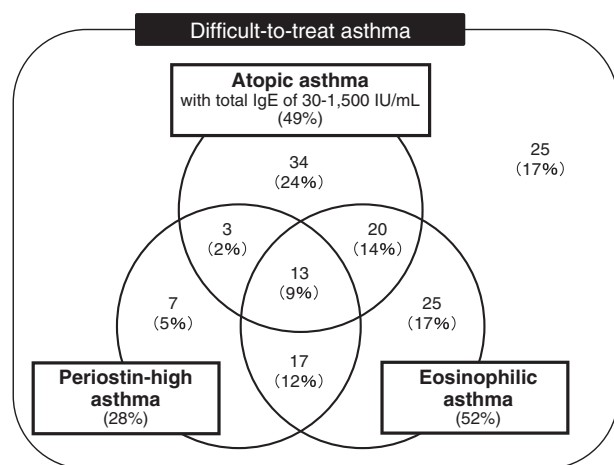


FIGURE 1. Subphenotypes of type 2 asthma. One hundred forty-four difficult-to-treat asthma patients classified according to type 2 asthma-related biomarkers. Atopic asthma is defined as 1 or more perennial inhaled allergen-specific IgE concentrations of more than 0.70 UA/mL. Periostin-high asthma and eosinophilic asthma were defined as serum periostin levels of 95 ng/mL or more and peripheral blood eosinophil counts of 300/ μ L or more, respectively.

effects of the treatment, as demonstrated in the case of the LE-HP phenotype. Serum periostin levels remained relatively robust regardless of the treatment,⁹ but further standardization of their cutoff values will be required. Treatment with omalizumab might have confounded biomarker assessment; however, reanalysis after the exclusion of 18 subjects treated with omalizumab showed consistent results (see Table E1 and Figure E1 in this article's Online Repository at www.jaci-inpractice.org).

In conclusion, the present study demonstrates that most patients with difficult-to-treat asthma in Japan present with type 2 asthma, and a substantial proportion of these cases overlap between 2 or more subphenotypes. Using multiple biomarkers for subphenotyping type 2 asthma would improve clinical characterization and may increase the possibility of using combined T_H2 -targeted therapies in cases refractory to standard treatment approaches.

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Conflicts of interest: K. Izuhara has received research support from Shino-test and Chugai Pharmaceutical and has received consultancy fees from Chugai Pharmaceutical and AstraZeneca and lecture fees from Astellas Pharma, Kyorin Pharma, Novartis Pharma, Boehringer-Ingelheim, and MSD. T. Betsuyaku received a grant from GlaxoSmithKline. K. Asano has received research support from the Japan Society for the Promotion of Science (Grant-in-Aid for Scientific Research (C) (25461504)) and the Japan Agency for Medical Research and Development; has received consultancy fees from Teijin Pharma; has provided expert testimony for Chugai Pharmaceutical; and has received lecture fees from Astellas Pharma, Kyorin Pharma, Novartis Pharma, Boehringer-Ingelheim, and MSD. T. Betsuyaku received a grant from GlaxoSmithKline. The rest of the authors declare that they have no relevant conflicts of interest.

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TABLE E1. Characteristics of the participants, stratified by peripheral blood eosinophil counts and serum periostin levels (18 patients treated with omalizumab were excluded)

Characteristic	LE-LP (n = 48)	HE-LP (n = 43)	LE-HP (n = 7)	HE-HP (n = 28)	P
Demographic data					
Men (%)	43.8	53.5	57.1	53.6	.74*
Age (y)	58.7 ± 15.0	59.3 ± 15.4	66.1 ± 12.2	63.4 ± 10.4	.34†
Age at asthma onset (y)	29.6 ± 24.2	33.0 ± 23.8	50.3 ± 9.1	44.5 ± 13.4‡	<.001†
<12 y (%)	33.3	31.0	0.0	3.6§	.008*
≥40 y (%)	33.3	47.6	85.7§	71.4§	.003*
Disease duration (y)	29.2 ± 17.6	26.8 ± 18.4	15.9 ± 15.1	21.0 ± 13.4	.09†
Body mass index (kg/m ²)	25.4 ± 6.3	23.8 ± 3.2	21.4 ± 2.5	22.8 ± 2.6‡	.02†
History of smoking (%)	12.5	20.9	42.9	17.9	.25*
Pack-years	6.6 ± 12.4	11.2 ± 23.2	26.9 ± 31.9	12.3 ± 20.4	.21†
Atopy (%)	64.6	62.8	14.3	50.0	.06*
Mite	56.3	55.8	14.3	32.1	.04*
Animal dander	18.8	30.2	0	10.7	.10*
Fungi	27.1	30.2	14.3	32.1	.81*
Insects	36.6	28.2	14.3	28.0	.62*
Exacerbation in the previous year					
Usage of short-term OCS (%)	64.6	69.8	71.4	67.9	.95*
Unscheduled visit (%)	58.3	55.8	57.1	57.1	.99*
Admission (%)	27.1	20.9	14.3	17.9	.74*
Comorbidities (%)					
Atopic dermatitis	20.0	29.3	0.0	25.0	.35*
Allergic rhinitis	62.2	69.0	57.1	75.0	.67*
Olfactory dysfunction	15.6	29.3	28.6	54.2‡	.01*
Aspirin intolerance	10.9	21.4	14.3	25.0	.42*
Laboratory data					
Eosinophils/μL of blood	144 ± 90	697 ± 589‡	152 ± 97	902 ± 620‡	<.001†
Range	0-295	302-3393	0-252	371-2400	
Total serum IgE (IU/mL)	211 (48-473)	396 (208-940)‡	341 (18-700)	355 (148-699)	.04¶
Serum periostin (ng/mL)	57 (46-67)	70 (59-81)‡	129 (109-189)‡	115 (104-133)‡	<.001¶
Pulmonary functions					
FEV ₁ (% predicted)	78.1 ± 23.9	88.4 ± 22.2	81.7 ± 28.5	75.7 ± 20.3	.33†
FEV ₁ /FVC (%)	64.8 ± 15.1	66.5 ± 14.1	64.5 ± 12.3	59.9 ± 11.8	.12†
Treatment					
Daily dose of ICS# (μg)	688 ± 306	753 ± 283	757 ± 230	750 ± 312	.70†
OCS (%)	33.3	34.9	57.1	32.1	.75*
GINA step 5 (%)	33.3	34.9	57.1	35.7	.68*
Asthma severity and quality-of-life scores					
Asthma Control Test	18.9 ± 4.5	18.8 ± 5.4	18.9 ± 6.6	20.0 ± 3.6	.80†
AQLQ	5.0 ± 1.2	4.9 ± 1.1	4.8 ± 0.8	5.1 ± 1.0	.91†

AQLQ, Asthma quality of life questionnaire; FVC, forced vital capacity; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroid; OCS, oral corticosteroid; VC, vital capacity.

Values are proportions of patients in each study group, means ± SDs, or median (interquartile range).

*Chi-square test.

†ANOVA.

‡P < .05 compared with the LE-LP group.

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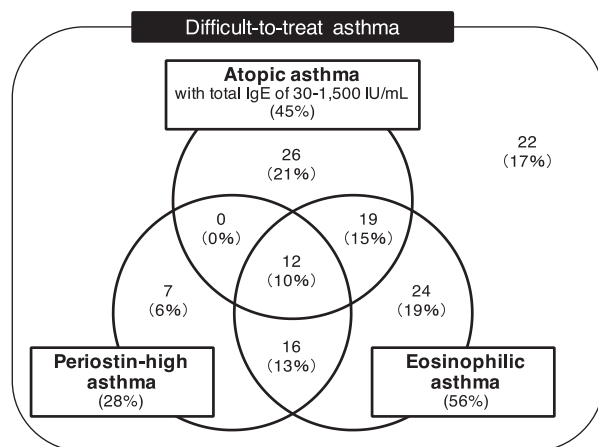


FIGURE E1. Subphenotypes of type 2 asthma (18 patients treated with omalizumab were excluded). One hundred twenty-six difficult-to-treat asthma patients classified according to type 2 asthma-related biomarkers. Eighteen patients treated with omalizumab were excluded. Atopic asthma is defined as 1 or more perennial inhaled allergen-specific IgE concentrations of more than 0.70 UA/mL. Periostin-high asthma and eosinophilic asthma were defined as serum periostin levels of 95 ng/mL or more and peripheral blood eosinophil counts of 300/ μ L or more, respectively.

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