Identification of biologic-responsive phenotypes in elderly people with eosinophilic asthma

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Background: Asthma in the elderly is not as well studied as in younger age groups. Age-related immunosenescence may result in diminished T_H2 inflammation, which raises a question about whether asthma in elderly patients responds well to anti-T_H2 asthma biologics.

Objective: We sought to determine whether asthma in elderly people has different T_H2 biomarkers and clinical features compared to nonelderly people, and if disease in the 2 age groups responds differently to anti-T_H2 biologics. We also aimed to identify treatment-responsive phenotypes with clinical and biomarker features that could be used to predict best response to biologics.

Methods: A retrospective chart review was conducted for 56 patients (30 elderly [age ≥62 years] and 26 nonelderly [ages 18-59 years] subjects) with severe asthma treated with dupilumab or benralizumab. Differences in baseline characteristics and response to treatment were analyzed. A hierarchical cluster analysis was also performed to identify treatment-responsive phenotypes. Significance threshold was $P = .05$ for all analyses.

Results: Baseline characteristics and T_H2 biomarkers (blood eosinophil level, total IgE, aeroallergen sensitivity) were similar between elderly and nonelderly subjects. The disease in both groups responded well to biologics (improvement in ACT scores, decreased exacerbations, decreased need for prednisone), but no significant response difference was found based on age groups. Cluster analysis identified 3 phenotypes, as follows: cluster 1, youngest age, moderate eosinophil levels, lowest total IgE, few environmental allergies, and least response to biologics; cluster 2, intermediate age, lowest eosinophil level, highest IgE level, many environmental allergies, and an intermediate response to biologics; and cluster 3, oldest ages, highest eosinophil levels, high total IgE, few environmental allergies, and best response to biologics. These results confirm trends seen in another study utilizing cluster analyses showing that subjects with highest levels of IgE and eosinophils responded better to biologic treatment for asthma.

Conclusion: Elderly people with asthma should be considered for biologic therapy no differently than younger people. There may be subgroups of patients with different biologic responses based on age, allergenicity, IgE, and eosinophil levels that could be used to predict treatment response. (J Allergy Clin Immunol Global 2024;3:100196.)

Key words: *Eosinophilic, asthma, biologic, elderly, phenotype, dupilumab, benralizumab*

Asthma is a common, highly morbid disorder that affects about 25 million Americans. While mortality is relatively low, the highest rate is seen in people over 65 years old, at 30.7 deaths per million in 2020.[1] Asthma affects all age groups, but it is least studied in elderly patients.[2,3] Immune responses are altered in the elderly as a result of immunosenescence, and years of airway remodeling can alter lung physiology.[3] As a result, it is generally believed that older people with asthma are less allergic, have lower eosinophil counts, and have lower lung function.[2-4] The consequence of these changes is that clinical features of asthma may be different in this age group, and response to anti-inflammatory therapy may be worse compared to younger individuals. The latter is of particular interest, as biologic medications targeting allergic inflammation have emerged as exceptionally effective therapies in severe asthma.

Although traditionally thought of as a childhood disease, aspects of asthma such as cost, quality of life, hospitalization, and mortality are increased in elderly people with asthma compared to younger people with asthma.[5] The treatment of geriatric asthma is also made difficult as a result of an increased concern for adverse effects due to polypharmacotherapy, comorbidities, and cost. The role of atopy in elderly patients with asthma is not as well studied as in younger populations, but diminished T-cell responses due to immunosenescence may lead to less environmental allergen sensitization, lower total IgE levels, and lower blood eosinophil levels.[2]

For patients with severe asthma that is not well managed by traditional bronchodilators and corticosteroids, biologic therapies are a newer treatment option that can provide relief. There are currently 6 monoclonal antibodies approved by the US Food and Drug Administration (FDA) to treat severe uncontrolled asthma as well as other allergic diseases: reslizumab,[6] mepolizumab,[7-9] omalizumab,[10] benralizumab,[11-13] dupilumab,[14-16] and tezepelumab.[17] These biologic therapies are highly effective and can reduce asthma exacerbations, improve disease control, and reduce the need for systemic corticosteroids.

Benralizumab was FDA approved in 2017 for patients 12 years and older with severe eosinophilic asthma and may be especially useful in patients with oral corticosteroid dependence. It is a humanized IgG_1 monoclonal antibody that targets the IL-5 receptor α on eosinophils, which leads to depletion of eosinophils via antibody-dependent cell-mediated cytotoxicity.[11-13] Dupilumab inhibits the IL-4R α chain, blocking the effects of IL-4 and IL-13. It was FDA approved in 2018 for patients 12 years and older, then expanded to 6 years and older in 2021 with

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Received for publication April 11, 2023; revised September 3, 2023; accepted for publication September 3, 2023.

Available online November 22, 2023.

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2772-8293

https://doi.org/10.1016/j.jacig.2023.100196

Abbreviations used
ACT: Asthma control test
BMI: Body mass index
FDA: US Food and Drug Administration
FEV_1: Forced expiratory volume in 1 second
FVC: Forced vital capacity

moderate-to-severe asthma and an eosinophilic phenotype, or with oral corticosteroid–dependent asthma.[14-16]

While phase 3 studies of asthma biologics have included elderly patients, the average age for the dupilumab study (LIBERTY ASTHMA QUEST)[16] was 47.9 ± 15.3 years and 50.1 ± 13.4, 47.6 ± 14.5, 50 ± 13.6, and 47.6 ± 14.5 years for benralizumab studies (SIROCCO every 4-week dosing, every 8-week dosing, CALIMA every 4-week dosing, every 8-week dosing, respectively).[12,13] These studies did not report outcomes as a function of age. Because these biologics primarily target type 2 pathways involved in asthmatic inflammation, it is possible that immunosenescence changes that reduce type 2 inflammation in elderly patients could lead to reduced effectiveness. However, we questioned whether the immunosenescence effects are generalizable to all populations of elderly patients, as our clinic population of elderly people with asthma appears to have high levels of type 2 biomarkers and seems to respond well to biologics. This is consistent with some studies that found no significant difference between some of the biomarkers between young and elderly people with asthma or find a mixed presentation of type 2 and non–type 2 phenotypes.[18,19] This could suggest that multiple phenotypes exist in the elderly asthmatic population that are not yet fully understood. We hypothesize that elderly people with asthma have similar levels of type 2 inflammation as nonelderly people with asthma in our population, and that responses to treatment would be similar in both groups. We sought to compare the clinical characteristics and biomarker profiles of elderly versus nonelderly people with asthma and to determine whether there were any differences in their response to biologic treatment with dupilumab or benralizumab.

METHODS

This study was approved by the Mount Nittany Medical Center institutional review board as well as the Penn State College of Medicine institutional review board. This was a retrospective study involving patients initially seen at the Mount Nittany allergy and immunology clinic between October 2018 and June 2021. The study outcomes were 2-fold: first, to determine whether there were differences in clinical features, biomarker expression, or response to biologics in elderly versus nonelderly people with asthma, and second, to identify treatment-responsive phenotypes whose clinical and biomarker features could be used to predict which patients had disease that would respond best to biologic therapy.

Patients were classified as having asthma according to medical history and forced expiratory volume in 1 second (FEV_1) reversible by more than 12% and more than 200 mL after bronchodilator or airway hyperresponsiveness from methacholine challenge producing more than 20% decrease in FEV_1 of less than 8 mg/mL. We also included patients who had a history and physical examination result consistent with asthma (wheezing, shortness of breath with absence of history of chronic obstructive pulmonary disease or other lung disease) in conjunction with reduced FEV_1/forced vital capacity (FVC) ratio < 0.7, or demonstrated evidence of airway hyperreactivity with more than a 12% variability in FEV_1 on serial spirometry obtained at clinic visits over the span of 12 months. We also included 2 subjects who had >10% increase in FEV_1 after maximal anti-inflammatory treatment with 40 mg of prednisone for ≥1 week. Their responses to oral corticosteroid treatment were as follows. The first subject was a 21-year-old in the dupilumab treatment group who had a 10% increase in FEV_1 (410 mL change). The second was a 55-year-old in the benralizumab treatment group who had an11% increase in FEV_1 (280 mL change). These subjects did not meet other lung function criteria for asthma diagnosis, but they were included because they had history and physical examination results consistent with asthma and their disease responded well to biologic therapy. Asthma control was assessed using the asthma control test (ACT) collected at the clinical visit immediately before initiation of the biologic and 12 months into treatment.

We selected people with eosinophilic asthma (defined as blood eosinophils ≥ 150 cells/μL) who were treated with either dupilumab or benralizumab. We selected these 2 biologics for study because the majority of people with eosinophilic asthma (~80%) in our severe asthma clinic were treated with 1 of these 2 medications, and each blocks a different component of T_H2 inflammation, allowing us to characterize treatment responses across a breadth of mechanisms. Clinical history, spirometry, and lab studies were obtained before initiation of a biologic. Analysis of treatment response was obtained 12 months after treatment. Treatment response was measured through analysis of ACT scores, number of acute asthma exacerbations needing emergency room– or hospital-level treatment (mean number per subject in 1 year), number of acute prednisone courses (mean number per subject in 1 year), number of subjects receiving daily prednisone, daily prednisone dose for those subjects receiving it daily, and pulmonary function (FVC%, FEV_1, FEV_1/FVC%). The study outcome was measured before and after treatment via biologic changes in these variables. For analysis of treatment response between clusters, we compared change in ACT score before and after treatment.

We selected 62 years as the cutoff for defining "elderly" because this provided a relatively similar number of subjects and a normal distribution in each group. This cutoff falls between the mean (59.1, SD 15.94) and median (63.5; interquartile range, 51.25, 71.75) age of the whole subject group. Subjects in the young group ranged in age from 21 to 59 years (n = 26) and in the elderly group ranged 62 to 88 years (n = 30).

Normally distributed data were analyzed by ANOVA with Tukey posttest for multiple comparisons or Student *t* test where appropriate. Fisher exact tests were used for categorical binary variables, and the chi-square test was used for categorical variables across more than 2 groups. Comparison of continuous variables before and after treatment was assessed by paired *t* test. Significance threshold was $P = .05$ for all analyses. Analyses were performed by GraphPad Prism v9 and Microsoft Excel 2019. Hierarchical cluster analysis was performed in Cluster 3.0 using the average-linkage method and visualized in TreeView v1.6.

TABLE I. Demographic and clinical features of study population's pretreatment with biologic agents according to age

Characteristic	Young (n = 26)	Elderly (n = 30)	*P* value
Age (years)	45.7 ± 12.8	70.7 ± 6.3	<.001
Sex, M/F (% female)	11/15 (58)	9/21 (70)	.406
Race, % White, Black, other	92.3, 3.8, 3.8	93.3, 3.3, 3.3	.989
BMI (kg/m^2)	36.6 ± 12.3	32.0 ± 8.3	.110
Age (years) at asthma onset	23.7 ± 17.8	43.1 ± 21.9	<.001
FVC (L)	3.4 ± 0.9	2.3 ± 0.8	<.001
FVC (%)	85.1 ± 19.6	73.4 ± 17.8	.0243
FEV_1 (L)	2.5 ± 0.7	1.8 ± 0.5	<.001
FEV_1 (%)	75.3 ± 19.3	70.8 ± 19.9	.387
FEV_1/FVC (%)	69.7 ± 17.2	71.9 ± 10.0	.576
ICS dose/d (μg)	901.5 ± 291.4	947.3 ± 303.6	.568
Subjects needing multiple controllers/total, n/N (%)	18/26 (69)	22/30 (73)	.774
Eosinophils (cells/μL)	879.6 ± 1253.2	705.0 ± 571.0	.518
Total IgE (IU/mL)	1331.1 ± 2454.8	443.0 ± 870.4*	.092
ACT score	14.1 ± 3.6	12.9 ± 4.1	.238
No. of asthma exacerbations in past year	1.7 ± 1.7	1.4 ± 1.8	.594
Acute courses of prednisone in past year	4.4 ± 2.7	4.4 ± 3.4	.983
Subjects with daily prednisone receipt, % (no.)	30.8 (8)	26.7 (8)	.774
Daily prednisone dose (mg)†	20.0 ± 20.7	23.1 ± 18.3	.754
Subjects with environmental allergies, % (no.)	80.8 (21)	80.0 (24)	>.999
Allergic subjects			
Total no. of environmental allergies	8.7 ± 6.9	6.8 ± 7.4	.396
Pollen allergy, % (no.)	65.4 (17)	56.7 (17)	.589
Cockroach allergy, % (no.)	26.9 (7)	23.3 (7)	.768
Dust mite allergy, % (no.)	50.0 (13)	36.7 (11)	.418
Pet dander allergy, % (no.)	57.7 (15)	53.3 (16)	.790
Mold allergy, % (no.)	46.2 (12)	30.0 (9)	.273

Data are presented as mean ± SDs unless otherwise indicated.
*Four subjects had no baseline IgE-level data.
†Excluding subjects not receiving daily prednisone.

RESULTS

Subject demographic and baseline pretreatment characteristics by age group

The study population comprised 56 subjects with eosinophilic asthma, including 26 young people (mean age, 45.7 years; median, 50.5 years; range, 21-59 years) and 30 elderly people (mean age, 70.7 years; median, 70.5 years; range, 62-88 years). Both groups were predominantly White and female (Table I).

The mean age at asthma onset in young and elderly people with asthma was 23.7 versus 43.1 years, respectively ($P < .001$). As expected, young people with asthma had significantly higher lung function than elderly people with asthma (FVC%: 85.1 ± 19.6 and 73.4 ± 17.8 respectively, $P = .0243$). FEV_1 and FEV_1/FVC % were not significantly different between the 2 groups.

Other baseline demographics and clinical features were similar in young and elderly groups including body mass index (BMI), inhaled corticosteroid dose per day, percentage needing multiple controller medications, mean number of acute courses of prednisone in the past year, percentage of subjects with daily prednisone receipt, and daily prednisone dose for subjects receiving maintenance oral corticosteroid treatment. Receipt of multiple controllers was defined as receipt of more than 1 class of asthma medication such as long-acting β-agonists, long-acting muscarinic antagonists, and antileukotrienes. There were also no differences in baseline asthma control in young versus elderly subjects as measured by calculated ACT score (14.1 vs 12.9) and mean number of asthma exacerbations in the past year (1.7 vs 1.4).

Markers of type 2 asthma were also similar in the 2 groups. Comparing young and elderly groups, there were no statistical differences in baseline eosinophil level (879.6 cells/μL ± 1253.2 vs 705.0 cells/μL ± 571.0) and mean total IgE level (1331.1 IU/mL ± 2454.8 vs 443.0 IU/mL ± 870.4). Regarding aeroallergen sensitivity, the majority of subjects tested positive for at least 1 allergen, with no significant difference in the number or type of allergen.

Demographics were also similar across groups when stratified according to age and specific biologic received (Table II). In the group of young people with asthma, the disease of 13 patients was treated with dupilumab and 13 with benralizumab. In the group of elderly people with asthma, the disease of 13 was treated with dupilumab and 17 with benralizumab.

Comparison of subject characteristics after receipt of biologic treatment

Overall, subjects' disease had an excellent response to biologics.

ACT score, number of asthma exacerbations, prednisone receipt, and spirometry values were compared before and after treatment with either dupilumab or benralizumab, separating subjects by age. There were no significant differences in asthma response to treatment between young or elderly people as measured by these factors for either biologic (Table III).

Identification of treatment response clusters

We next sought to determine whether subgroups of subjects existed, irrespective of age, with markers that might predict

TABLE II. Demographic and clinical features of study population before pretreatment with biologic therapy, separated by age and biologic

Characteristic	Dupilumab			Benralizumab		
	Young (n = 13)	Elderly (n = 13)	*P* value	Young (n = 13)	Elderly (n = 17)	*P* value
Age (years)	42.9 ± 13.1	67.3 ± 4.6	<.001	48.5 ± 12.5	73.4 ± 6.2	<.001
Sex, M/F (% female)	4/9 (69)	3/10 (77)	1.000	7/6 (46)	6/11 (65)	.460
Race, % White, Black, other	84.6, 7.7, 7.7	92.3, 7.7, 0	.568	100, 0, 0	94.1, 0, 5.9	.374
BMI (kg/m^2)	32.2 ± 10.3	31.1 ± 7.9	.739	39.6 ± 13.6	31.1 ± 6.6	.054
Age at asthma onset (years)	15.9 ± 11.9	37.3 ± 23.1	.0080	31.4 ± 19.7	47.5 ± 20.5	.0379
FVC (L)	3.4 ± 0.7	2.3 ± 0.8	<.001	3.4 ± 1.1	2.3 ± 0.8	.0074
FVC (%)	90.2 ± 20.6	75.2 ± 21.7	.082	79.9 ± 17.7	72.1 ± 14.8	.209
FEV_1 (L)	2.6 ± 0.7	1.8 ± 0.6	.0039	2.5 ± 0.8	1.8 ± 0.5	.0140
FEV_1 (%)	80.6 ± 17.1	73.3 ± 24.4	.387	70.1 ± 20.6	68.8 ± 16.2	.858
FEV_1/FVC (%)	66.7 ± 22.0	71.8 ± 12.3	.478	72.8 ± 10.6	72.0 ± 8.3	.835
Inhaled corticosteroids (dose/d)	955.4 ± 246.7	961.5 ± 138.7	.938	847.7 ± 331.2	936.5 ± 390.3	.507
Subjects needing multiple controllers, n/N (%)	10/13 (77)	10/13 (77)	1.000	8/13 (62)	12/17 (71)	.705
Eosinophils (cells/μL)	542.3 ± 565.3	372.3 ± 257.4	.338	1216.9 ± 1645.0	959.4 ± 618.5	.599
Total IgE (IU/mL)	1322.6 ± 2372.2	347.2 ± 420.7	.169	1339.5 ± 2631.9	538.8 ± 1175.3*	.331
ACT score	15.3 ± 3.3	12.2 ± 4.7	.067	12.9 ± 3.5	13.4 ± 3.5	.711
No. of asthma exacerbations in past year	1.2 ± 1.6	1.1 ± 1.8	.910	2.2 ± 1.7	1.6 ± 1.9	.446
Acute courses of prednisone in past year	4.5 ± 3.2	4.2 ± 3.4	.815	4.3 ± 2.2	4.5 ± 3.5	.834
Subjects with daily prednisone receipt, % (no.)	38.5 (5)	30.8 (4)	1.000	23.1 (3)	23.5 (4)	1.000
Daily prednisone dose (mg)†	24 ± 26.1	17.5 ± 5	.612	13.3 ± 5.8	28.8 ± 25.9	.324
Subjects with environmental allergies, % (no.)	85 (11)	77 (10)	1.000	77 (10)	82 (14)	1.000
Allergic subjects						
Total no. of environmental allergies	10.5 ± 7.8	9.0 ± 8.0	.661	6.6 ± 5.4	5.3 ± 6.8	.604
Pollen allergy, % (no.)	82 (9)	80 (8)	1.000	80 (8)	64 (9)	.653
Cockroach allergy, % (no.)	36 (4)	30 (3)	1.000	30 (3)	29 (4)	1.000
Dust mite allergy, % (no.)	73 (8)	60 (6)	.659	50 (5)	36 (5)	.678
Pet dander allergy, % (no.)	55 (6)	80 (8)	.361	90 (9)	57 (8)	.172
Mold allergy, % (no.)	73 (8)	50 (5)	.387	40 (4)	29 (4)	.673

Data are presented as mean ± SDs unless otherwise indicated.
*Four subjects had no baseline IgE-level data.
†Excluding subjects not receiving daily prednisone.

response to biologics. Cluster analysis allows for the unbiased identification of subgroups based on combinations of clinical or biomarker data. We performed an unsupervised clustering analysis using the clinical features shown in Table IV.

We identified 3 main clusters, shown as a heat map in Fig 1.

Baseline BMI, number of prednisone courses per year, and reduction in prednisone courses after biologic treatment were similar in all 3 clusters (Table IV). However, the clusters varied with response to biologics, age, lung function, eosinophil levels, total IgE level, and aeroallergen sensitivity (Fig 2).

For the purpose of cluster analysis, response to biologics was defined by change in ACT score. Cluster 1 included the youngest subjects (mean age, 55.5 years) and was characterized by the shortest duration of asthma, lowest total IgE levels, low number of environmental allergies, and intermediate level of blood eosinophils relative to the other clusters. Subjects in cluster 1 also had the best lung function (both FVC% and FEV_1 predicted). Subjects in cluster 2 were older (mean age, 60.3 years), but were younger than those in cluster 3. Cluster 2 included patients with very high total IgE levels (average ± SD, 2332.8 ± 2534.1 IU/mL) and many environmental allergies. Subjects in this cluster were polysensitized, and >90% had allergies to molds, dust mites, and pollens. Cluster 3 included the oldest subjects, with an average age of 66.6 years. These subjects had high total IgE levels (average ± SD, 1022.2 ± 2875.1 IU/mL) but had few environmental allergies; the mean total number of positive allergen tests was 3.0 ± 3.3. These subjects were most commonly allergic to pet dander (69.2%), trees (46.1%), and weeds (46.1%). Subjects in cluster 3 also had the highest blood eosinophil levels (1253.1 ± 1752.6 cells/μL). This cluster also had the lowest lung function, both FEV_1 and FVC% predicted.

All of the clusters were characterized by need for many courses of prednisone (average of >4 per year), and all had reduction in number of courses after biologic treatment that was not statistically different between the groups. However, asthma control, as measured by ACT score, was different at baseline between the clusters with the highest ACT score of 14.5 ± 3.9 for cluster 1 and the lowest score of 11.0 ± 2.8 for cluster 3. After biologic therapy, cluster 3 had the greatest improvement in asthma control (ACT change of 8.8 ± 3.5), while cluster 1 had the lowest change in ACT score (4.7 ± 3.9).

DISCUSSION

Asthma in the elderly has not been as well studied as asthma in younger populations. Prior studies have demonstrated that elderly people with asthma have lower T_H2 inflammation compared to younger patients, which raises the question of whether their disease might also respond to anti-T_H2 biologic therapy.[4,20-22] In our cohort, we did not observe significant differences in markers of T_H2 inflammation in elderly versus young subjects for blood eosinophil levels, total IgE, or allergic sensitization. This may

TABLE III. Biologic changes before and after treatment

Characteristic	D-Y (n = 13)	Post vs pre *P* value	D-E (n = 13)	Post vs pre *P* value	E vs Y *P* value	B-Y (n = 13)	Post vs pre *P* value	B-E (n = 17)	Post vs pre *P* value	E vs Y *P* value
Change in ACT score	4.5 ± 4.3	.003	6.1 ± 4.1	.002	.358	7.8 ± 6.6	<.001	6.6 ± 4.2	<.001	.367
Change in no. of asthma exacerbations in past year*	−0.1 ± 1.6	.865	−0.7 ± 1.6	.145	.338	−1.5 ± 1.5	.003	−1.5 ± 1.8	.003	.911
Change in no. of acute courses of prednisone in past year	−2.8 ± 4.4	.039	−2.0 ± 2.6	.016	.559	−3.8 ± 2.3	<.001	−3.9 ± 3.5	<.001	.973
Change in subjects with daily prednisone receipt, % (no.)	−15.4 (−2)	.678	−7.69 (−1)	>.999	.793	−15.4 (−2)	.593	−23.5 (−4)	.044	.072
Subjects needing daily prednisone	(n = 6)		(n = 4)			(n = 3)		(n = 4)		
Change in daily prednisone dose (mg)†	−0.8 ± 10.2	.704	−5.6 ± 9.7	.328	.477	−6.7 ± 5.8	.183	−28.8 ± 25.9	.235	.187
Subjects with posttreatment spirometry	(n = 5)		(n = 6)			(n = 6)		(n = 11)		
ΔFVC (L)	−0.1 ± 0.3	.684	0.3 ± 0.3	.042	.056	0.3 ± 0.6	.249	0.3 ± 0.5	.067	.948
ΔFVC (%)	−3.0 ± 9.0	.498	4.0 ± 15.5	.554	.377	7.2 ± 14.0	.265	8.5 ± 12.7	.052	.856
ΔFEV_1 (L)	−0.6 ± 1.1	.241	−0.1 ± 0.6	.832	.311	0.5 ± 0.5	.095	−0.1 ± 0.7	.707	.102
ΔFEV_1 (%)	−15.8 ± 29.1	.237	0.5 ± 21.3	.956	.296	12.0 ± 14.6	.100	5.1 ± 12.8	.215	.356
ΔFEV_1/FVC (%)	17.1 ± 46.1	.373	4.2 ± 8.3	.264	.568	3.0 ± 11.2	.546	−3.1 ± 5.2	.076	.255

Data are presented as mean ± SDs unless otherwise indicated. *B-E,* Benralizumab–elderly; *B-Y,* benralizumab–young; *D-E,* dupilumab–elderly; *D-Y,* dupilumab–young; *E,* elderly; *Y,* young.

*Excluding subjects not receiving daily prednisone.

†Excluding subjects without follow-up spirometry after receipt of biologic treatment.

TABLE IV. Cluster analysis

Characteristic	Cluster 1 (n = 32)	Cluster 2 (n = 11)	Cluster 3 (n = 13)	*P* value
Age (years)	55.5 ± 16.8	60.3 ± 14.7	66.6 ± 12.2	.071
Asthma duration (years)	19.7 ± 16.7	35.7 ± 20.7	26.7 ± 18.9	.040
BMI (kg/m^2)	34.2 ± 10.6	31.9 ± 9.5	35.9 ± 12.0	.668
Baseline ACT score	14.5 ± 3.9	13.6 ± 3.5	11.0 ± 2.8	.015
Baseline acute no. of prednisone courses in past year	4.7 ± 2.9	4.2 ± 3.8	4.3 ± 3.1	.836
Total IgE (IU/mL)	393.0 ± 777.9	2332.8 ± 2534.1	1022.2 ± 2875.1	.014
Eosinophil level (cells/μL)	701.5 ± 486.2	480.0 ± 292.9	1253.1 ± 1752.6	.099
FVC (%)	88.2 ± 15.3	73.4 ± 20.6	60.3 ± 11.3	<.001
FEV_1 (%)	83.2 ± 16.4	63.0 ± 17.0	55.8 ± 11.6	<.001
FEV_1/FVC (%)	72.3 ± 15.6	66.6 ± 11.0	71.1 ± 10.4	.505
$FEV_1\Delta BD$ (%)	6.3 ± 9.1	10.8 ± 8.8	12.8 ± 11.1	.116
$FEV_1\Delta BD$ (mL)	157.3 ± 240.5	194.4 ± 162.4	178.3 ± 178.2	.889
Subjects with environmental allergies, % (no.)	69 (22)	100 (11)	92 (12)	.037
Mold allergy (%)	28.1	90.1	15.4	<.001
Dust mite allergy (%)	37.5	100	23.1	<.001
Pet dander allergy (%)	40.6	81.8	69.2	.031
Tree allergy (%)	28.1	100	46.1	<.001
Grass allergy (%)	31.2	90.1	7.7	<.001
Weed allergy (%)	28.1	100	46.1	<.001
Cockroach allergy (%)	25.0	36.4	15.4	.496
Total no. of environmental allergies	3.1 ± 4.2	16.3 ± 6.4	3.0 ± 3.3	<.001
ACT score change after treatment	4.7 ± 3.9	7.0 ± 2.8	8.8 ± 3.5	.004
Acute no. of prednisone courses change after treatment	−3.5 ± 3.6	−3.2 ± 3.6	−2.5 ± 2.6	.689

Data are presented as mean ± SDs unless otherwise indicated. *BD*, Bronchodilator.

in part be due to selection bias; all of the people with asthma selected for this study had elevated eosinophils in ranges to meet eligibility criteria for receipt of dupilumab and benralizumab. However, there was significant variability in blood eosinophil levels and total IgE in this group, and there was no significant relationship of these markers with age based on linear regression analysis (see Fig E1 in the Online Repository available at www.jaci-global.org).

As a result, our cohort of elderly people with asthma appears to have similar levels of T_H2 inflammation as their younger counterparts. A similar finding was recently reported by Suzukawa et al in a Japanese population, so the previous findings that the elderly have less T_H2 inflammation may not be generalizable to all populations.[20]

The only statistical differences between age groups were lung function measures and age at asthma onset. The former is expected, given normal decline in lung function over time and potential airway remodeling. The later age at onset in elderly subjects could be partially explained by a delay in diagnosis, differences in environmental exposures early in life between the

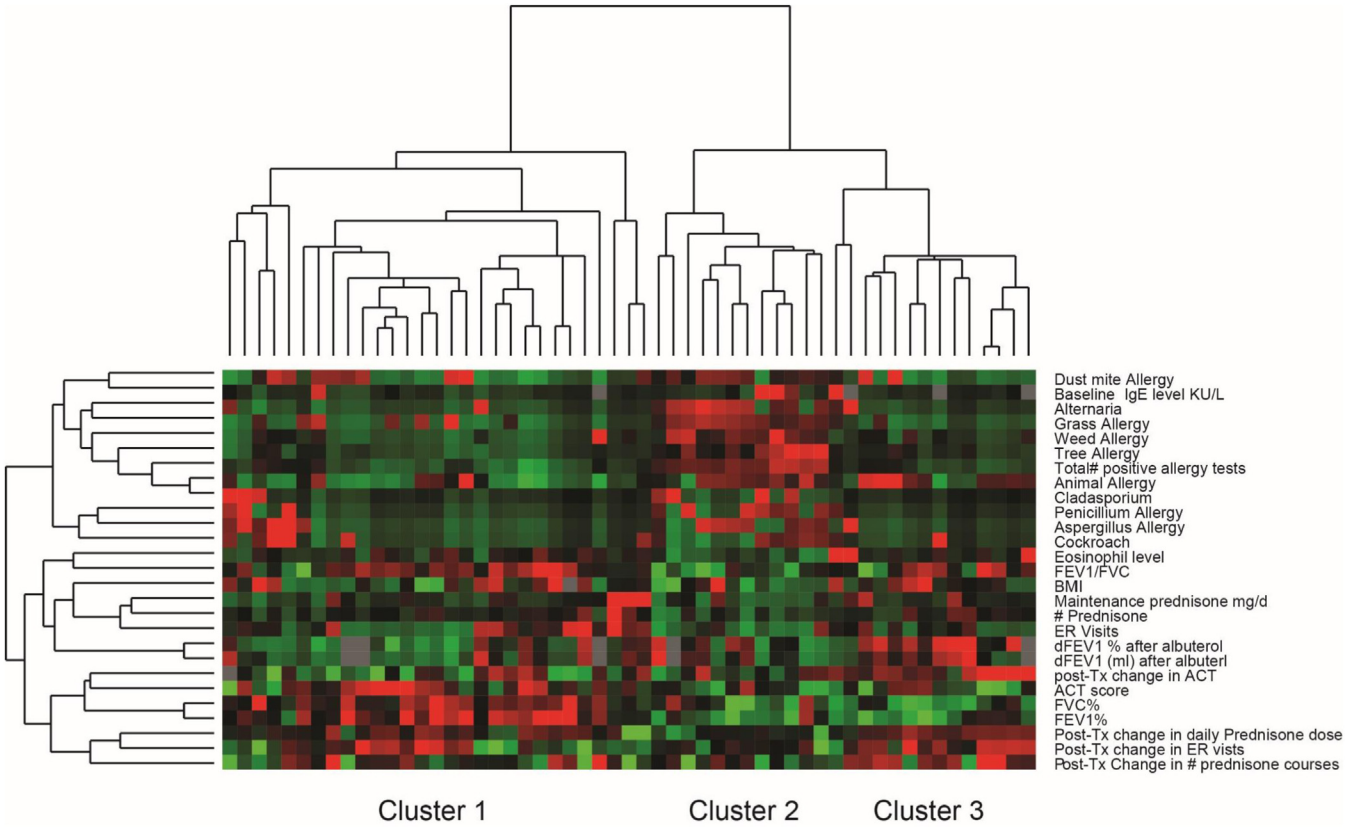

FIG 1. Heat map of cluster analysis of clinical/laboratory variables and treatment response. Three clusters were identified with different clinical features and treatment responses.

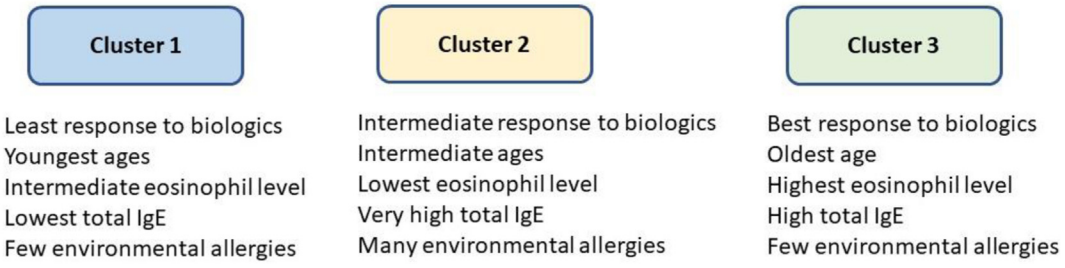

FIG 2. Clinical and laboratory characteristics of different treatment-responsive clusters.

2 groups, recall bias, or a fundamentally distinct phenotype. Age-related immune senescence has also been proposed to play a role in adult-onset asthma.[23,24] Similarities in T_H2 markers between the elderly and younger groups suggest that this is not the case in our population, but our study was limited by the biomarkers available for clinical use (blood eosinophil level, total IgE level, specific IgE to aeroallergens).

Disease in both age groups responded well to biologic treatment (based on change in ACT scores, decreased number of exacerbations, and decreased prednisone receipt), with similar treatment responses to dupilumab and benralizumab, indicating that elderly people with asthma should be considered for biologic treatments for asthma similarly to their younger counterparts. In fact, according to the clusters we identified, disease of some elderly people with asthma may respond better to biologics than younger patients, at least based on ACT scores (cluster 3). This could be in part because this cluster had the highest level of blood eosinophils, and this has previously been demonstrated to be predictive of antieosinophil biologic therapy response.[13] It is also interesting to note that this cluster also had a high level of total IgE but the lowest number of positive aeroallergen test results. Further study is needed to further characterize this subgroup, but this pattern of blood work results could be a useful tool to predict biologic response.

A study by Di Bona et al on effectiveness of benralizumab in severe eosinophilic asthma utilized a similar cluster analysis approach to identify response subgroups.[25] They identified 4 cluster groups, with 2 groups, both with increased eosinophils and IgE, responding better to benralizumab than groups with only 1 elevated marker. This is consistent with our data of cluster 3, with the highest elevation in eosinophils and IgE responding best to biologic treatment.

Limitations of this study include its retrospective design, the relatively small sample size at a single center, its lack of racial diversity, and the inability to obtain posttreatment lung function in a significant portion of subjects. Our study coincided with the start of the pandemic, and our institution restricted spirometry as a high-risk procedure in the first year of the pandemic. As a result, we focused mainly on ACT scores as the outcome measure. Our study did not rigorously measure adverse effects of biologics. None of the subjects experienced severe adverse effects (allergic reaction, rashes, parasitic infection, severe conjunctivitis, or severe musculoskeletal pain). However, Mir-Ihara et al examined adverse effects of multiple biologics in elderly versus young people with asthma and did not find any significant difference in adverse events in multiple biologics between the 2 populations.[26] The study was also limited by combining subjects treated with dupilumab and benralizumab into a single group for the cluster analysis despite a possible difference in response biomarkers between the 2 biologics.

In conclusion, elderly people with asthma should be considered for biologic therapy no differently than their younger counterparts. There may be subgroups of patients with disease with different biologic responses based on age, allergenicity, and IgE and eosinophil levels that could be used to predict treatment response. More studies need to be done to further characterize asthma phenotypes in the elderly and understand how disease in this age group responds to asthma therapies.

DISCLOSURE STATEMENT

Disclosure of potential conflict of interest: The authors declare that they have no relevant conflicts of interest.

Key messages

- **Disease of elderly people with asthma responds well to biologics.**
- **There are subgroups with different biologic responses based on age, allergenicity, and IgE and eosinophil levels that could be used to predict treatment response.**

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