Original Article

Prevalence of Patients Eligible for Anti-IL-5 Treatment in a Cohort of Adult-Onset Asthma

Pinja Ilmarinen, PhD[a], Leena E. Tuomisto, MD, PhD[a], Onni Niemelä, MD, PhD[b,c], and Hannu Kankaanranta, MD, PhD[a,c]

Seinäjoki and Tampere, Finland

What is already known about this topic? Antibodies against the IL-5 pathway have been developed for the treatment of late-onset eosinophilic corticosteroid-resistant asthma. Estimates of 5% to 10% on the prevalence of severe asthma have been proposed with unclear basis.

What does this article add to our knowledge? The prevalence of severe asthma was 5.9%, and 2% fulfilled the criteria for anti-IL-5 therapy in an unselected cohort of adult-onset asthma. Only 1 patient met criteria for both groups, and both groups represent a high burden to health care.

How does this study impact current management guidelines? This study on the prevalence of severe asthma and anti-IL-5 eligible patients indicates that of 100 patients with adult-onset asthma, 6 have severe asthma and 2 are eligible to anti-IL-5 therapy.

BACKGROUND: Antibodies against the IL-5 pathway have been developed for the treatment of late-onset eosinophilic corticosteroid-resistant asthma. However, the prevalence of severe asthma and the proportion of patients who could benefit from such treatment among the general population of asthmatics remain unknown.

OBJECTIVE: To evaluate the prevalence and characteristics of patients eligible to anti-IL-5 treatment and severe asthma in an unselected cohort of adult-onset asthma.

METHODS: Seinäjoki Adult Asthma Study is a 12-year follow-up study of patients with new-onset adult asthma (n = 203). Prevalence was estimated based on information collected at 12-year follow-up visit. Health care use was collected from the whole 12-year follow-up period.

RESULTS: The prevalence of anti-IL-5-treatable patients was 2%, when the following criteria were used: daily use of medium-to-high inhaled corticosteroid (ICS) dose and long-acting β_2-agonist, ≥2 exacerbations/previous year and blood eosinophil count ≥300 cells/μL or fraction of exhaled nitric oxide ≥ 50 ppb. The prevalence of severe asthma, as defined according to European Respiratory Society/American Thoracic Society, was 5.9%, and only 1 patient met criteria for both groups. When compared with anti-IL-5 eligible patients, severe asthmatics were more often current smokers at diagnosis, obese, used higher ICS dose, and had higher blood neutrophils 12 years after diagnosis. Both groups differed from nonsevere asthma by a higher number of all and unplanned respiratory-related visits to health care. Severe asthmatics showed the highest number of hospitalizations.

CONCLUSIONS: In a cohort of unselected consecutive patients with adult-onset asthma, 5.9% fulfilled criteria for severe asthma and 2% qualified for anti-IL-5 treatment. Both groups represent a high burden to health care and specifically targeted treatment could lead to lower use of health care at long term. **(J Allergy Clin Immunol Pract 2019;7:165-74)**

Key words: *Asthma; Adult; Adult-onset; Prevalence; Interleukin-5; Eosinophil; Severe; Mepolizumab; Reslizumab; Benralizumab*

[a]Department of Respiratory Medicine, Seinäjoki Central Hospital, Seinäjoki, Finland
[b]Department of Laboratory Medicine, Seinäjoki Central Hospital, Seinäjoki, Finland
[c]Faculty of Medicine and Life Sciences, University of Tampere, Tampere, Finland

The analysis and write-up of this study was funded by AstraZeneca, Mölndal, Sweden. AstraZeneca was given an opportunity to comment the study report before it was submitted for publication. The Seinäjoki Adult Asthma Study (SAAS) project has been funded by Finnish Anti-Tuberculosis Association Foundation (Helsinki, Finland), Tampere Tuberculosis Foundation (Tampere, Finland), Jalmari and Rauha Ahokas Foundation (Helsinki, Finland), the Research Foundation of the Pulmonary Diseases (Helsinki, Finland), the Competitive State Research Financing of the Expert Responsibility Area of Tampere University Hospital (Tampere, Finland), and the Medical Research Fund of Seinäjoki Central Hospital (Seinäjoki, Finland); neither AstraZeneca nor the other funders have any involvement in the planning or execution of the SAAS study.

Conflicts of interest: P. Ilmarinen, L. E. Tuomisto, and H. Kankaanranta report a grant from AstraZeneca related to the submitted work. Outside the submitted work P. Ilmarinen reports payment for lectures from Mundipharma, Orion Pharma, and Astra Zeneca. L. E. Tuomisto reports grants from Chiesi Pharma AB and Orion Pharma and payment for lectures from Filha ry, Astra Zeneca, and Mundipharma. O. Niemelä reports no conflict of interest. H. Kankaanranta reports personal fees and nonfinancial support from Almirall, AstraZeneca, and Boehringer-Ingelheim; personal fees from Chiesi Pharma AB, GlaxoSmithKline, Leiras-Takeda, MSD, Novartis, Mundipharma, Medith, Resmed Finland, Roche, and Orion Pharma; and nonfinancial support from Intermune.

Received for publication October 4, 2017; revised May 22, 2018; accepted for publication May 23, 2018.

Available online June 9, 2018.

Corresponding author: Pinja Ilmarinen, PhD, Department of Respiratory Medicine, Seinäjoki Central Hospital, FIN-60220 Seinäjoki, Finland. E-mail: pinja.ilmarinen@epshp.fi.

2213-2198

https://doi.org/10.1016/j.jaip.2018.05.032

Abbreviations used
ACT- Asthma Control Test
ATS- American Thoracic Society
CI- Confidence interval
ERS- European Respiratory Society
FeNO- Fraction of exhaled nitric oxide
FEV_1- Forced expiratory volume in 1 second
GINA- Global Initiative for Asthma
ICS- Inhaled corticosteroid
LABA- Long-acting β_2-agonist
OCS- Oral corticosteroid
SA- Severe asthma
SAAS- Seinäjoki Adult Asthma Study

Recently, asthma has been considered to manifest in different phenotypes requiring different treatment approaches. Age at onset is a critical factor separating different phenotypes. Asthma starting in childhood often coexists with atopy/allergy, is dominated by Th2 inflammation, and responds well to therapy with inhaled corticosteroids (ICS). However, asthma starting at adulthood is more often nonatopic, less responsive to ICS treatment, and has less favorable prognosis. Adult-onset asthma has been proposed to consist of subphenotypes such as obesity-related, smoking, severe obstructive, mild-to-moderate/well-controlled, and atopic asthma.[1-3] Late-onset eosinophilic (often severe) asthma has been considered to be one of the adult-onset asthma phenotypes.[1,3]

Late-onset eosinophilic asthma is characterized by persistent eosinophilic airway inflammation despite the use of corticosteroid therapy. It is associated with a lower rate of allergy; frequently there is no obvious family history of asthma and it is often severe from onset.[3] Many of these patients suffer from frequent exacerbations and may respond poorly to inhaled steroid therapy. This condition is associated with substantial health care costs due to unplanned health care visits, emergency department visits, and hospital admissions. Previous studies have emphasized the importance of eosinophils in mediating exacerbations,[4] and therefore the resolution of eosinophilic inflammation has been suggested as a promising therapeutic strategy to reduce exacerbations. IL-5 is a critical cytokine for eosinophil maturation, survival, and activation.[5,6] Neutralization of its effects by anti-IL-5 antibodies such as mepolizumab or reslizumab leads to the reduced number of eosinophils. Benralizumab is an anti-IL5 receptor antibody that depletes eosinophils through antibody-dependent cell-medicated cytotoxicity. In clinical trials in patients with severe glucocorticoid-resistant eosinophilic asthma, these antibodies decreased exacerbation rate, had a glucocorticoid-sparing effect, and improved asthma-related quality of life and lung function.[7-11]

Typically, inclusion criteria for anti-IL-5 studies have been the use of moderate-to-high ICS dose together with long-acting β_2-agonist (LABA) or another controller and at least 2 exacerbations requiring oral corticosteroid (OCS) during the previous year.[7-11] For blood eosinophil levels, $\geq$150, $\geq$300, or $\geq$400 cells/μL have been used as a criterion for inclusion or alternatively, fraction of exhaled nitric oxide (FeNO) $\geq$50 ppb, or sputum eosinophil count $\geq$3%.[7-11] The proportion of patients with eosinophilic asthma who could benefit from anti-IL-5 therapy among a general population of adult-onset asthmatics has, however, remained unknown.

The proportion of patients with severe asthma (SA) has been approximated to be 5% to 10% among all patients with asthma.[12] However, there have been difficulties in assessing the true prevalence due to the lack of accurate definition[13] and exclusion of significant patient groups (smoking, aged individuals, and patients with significant comorbidities) from most published clinical cohorts. A European Respiratory Society/American Thoracic Society (ERS/ATS) committee defined SA as asthma requiring treatment with high ICS dose together with add-on medication or OCS to prevent it from becoming uncontrolled or which remains uncontrolled despite this therapy.[12]

This study was carried out to evaluate the proportion of patients fulfilling combinations of possible clinical criteria for the use of anti-IL-5 therapies as well as the prevalence of SA in a real-life cohort of patients with clinically defined adult-onset asthma 12 years after diagnosis. Another aim was to compare the clinical characteristics of patients with non-SA and SA and those fulfilling criteria for anti-IL-5 therapy.

METHODS

Study design and patients

This study is part of Seinäjoki Adult Asthma Study (SAAS). SAAS (ClinicalTrials.gov ID NCT02733016) is a prospective, single-center (Seinäjoki Central Hospital, Seinäjoki, Finland) 12-year follow-up study of a cohort of patients having new-onset asthma diagnosed at adult age ($\geq$15 years). Institutional permissions were obtained and the participants gave written informed consent to the study protocol approved by the ethics committee of Tampere University Hospital, Tampere, Finland. More than 94% of the patients diagnosed with novel asthma in the study site were recruited to the study.[14] In 2001, the study population represented >38% of novel diagnoses of asthma made to adults in the whole geographical area. The protocol, inclusion and exclusion criteria, and the background data of the SAAS study have been published separately.[14] Briefly, asthma was diagnosed by a respiratory specialist during 1999-2002 based on typical symptoms, and diagnosis was confirmed by objective lung function measurements.[14] After diagnosis, the patients were treated and monitored by their own physician according to the principles of Finnish Asthma Program[15] and guidelines.[16] The total cohort consisted of 257 patients and 203 patients returned to the 12-year follow-up visit.[17] At this visit, asthma status and control, comorbidities, and medication were evaluated using structured questionnaires, and lung function and inflammatory parameters were measured. The basic characteristics, 12-year prognosis (remission and asthma control), detailed smoking characteristics, and comorbidities of the study cohort have been previously published.[17-19]

Data were also gathered from all asthma-related visits to health care (primary care, private health care, and hospital clinics), exacerbations, acute respiratory tract infections, and hospitalizations during the whole 12-year follow-up period. Data from the 12-year follow-up visit and the time in between the visits were used in assessing the proportion of anti-IL-5 eligible patients and SA. To assess adherence in these patients, the numbers of ICS-containing inhalers/canisters and OCS bought from pharmacies in 2012-2013 were retrieved from Social Insurance Institution of Finland.

Exacerbations and medication

The number of exacerbations was self-reported employing a structured questionnaire filled at 12-year follow-up visit or evaluated from the patient records (previous year). Medication for asthma was

self-reported at structured questionnaire. If the information was missing, medication was evaluated from the previous asthma-related visit to health care.

Lung function, inflammatory parameters, and other clinical measurements

Lung function measurements were performed with a spirometer according to international recommendations.[20] Detailed information on the lung function measurements, determination of inflammatory parameters, comorbidities, and on other clinical measurements can be found in this article's Online Repository at www.jaci-inpractice.org.

Severe asthma

SA was defined according to the ATS/ERS Task Force as asthma requiring treatment with high ICS dose together with add-on medication or OCS to prevent it from becoming uncontrolled or which remains uncontrolled despite this therapy.[12] Uncontrolled asthma was defined as one of the following at the 12-year follow-up visit: (1) poor symptom control (Asthma Control Test [ACT] score < 20), (2) frequent exacerbations ($\geq$2 bursts of OCS in the previous year), (3) serious exacerbations ($\geq$1 hospitalization in the previous year due to asthma), and (4) airflow limitation (pre−forced expiratory volume in 1 second (FEV_1) $<$ 80% predicted).[12]

Primary and secondary endpoints

The primary endpoint of this study was to assess the proportion of patients who could benefit from anti-IL-5 therapy, that is, patients fulfilling the following criteria: (1) daily use of medium-to-high ICS dose ($\geq$800 μg budesonide equivalent) and LABA, (2) $\geq$2 exacerbations per previous year before the 12-year follow-up visit, and (3) blood eosinophil level $\geq$300 cells/μL or FeNO $\geq$50 ppb at the 12-year follow-up visit in the SAAS cohort.

The secondary endpoints were to assess the proportion of patients with SA (fulfilling ERS/ATS criteria) and the proportion of patients fulfilling different combinations of the clinical criteria related to eligibility to anti-IL-5 treatment. A further aim was to see whether anti-IL-5 eligible patients and SA overlap. A comparison of basic and clinical characteristics and health care use of patients fulfilling criteria for anti-IL-5 therapy to those fulfilling criteria of SA and to the patients with non-SA was also assessed as a secondary endpoint.

Statistical analysis

Continuous data are expressed as mean ± standard deviation or median and interquartile range. A comparison between 3 groups was performed by using 1-way analysis of variance with Tukey's post hoc, Kruskal-Wallis, or χ^2 test. Bootstrapping[21] was used to estimate 95% confidence interval (CI) for the primary/secondary outcome estimate. By this method, 1000 samples with replacement were drawn from the original dataset of the same size as the original sample allowing us to quantify more precisely the accuracy of primary outcome estimate. Statistical analyses were performed using SPSS software, version 23 (IBM SPSS, Armonk, NY). P value $< .05$ was regarded as statistically significant.

RESULTS

Patient characteristics

The characteristics of patients at 12-year follow-up visit are shown in Table I. Patients were mostly females, nonatopic, overweight, and approximately half had smoking history. The proportion of daily ICS users was 76.4%. Asthma was uncontrolled in 29.6% of patients. Two patients (1%) were using continuous OCS for asthma indication at 12-year follow-up visit, and 2 patients (1%) for other indication.

TABLE I. Characteristics of patients at 12-year follow-up as previously reported[17]

Characteristic	Cohort at follow-up (n = 203)
Age (y)	58 (14)
Male gender, n (%)	85 (41.9)
BMI (kg/m^2)	28.1 (24.4-31.2)
BMI <25, n (%)	59 (29.0)
BMI 25-29.99, n (%)	73 (36.0)
BMI ≥30, n (%)	71 (35.0)
Smokers (incl. ex), n (%)	107 (52.7)
Smoking history, pack-year	16 (7-30)
Total IgE (kU/L)	61 (24-163)
Daily ICS use, n (%)	155 (76.4)
Blood eosinophils (10^9/L)	0.17 (0.10-0.27)
Blood eosinophils ≥0.3, n (%)	35 (17.3)
Pre-BD FEV_1 %	86 (76-96)
Pre-BD FEV_1 <80% predicted, n (%)	61 (30.0)
Pre-BD FVC %	96 (87-106)
Pre-BD FEV_1/FVC	0.73 (0.66-0.79)
Post-BD FEV_1 %	90 (80-98)
Post-BD FEV_1 <80% predicted, n (%)	48 (23.6)
Post-BD FVC %	99 (88-107)
Post-BD FEV_1/FVC	0.75 (0.69-0.80)
D_{LCO} (%)	92 (19)
D_{LCO}/VA (%)	94 (17)
AQ20 score	4 (2-7)
ACT score	22 (19-24)
ACT score <20, n (%)	56 (27.6)

ACT, Asthma Control Test; *AQ20*, Airways Questionnaire 20; *BD*, bronchodilator; *BMI*, body mass index; D_{LCO}, diffusing capacity; D_{LCO}/VA, diffusing capacity adjusted by the alveolar volume; FEV_1, forced expiratory volume in 1 s; *FVC*, forced vital capacity; *GINA*, Global Initiative for Asthma; *ICS*, inhaled corticosteroid.
Shown are mean (standard deviation) or median (25th-75th percentile).
Asthma control was evaluated by GINA 2010.[22]

Patients eligible to anti-IL-5 therapy

The primary endpoint of this study was fulfilled by 4 of 203 (2% of patient cohort) (Figure 1, *A*). With blood eosinophil cutoff set from 150 to 400 cells/μL, proportion varied between 1% and 3% (Figure 1, *A*). When criteria for exacerbations and medication use were removed, 20.3% of patients fulfilled criteria for blood eosinophils ≥300 cells/μL or FeNO ≥50 ppb. With blood eosinophil cutoffs from 150 to 400, proportion varied from 58.7% to 14.5% (Figure 1, *B*).

Sometimes asthma exacerbation may be confused with acute respiratory tract infection, and consequently, antibiotics or doubling of ICS dose is prescribed instead of OCS. Therefore, we applied an explorative approach. In addition to the patients who were prescribed OCS at least twice per year, the extended definition included also patients with ≥2 acute visits to health care where antibiotics or doubling of ICS dose was prescribed during the previous year. In the cohort, 11.3% of the patients fulfilled criteria for extended definition of exacerbations and used medium or high ICS dose and LABA for their daily therapy. When criteria for elevated eosinophils (≥300 cells/μL) or FeNO (≥50 ppb) were added, 3% (n = 6) patients remained.

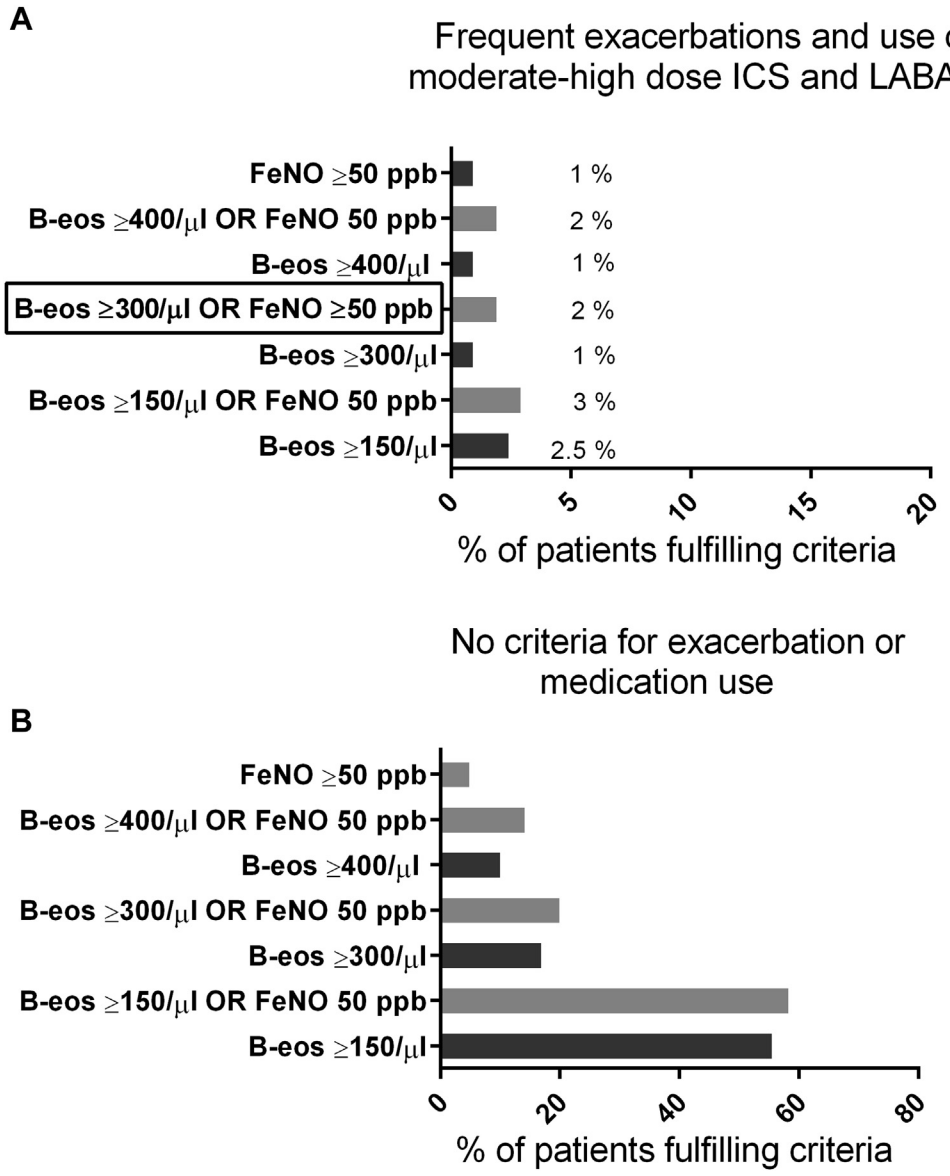

FIGURE 1. Prevalence of patients fulfilling different combinations of the clinical criteria related to eligibility to anti-IL-5 therapy in the cohort of adult-onset asthma (n = 203). **A**, Prevalence of patients fulfilling different criteria for the level of blood eosinophils or FeNO, exacerbations, and use of medication. **B**, Prevalence of patients fulfilling different criteria for the level of blood eosinophils (B-eos) or FeNO without the need to fulfill criteria for frequent exacerbations or use of medium-to-high ICS dose for asthma. *FeNO*, Fraction of exhaled nitric oxide; *ICS*, inhaled corticosteroid; *LABA*, long-acting β_2-agonist.

Prevalence of severe asthma

We used the ATS/ERS Task Force[12] definition of SA. Of the patients, 14 (6.9%) were using high-intensity medication for asthma (high ICS dose plus second controller and/or OCS for ≥50% of the previous year) and 12 (5.9%) still remained uncontrolled fulfilling criteria of SA.[12] The proportion of patients defined as uncontrolled according to the ACT score <20, ≥2 exacerbations last year, or prebronchodilator FEV_1 <80% predicted are shown in Figure 2. There was only 1 patient who fulfilled criteria for both SA and anti-IL-5 eligibility due to different criteria for ICS dose, and in further analyses, this patient was included only into the anti-IL-5 group. Three anti-IL-5 eligible patients were not regarded as having SA due to ICS dose not classified as high according to ERS/ATS criteria.

Characteristics of patients with nonsevere asthma, severe asthma, and those eligible to anti-IL-5 therapy

Patients with non-SA, SA, and those eligible to anti-IL-5 therapy were similar in respect to gender, age of asthma onset, and lung function parameters at diagnosis and 12-year follow-up visit (Table II and Table E1, available in this article's Online Repository at www.jaci-inpractice.org). Patients with SA were more often current smokers at diagnosis (Table E1) and had

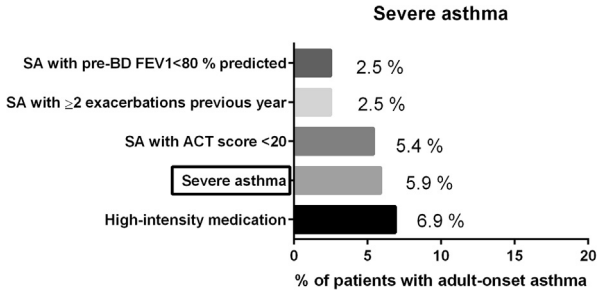

FIGURE 2. Prevalence of severe asthma (SA) in patients with adult-onset asthma. High-intensity medication refers to daily use of high ICS dose together with second controller (LABA, LTRA, or theophylline), or systemic steroid for at least 50% of the previous year. Definition of severe asthma includes the use of high-intensity medication and uncontrolled asthma as defined by ACT score <20, ≥2 exacerbations previous year, and/or pre-bronchodilator FEV_1 <80% predicted. *ACT*, Asthma control test; *FEV_1*, forced expiratory volume in 1 second; *ICS*, inhaled corticosteroid; *LABA*, long-acting β_2-agonist; *LTRA*, leukotriene receptor antagonist.

higher body mass index at the 12-year follow-up visit (Table II) when compared with the 2 other groups. In addition, patients with SA had more often systemic rheumatic disease, thyroid disorder, or treated dyspepsia as comorbidity at 12-year follow-up visit (Table E2, available in this article's Online Repository at www.jaci-inpractice.org). Differences existed in parameters related to asthma medication, exacerbations, symptoms, and asthma control, which was expected because these parameters were used in the categorization of patients (Tables II and III). FeNO and total IgE level were the highest in patients fulfilling criteria to anti-IL-5 therapy and lowest in patients with SA (Table II). Instead, blood neutrophils were highest in patients with SA and lowest in anti-IL-5 eligible patients at 12-year follow-up visit (Table II). To assess adherence to steroid treatment the numbers of ICS-containing inhalers/canisters as well as packages of OCS bought from pharmacies around the follow-up visit (2012-2013) were retrieved. All anti-IL-5-eligible patients had bought several ICS-containing inhalers annually (mean 8.2/year) and at least 1 OCS package (mean bought total OCS dose 1688 mg prednisolone equivalent/2 years corresponding to >5 ten-day courses of 30 mg oral prednisolone daily). One patient classified as having SA had low adherence at the follow-up visit but better adherence in long term. All of the remaining 10 patients classified as having SA had bought (2012-2013) annually several ICS-containing inhalers/canisters (mean 13.5/year) and 8 had bought at least 1 package of OCS. Two were on a continuous OCS therapy. The mean bought total OCS dose was 1975 mg prednisolone equivalent/2 years in those 6 patients not being on a continuous OCS therapy.

Use of health care in patients with nonsevere asthma, severe asthma, and those eligible to anti-IL-5 treatment

During the 12-year follow-up period, the use of health care was different between non-SA, SA, and anti-IL-5 groups: number of all asthma-related visits to health care and number of unplanned visits (visits due to exacerbations and respiratory tract infections) were higher in SA and anti-IL-5 eligible patients when compared with nonsevere patients (Figure 3). Patients with SA also had more frequent planned visits to health care than patients with non-SA (Figure 3, *B*). However, there was no statistically significant difference between SA and anti-IL-5 eligible patients in the number of all planned or unplanned health care visits. In addition, all anti-IL-5 eligible patients had ≥3 sick leaves in the past 2 years before the 12-year follow-up visit, whereas the proportion was 16.7% in patients with SA (Table III). However, patients with SA had most hospitalizations during the whole 12-year follow-up period (Table III).

In total, anti-IL-5 eligible patients accounted for 4.7% of all asthma-related visits to health care and 7.9% of unplanned asthma-related visits to health care, being 2-to 4-fold higher than expected. Patients with SA accounted for 13% to 13.9% of all and unplanned asthma-related visits to health care being more than double than would be expected. Interestingly, the most drastic difference was found in hospitalizations: although anti-IL-5 eligible patients accounted for only 2% of all hospital admissions (the same as expected), patients with SA accounted for 31% of all hospitalizations, which is 5-fold more than expected.

Estimation of confidence interval for the prevalence of anti-IL-5 eligible patients and severe asthma

Of the total cohort of adult-onset asthma, 2% were eligible for anti-IL-5 therapy and 5.9% were classified as having SA. By using the bootstrapping method, the 95% CI limits for these estimates are 0.5% to 4.1% for anti-IL-5 eligible patients and 2.9% to 9.4% for SA.

DISCUSSION

In this study, we have evaluated the prevalence of patients eligible for anti-IL-5 therapy in a cohort of adult-onset asthma with inclusion of all levels of asthma severity and patient groups such as smokers and those with comorbidities. Of the total cohort, 2% were found to fulfill the criteria for anti-IL-5 eligibility, namely daily use of medium-to-high ICS dose and LABA, at least 2 exacerbations during the previous year, blood eosinophils ≥300 cells/μL, and/or FeNO ≥50 ppb. In addition, we evaluated the prevalence of SA as defined by the ERS/ATS criteria in this cohort, being 5.9% of all patients (Figure 4). Furthermore, only 1 patient fulfilled criteria for both groups (Figure 4). Patients with SA and those who fulfilled criteria for anti-IL-5 eligibility were separated from nonsevere patients by higher use of health care (all and unplanned asthma-related visits to health care), showing that both of these patient groups represent a major burden to health care. In addition, when comparing patients with SA with anti-IL-5 eligible patients, severe asthmatics were more often current smokers at diagnosis and were obese, used higher ICS dose, and had higher blood neutrophils 12 years after diagnosis.

Epidemiological studies on different asthma phenotypes are rare. To our knowledge, this is the first study where the prevalence of anti-IL-5-treatable asthma among patients with adult-onset asthma was evaluated. The prevalence of anti-IL-5 eligibility among SA has been assessed in a Belgian SA cohort including smoking patients and those with comorbidities and 30% of patients with SA were found to be eligible for anti-IL-5.[23] The criteria for anti-IL-5 eligibility were similar to

TABLE II. Characteristics of patients with nonsevere asthma, severe asthma, and those eligible† to anti-IL-5 therapy at 12-year follow-up visit

Characteristic	Nonsevere	Severe	Eligible to anti-IL-5	*P* value
No. of patients	188	11	4	
Female, n (%)	108 (57.4%)	7 (63.6%)	3 (75.0%)	.726
Age at onset (y)	47 (37-56)	52 (41-55)	49 (40-70)	.748
BMI (kg/m^2)	28.4 (5.5)	32.5 (5.8)*	25.6 (5.1)	**.033**
With smoking history, n (%)	97 (51.6 %)	8 (72.7%)	2 (50.0%)	.392
Current smokers, n (%)	26 (13.8%)	4 (36.4%)	0	.086
Pack-years of smokers	16 (7-30)	18 (15-21)	31 (42)	.799
Atopic, n (%)	63 (37.3%)	3 (30%)	2 (50.0%)	.778
Lung function				
Pre-BD FEV_1 (% pred)	86 (18)	81 (19)	79 (16)	.557
Post-BD FEV_1 (% pred)	89 (17)	83 (19)	81 (18)	.399
Post-FEV_1/FVC	0.76 (0.69-0.81)	0.72 (0.68-0.74)	0.71 (0.51-0.79)	.150
DL_{CO}/VA, % predicted	96 (16)	92 (18)	87 (25)	.462
Daily medication				
ICS, n (%)	140 (74.5%)	11 (100%)	4 (100%)	.081
LABA, n (%)	82 (43.6%)	10 (90.9%)*	4 (100%)	**.001**
LTRA, n (%)	22 (11.7%)	5 (45.5%)*	0	**.005**
LAMA, n (%)	5 (2.7%)	2 (18.2%)*	1 (25%)*	**.003**
Theophylline, n (%)	2 (1.1%)	2 (18.2%)	0	**<.001**
No. of add-on drugs	1 (0-1)	2 (1-2)*	1.5 (1-2)	**<.001**
ICS dose‡	786 (406)	2140 (844)*	1333 (577)**	**<.001**
High ICS dose,§ n (%)	4 (2.1%)	11 (100%)*	1 (25 %)*,**	**<.001**
Systemic steroid, n (%)	1 (0.5%)	3 (27.3%)	0	**<.001**
Symptoms/quality of life				
AQ20 score	4 (1-7)	8 (4-15)*	8 (3-10)	**.005**
ACT score	22 (20-24)	16 (10-19)*	18.5 (13.3-23.8)	**<.001**
ACT $\geq$ 20	144 (76.6%)	1 (9.1%)*	2 (50%)	**<.001**
ACT 16-19	26 (13.8%)	5 (45.5%)	0	
ACT < 16	18 (9.6%)	5 (45.5%)	2 (50%)	
Asthma control, GINA 2010, n (%)				.055
Controlled	68 (36.2%)	1 (9.1%)	0	
Partially controlled	69 (36.7%)	4 (36.4%)	1 (25.0%)	
Uncontrolled	51 (27.1%)	6 (54.5%)	3 (75.0%)	
Inflammation				
Blood eosinophils ($\times 10^9$/L)	0.17 (0.10-0.27)	0.13 (0.10-0.28)	0.46 (0.12-0.71)	.203
Blood eosinophils $\geq$ 0.3 $\times 10^9$/L	31 (16.6%)	2 (18.2%)	2 (50.0%)	.217
FeNO (ppb)	11 (5-18)	8 (6-15)	41 (13-56)	**.043**
FeNO $\geq$ 50 ppb	8 (4.5%)	0	2 (50.0 %)*,**	**<.001**
Total IgE (kU/L)	61 (25-161)	22 (9-76)	307 (67-552)	**.038**
Blood neutrophils ($\times 10^9$/L)	3.9 (1.4)	6.3 (2.5)*	2.5 (0.6)**	**<.001**

ACT, Asthma Control Test; *AQ20*, Airways Questionnaire 20; *ATS*, American Thoracic Society; *BD*, bronchodilator; *BMI*, body mass index; *D_{LCO}/VA*, diffusing capacity adjusted by the alveolar volume; *ERS*, European Respiratory Society; *FeNO*, fraction of exhaled nitric oxide; *FEV_1*, forced expiratory volume in 1 s; *FVC*, forced vital capacity; *GINA*, Global Initiative for Asthma; *ICS*, inhaled corticosteroid; *LAMA*, long-acting muscarinic receptor antagonist; *LABA*, long-acting β_2-agonist; *LTRA*, leukotriene receptor antagonist.
Shown are n (%) for categorical variables, and mean (standard deviation) or median (interquartile range) for continuous variables.
Bold indicates statistical significance ($P < .05$).
*$P < .05$ vs nonsevere.
**$P < .05$ vs severe group.
†Anti-IL-5 eligible patients refer to those who fulfill criteria for the primary endpoint of this study (daily use of medium-to-high ICS dose and LABA, ≥2 exacerbations per previous year, and blood eosinophil level ≥ 300 cells/μL or FeNO ≥ 50 ppb).
‡ICS dose as budesonide equivalents (μg).
§Based on ERS/ATS criteria.[14]

the criteria used in the primary endpoint of our study but with higher ICS dose requirement (≥880 μg fluticasone equivalent) and with inclusion of sputum eosinophils ≥3%. A multicenter study also assessed eligibility to anti-IL-5 antibodies mepolizumab and reslizumab among "real-world" patients with SA and found eligibilities of 20% and 6% for these agents, respectively.[24] However, the results are difficult to compare with our result due to different patient cohorts (severe vs general) and different criteria used for eligibility (eosinophil count ≥150 for mepolizumab or ≥400 cells/μL for reslizumab vs ≥300 cells/μL in our

TABLE III. Characteristics of patients with nonsevere asthma, severe asthma, and those eligible† to anti-IL-5 therapy during the 12-year follow-up period

Characteristic	Nonsevere	Severe	Eligible to anti-IL-5	*P* value
No. of patients	188	11	4	
Lung function decline per year‡				
ΔFEV‡ (mL)	−46 (36)	−65 (43)	−65 (31)	.152
ΔFEV_1 (% predicted)	−0.5 (1.0)	−1.0 (1.4)	−1.2 (0.9)	.183
Exacerbations				
Use of oral steroid courses§	56 (30.1%)	5 (50%)	4 (100%)*	**.006**
No. of OCS bursts/2 y¶	1 (1-2)	3 (1-7)	5 (3-9)*	**.002**
≥3 sick leaves/2 y#	3 (2.0%)	1 (16.7%)	3 (100%)††*	**<.001**
Use of health care				
Hospitalizations, n	0 (0-0)	2 (0-4)*	0.5 (0-1.75)	**.005**
≥1 hospitalization, any respiratory reason (planned and unplanned)	43 (23.0%)	6 (54.5%)	2 (50.0%)	**.033**
≥1 hospitalization, any respiratory reason (unplanned)	17 (9.1%)	4 (36.4%)*	1 (25.0%)	**.013**
≥1 hospitalization, asthma-related (planned and unplanned)	29 (15.6%)	4 (36.4%)	1 (25.0%)	.185
≥1 hospitalization, asthma-related (unplanned)	10 (5.4%)	1 (9.1%)	0	.774
Hospital days, any respiratory reason (planned and unplanned)	0 (0-0)	2 (0-22)*	1.5 (0-4.5)	**.015**
Hospital days, any respiratory reason (unplanned)	0 (0-0)	0 (0-21)*	0 (0-2)	**.007**
Hospital days, asthma-related (planned and unplanned)	0 (0-0)	0 (0-14)	0 (0-4)	.134
Hospital days, asthma-related (unplanned)	0 (0-0)	0 (0-0)	0 (0-0)	.746

FeNO, Fraction of exhaled nitric oxide; *FEV_1*, forced expiratory volume in 1 s; *ICS*, inhaled corticosteroid; *LABA*, long-acting β_2-agonist; *OCS*, oral corticosteroid.
Shown are n (%) for categorical variables, and mean (standard deviation) or median (interquartile range) for continuous variables.
Bold indicates statistical significance ($P < .05$).
*$P < .05$ vs nonsevere.
†Anti-IL-5 eligible patients refer to those who fulfill criteria for the primary endpoint of this study (daily use of medium-to-high ICS dose and LABA, ≥2 exacerbations per previous year, and blood eosinophil level ≥ 300 cells/μL or FeNO ≥ 50 ppb).
‡Decline in FEV_1 from the point of maximal lung function within 2.5 y after diagnosis (and start of therapy) to the 12-year follow-up visit.
§Patients who have used oral steroid bursts at least once during the 12-year follow-up period.
¶Number of oral steroid bursts in previous 2 y before 12-y follow-up visit among those who needed oral steroid bursts.
#Sick leaves related to asthma in the past 2 y before the 12-y follow-up visit.
††One patient with missing information.

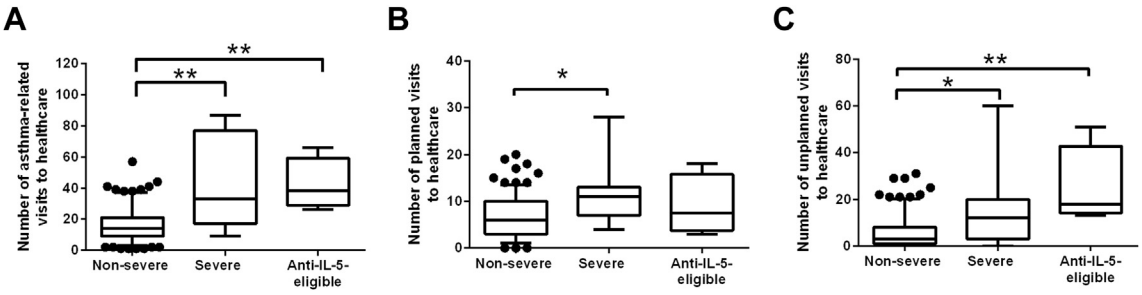

FIGURE 3. **A**, Asthma-related visits to health care in patients with nonsevere asthma, severe asthma, and eligible for anti-IL-5 therapy. **B**, Planned visits include asthma-related follow-up visits. **C**, Unplanned visits include visits related to exacerbations and acute respiratory tract infections. Anti-IL-5 eligible patients refer to those who fulfill criteria for the primary endpoint of this study (daily use of medium-to-high ICS dose and LABA, ≥2 exacerbations per previous year, and blood eosinophil level ≥ 300 cells/μL or FeNO ≥ 50 ppb). *FeNO*, Fraction of exhaled nitric oxide; *ICS*, inhaled corticosteroid; *LABA*, long-acting β_2-agonist.

study, exacerbation frequency ≥2 for mepolizumab and in our study, ≥1 for reslizumab). In addition, criteria for FeNO were not included in that study consistently with the Food and Drug Administration–approved criteria for anti-IL-5 antibodies. ERS/ATS criteria[12] (used in our study) for high ICS dose in SA were very strict and much higher than that defined by Global Initiative for Asthma (GINA), and as a consequence most anti-IL-5 eligible patients were not defined as severe asthmatics in our study. Only 1 patient overlap in these 2 groups is a surprising and interesting finding and reflects the strict criteria for SA by ATS/ERS and confusing current state of multiple definitions for high ICS dose. Despite not belonging to the group of SA, all anti-IL-5-treatable patients fulfilled 1 or more features of uncontrolled asthma (3 patients uncontrolled, 1 partially controlled according to GINA 2010). If patients with SA and those with anti-IL-5 eligibility are combined, the proportion of anti-IL-5 eligible patients in this group is 27%, similarly to the Belgian registry.

We also evaluated the prevalence of eosinophilic phenotype of adult-onset asthma in the whole study cohort by using different cutoff points. The proportions of eosinophilic asthma by using

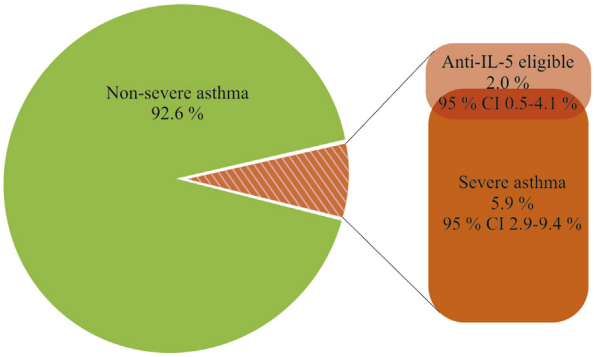

FIGURE 4. Prevalence of anti-IL-5 eligible asthma, severe asthma, and nonsevere asthma in cohort of adult-onset asthma (SAAS). One patient overlap existed in the groups of anti-IL-5 eligibility and severe asthma. *CI*, Confidence interval; *SAAS*, Seinäjoki Adult Asthma Study.

the cut-point of 300 or 400 cells/μL for blood eosinophils were 17.3% and 10.4%, respectively. Previous studies found 26.4%[25] and 16%[26] prevalence by using the same cutoffs, respectively, but used selected cohorts (exclusion of patients with coexisting chronic obstructive pulmonary disease[26] or inclusion of those with regular treatment [medium-to-high ICS dose] to asthma[25]).

So far, little is known about the prevalence of SA among all asthmatics even though estimates of 5% to 10% have often been proposed with unclear basis for the estimate. Previous pharmacy-based studies have found the prevalence of SA from 3.6% (Dutch study)[13] to 4.6% (Israeli study).[27] In the Dutch study, only 3.6% were defined as having SA after excluding those with poor adherence or an incorrect inhalation technique. In our study with patients having asthma diagnosis clinically confirmed by respiratory specialist and lung function measurements, 5.9% (CI 2.9% to 9.4%) were classified as having SA according to the definition agreed by the ATS/ERS Task Force.[12] Even though the prevalence estimates (3.6% to 4.6%) obtained from the pharmacy-based studies[13,27] are somewhat lower, they fall within the 95% CI (2.9% to 9.4%) for SA obtained in the present study, and suggest that pharmacy database studies may be a way forward to obtain crude estimates of SA. Differences in the age of asthma onset, lack of objective asthma diagnosis, exclusion of heavy smokers, and definition of SA may affect the difference seen between the prevalence of SA in our and the previous studies.[13,27]

SA is not a single disease, but a heterogeneous group with many subphenotypes. Age at disease onset has been found as a differentiating factor for asthma phenotypes in many studies, separating allergic and atopic early-onset phenotype from less allergic adult-onset phenotypes.[1,3,28,29] Adult-onset subphenotypes such as eosinophilic inflammation-predominant, mild-to-moderate well-controlled, obese noneosinophilic, smoking asthma, and severe obstructive asthma have been identified by several cluster analyses.[1] Late-onset severe eosinophilic asthma represents only 1 subphenotype, and in a study of this size, a random predominance of a particular phenotype may have affected the proportion of subjects identified as anti-IL-5 eligible. In the Belgian SA registry,[23] the prevalence of the eosinophilic phenotype (blood eosinophils ≥300 cells/μL) in the SA cohort was 36%. Inflammation in our patients with SA was often neutrophil predominant. This is in concordance with previous studies in which SA has been associated with neutrophilic airway inflammation.[30,31] Whether neutrophilic inflammation is due to different pathological mechanisms in SA, or a response to high-dose glucocorticoid treatment in these patients, remains unknown. Neutrophilia as well as low number of patients with SA with elevated blood eosinophils in our cohort may also be related to good adherence to ICS treatment.

To our knowledge, there exist no studies with comparison between SA and anti-IL-5 eligible patients. Severe (uncontrolled) asthma has been associated with the increased use of health care, obesity, and smoking in previous studies when compared with nonsevere asthmatics,[27] being consistent with our results. Number of hospital admissions and visits to general practitioner and asthma specialist have been reported to be higher in patients with SA as compared with nonsevere patients in follow-up for 1 year.[27] In a US study with 11-month follow-up, patients with eosinophilic (≥400 cells/μL) SA (severity defined solely by use of medication) were reported to be more often hospitalized but had no more outpatient or emergency room visits when compared with those with normal eosinophils.[32] In contrast, in our study, anti-IL-5 eligible patients visited health care frequently, had the high number of oral steroid courses and sick leaves, but hospitalizations were not increased as compared with SA. Frequency of hospitalizations in patients with SA may be partly explained by obesity and smoking as well as comorbidities, all being associated with poor outcome of asthma.[17,19,33]

The estimate for anti-IL-5 eligible patients in this general population of asthmatics was 2%. A major limitation of this study is the relatively small sample size. However, by using bootstrap analysis relatively narrow, 95% CI of 0.5% to 4.1% for anti-IL-5 eligibility was obtained. Another limitation affecting the generalizability of our findings is the relatively low rate of patients with uncontrolled asthma in our cohort (29.6%) when compared with previous studies varying from 27% to 74%.[34-37] Different patient population and method for assessing control of asthma as well as better adherence to treatment in our study may explain the difference. On the other hand, good adherence to treatment is essential when considering biological drugs and can be considered as a strength when assessing the prevalence of anti-IL-5 eligibility. Many patients with SA suffer from multimorbidity (including reflux disease or sinusitis),[38] and if comorbidities are addressed properly, this can lead to restoration of asthma control and obviate the need for prescribing a biologic agent. Our anti-IL-5 eligible patients had very few comorbidities altogether, and none of the 4 anti-IL-5 eligible patients reported reflux disease. Sinusitis was not objectively evaluated in the follow-up visit in each patient but during the 12-year time, 3 of the 4 anti-IL-5 eligible patients had had several visits to health care because of sinus problems and were prescribed permanent nasal steroid for long-term rhinitis. However, we cannot exclude the possibility that sinus problems have affected asthma development into severe form and whether they could have been better addressed. In addition, our study excluded childhood-onset asthmatics, also limiting the generalizability of the findings.

This study was carried out by using criteria equivalent to the clinical indications approved or used in studies. Despite the clinical benefits of anti-IL-5 treatment, the drugs are costly, and according to a preliminary cost-effectiveness analysis of mepolizumab, it may exceed commonly used thresholds.[39] The preliminary cost-effectiveness analysis has been based on data available from clinical trials. Thus, it is possible that in the future anti-IL-5 therapy will be targeted differently. Recent studies suggest that the characteristics of patients obtaining better benefit may include those with higher eosinophil levels[40,41] and asthma onset after 40 years.[42]

In summary, in an unselected cohort of adult-onset asthma, we have shown 2% prevalence of eosinophilic steroid-resistant exacerbation-prone asthma that could benefit from the anti-IL-5 antibody and 5.9% prevalence of SA. Only 1 patient met criteria for both groups. Patients with SA and those eligible for anti-IL-5 therapy differed by current smoking, obesity, and more neutrophil-predominant disease in patients with SA. According to our results including exceptionally long 12-year follow-up data of health care use, both groups are a high burden to health care, suggesting that the current treatments are ineffective for these patients. It is important to identify these phenotypes as early as possible because they may benefit from targeted treatment that could lead to lower long-term use of health care.

Acknowledgment

Aino Sepponen, RN, is gratefully acknowledged for her help through all the stages of this work.

REFERENCES

1. Ilmarinen P, Tuomisto LE, Kankaanranta H. Phenotypes, risk factors and mechanisms of adult-onset asthma. Mediators Inflamm 2015;2015:514868.
2. Ilmarinen P, Tuomisto LE, Niemelä O, Tommola M, Haanpää J, Kankaanranta H. Cluster analysis on longitudinal data of patients with adult-onset asthma. J Allergy Clin Immunol Pract 2017;5:967-978.e3.
3. Wenzel SE. Asthma phenotypes: the evolution from clinical to molecular approaches. Nat Med 2012;18:716-25.
4. Green RH, Brightling CE, McKenna S, Hargadon B, Parker D, Bradding P, et al. Asthma exacerbations and sputum eosinophil counts: a randomised controlled trial. Lancet 2002;360:1715-21.
5. Ilmarinen P, Kankaanranta H. Eosinophil apoptosis as a therapeutic target in allergic asthma. Basic Clin Pharmacol Toxicol 2013;114:109-17.
6. Kankaanranta H, Moilanen E, Zhang X. Pharmacological regulation of human eosinophil apoptosis. Curr Drug Targets Inflamm Allergy 2005;4:433-45.
7. Bel EH, Wenzel SE, Thompson PJ, Prazma CM, Keene ON, Yancey SW, et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. N Engl J Med 2014;371:1189-97.
8. Pavord ID, Korn S, Howarth P, Bleecker ER, Buhl R, Keene ON, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. Lancet 2012;380:651-9.
9. Bjermer L, Lemiere C, Maspero J, Weiss S, Zangrilli J, Germinaro M. Reslizumab for inadequately controlled asthma with elevated blood eosinophil levels: a randomized phase 3 study. Chest 2016;150:789-98.
10. Haldar P, Brightling CE, Hargadon B, Gupta S, Monteiro W, Sousa A, et al. Mepolizumab and exacerbations of refractory eosinophilic asthma. N Engl J Med 2009;360:973-84.
11. Castro M, Wenzel SE, Bleecker ER, Pizzichini E, Kuna P, Busse WW, et al. Benralizumab, an anti-interleukin 5 receptor alpha monoclonal antibody, versus placebo for uncontrolled eosinophilic asthma: a phase 2b randomised dose-ranging study. Lancet Respir Med 2014;2:879-90.
12. Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J 2014;43:343-73.
13. Hekking PP, Wener RR, Amelink M, Zwinderman AH, Bouvy ML, Bel EH. The prevalence of severe refractory asthma. J Allergy Clin Immunol 2015;135:896-902.
14. Kankaanranta H, Ilmarinen P, Kankaanranta T, Tuomisto LE. Seinajoki Adult Asthma Study (SAAS): a protocol for a 12-year real-life follow-up study of new-onset asthma diagnosed at adult age and treated in primary and specialised care. NPJ Prim Care Respir Med 2015;25:15042.
15. Haahtela T, Tuomisto LE, Pietinalho A, Klaukka T, Erhola M, Kaila M, et al. A 10 year asthma programme in Finland: major change for the better. Thorax 2006;61:663-70.
16. Haahtela T, Lehtimaki L, Ahonen E, Harju T, Jartti T, Kankaanranta H, et al. Update on current care guidelines: asthma. Duodecim 2013;129:994-5.
17. Tuomisto LE, Ilmarinen P, Niemela O, Haanpaa J, Kankaanranta T, Kankaanranta H. A 12-year prognosis of adult-onset asthma: Seinajoki Adult Asthma Study. Respir Med 2016;117:223-9.
18. Tommola M, Ilmarinen P, Tuomisto LE, Haanpää J, Kankaanranta T, Niemelä O, et al. The effect of smoking on lung function: a clinical study on adult-onset asthma. Eur Respir J 2016;48:1298-306.
19. Ilmarinen P, Tuomisto LE, Niemelä O, Danielsson J, Haanpää J, Kankaanranta T, et al. Co-morbidities and elevated IL-6 associate with negative outcome in adult-onset asthma. Eur Respir J 2016;48:1052-62.
20. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J 2005;26:319-38.
21. Mantalos P, Zografos K. Interval estimation for a binomial proportion: a bootstrap approach. J Stat Comput Simul 2008;78:1251-65.
22. Global Initiative for Asthma. From the global strategy for asthma management and prevention. Updated 2010. Available from: http://www.ginasthma.org/. Accessed October 27, 2014.
23. Schleich F, Brusselle G, Louis R, Vandenplas O, Michils A, Pilette C, et al. Heterogeneity of phenotypes in severe asthmatics. The Belgian severe asthma registry (BSAR). Respir Med 2014;108:1723-32.
24. Albers FC, Müllerovr H, Gunsoy NB, Shin J-Y, Nelsen LM, Bradford ES, et al. Biologic treatment eligibility for real-world patients with severe asthma: the IDEAL study. J Asthma 2018;55:152-60.
25. de Groot JC, Storm H, Amelink M, de Nijs SB, Eichhorn E, Reitsma BH, et al. Clinical profile of patients with adult-onset eosinophilic asthma. ERJ Open Res 2016;2:00100-002015.
26. Price DB, Rigazio A, Campbell JD, Bleecker ER, Corrigan CJ, Thomas M, et al. Blood eosinophil count and prospective annual asthma disease burden: a UK cohort study. Lancet Respir Med 2015;3:849-58.
27. Varsano S, Segev D, Shitrit D. Severe and non-severe asthma in the community: a large electronic database analysis. Respir Med 2017;123:131-9.
28. Miranda C, Busacker A, Balzar S, Trudeau J, Wenzel SE. Distinguishing severe asthma phenotypes: role of age at onset and eosinophilic inflammation. J Allergy Clin Immunol 2004;113:101-8.
29. Haldar P, Pavord ID, Shaw DE, Berry MA, Thomas M, Brightling CE, et al. Cluster analysis and clinical asthma phenotypes. Am J Respir Crit Care Med 2008;178:218-24.
30. Wenzel SE, Szefler SJ, Leung DY, Sloan SI, Rex MD, Martin RJ. Bronchoscopic evaluation of severe asthma. Persistent inflammation associated with high dose glucocorticoids. Am J Respir Crit Care Med 1997;156:737-43.
31. Macedo P, Hew M, Torrego A, Jouneau S, Oates T, Durham A, et al. Inflammatory biomarkers in airways of patients with severe asthma compared with non-severe asthma. Clin Exp Allergy 2009;39:1668-76.
32. Casciano J, Krishnan JA, Small MB, Buck PO, Gopalan G, Li C, et al. Burden of asthma with elevated blood eosinophil levels. BMC Pulm Med 2016;16:100.
33. Kankaanranta H, Kauppi P, Tuomisto LE, Ilmarinen P. Emerging co-morbidities in adult asthma: risks, clinical associations and mechanisms. Mediators Inflamm 2016;2016:3690628.
34. Mintz M, Gilsenan AW, Bui CL, Ziemiecki R, Stanford RH, Lincourt W, et al. Assessment of asthma control in primary care. Curr Med Res Opin 2009;25:2523-31.
35. Peters SP, Jones CA, Haselkorn T, Mink DR, Valacer DJ, Weiss ST. Real-world Evaluation of Asthma Control and Treatment (REACT): findings from a national Web-based survey. J Allergy Clin Immunol 2007;119:1454-61.
36. Lenoir M, Williamson A, Stanford RH, Stempel DA. Assessment of asthma control in a general population of asthmatics. Curr Med Res Opin 2006;22:17-22.
37. Carlton BG, Lucas DO, Ellis EF, Conboy-Ellis K, Shoheiber O, Stempel DA. The status of asthma control and asthma prescribing practices in the United

States: results of a large prospective asthma control survey of primary care practices. J Asthma 2005;42:529-35.
38. Lang DM. Multimorbidity: the new normal. Ann Am Thorac Soc 2013;10:491-3.
39. Whittington MD, McQueen RB, Ollendorf DA, Tice JA, Chapman RH, Pearson SD, et al. Assessing the value of mepolizumab for severe eosinophilic asthma: a cost-effectiveness analysis. Ann Allergy Asthma Immunol 2017;118:220-5.
40. Ortega HG, Yancey SW, Mayer B, Gunsoy NB, Keene ON, Bleecker ER, et al. Severe eosinophilic asthma treated with mepolizumab stratified by baseline eosinophil thresholds: a secondary analysis of the DREAM and MENSA studies. Lancet Respir Med 2016;4:549-56.
41. Cabon Y, Molinari N, Marin G, Vachier I, Gamez AS, Chanez P, et al. Comparison of anti-interleukin-5 therapies in patients with severe asthma: global and indirect meta-analyses of randomized placebo-controlled trials. Clin Exp Allergy 2017;47:129-38.
42. Brusselle G, Germinaro M, Weiss S, Zangrilli J. Reslizumab in patients with inadequately controlled late-onset asthma and elevated blood eosinophils. Pulm Pharmacol Ther 2017;43:39-45.

ONLINE REPOSITORY

Lung function, inflammatory parameters, and other clinical measurements

Lung function measurements were performed with a spirometer (Vmax Encore 22, Viasys Healthcare, Palm Springs, Calif) that was calibrated daily. Postbronchodilator measurements were taken 15 minutes after inhalation of salbutamol (400 μg). Finnish reference values were used.[E1] Fraction of exhaled nitric oxide was measured with a portable rapid-response chemiluminescent analyzer according to American Thoracic Society standards[E2] (flow rate 50 mL/s; NIOX System, Aerocrine, Sweden). Venous blood was collected and white blood cell differential counts were determined. Total IgE levels were measured by using ImmunoCAP (Thermo Scientific, Uppsala, Sweden). Laboratory assays were performed in an accredited laboratory (SFS-EN ISO/IEC 17025:2005 and ISO 15189:2007) of Seinäjoki Central Hospital. The definition of comorbidities and their classification was based on a previous study.[E3] Comorbidities were self-reported or based on self-reported medication, and unclear cases were confirmed from patient records.[E4] Patients completed Airways Questionnaire 20 (AQ20) and Asthma Control Test. AQ20 is a short and simple well-validated questionnaire to measure and quantify disturbances in the airway-specific quality of life.[E5] Assessment of asthma control was performed according to the Global Initiative for Asthma (2010) report.[E6]

TABLE E1. Baseline characteristics of patients with nonsevere asthma, severe asthma, and those eligible* to anti-IL-5 therapy

Characteristic	Nonsevere	Severe	Eligible to anti-IL-5	*P* value
No. of patients	188	11	4	
BMI	27.3 (4.9)	30.9 (6.3)	26.4 (3.2)	.059
Smokers, ex + current	93 (49.5%)	8 (72.7%)	2 (50.0%)	.325
Current smokers	30 (16.0%)	5 (45.5%)†	1 (25.0%)	**.042**
Pack years of smokers	11 (5-21)	15 (9-17)	25 (0-ND)	.859
Duration of asthma symptoms before diagnosis (mo)	12 (12-36)	12 (9-36)	30 (8-102)	.873
Symptoms of asthma <16 y	40 (21.6%)	4 (36.4%)	1 (25%)	.520
Lung function				
Pre-BD FEV_1	80 (18)	84 (13)	69 (28)	.375
Post-BD FEV_1	86 (18)	88 (11)	81 (26)	.746
Pre-BD FVC	89 (16)	91 (16)	83 (14)	.742
Post-BD FVC	92 (16)	93 (12)	92 (5)	.954
Pre-BD FEV_1/FVC	0.74 (0.10)	0.77 (0.06)	0.65 (0.20)	.150
Post-BD FEV_1/FVC	0.78 (0.10)	0.78 (0.06)	0.70 (0.21)	.360
FEV_1 reversibility (mL)	160 (70-330)	140 (0-200)	365 (148-470)	.253
FEV_1 reversibility (% change from baseline)	6.1 (2.7-11.3)	4.0 (0-7.1)	20.7 (4.7-39.0)	.177
DL_{CO}/VA (% predicted)	101 (18)	97 (20)	92 (11)	.540
Response to treatment (ΔFEV_1 DG-$Max_{0\text{-}2.5}$) (mL)	255 (70-590)	290 (20-540)	280 (225-1700)	.689
Response to treatment (ΔFEV_1 DG-$Max_{0\text{-}2.5}$) (% predicted)	9.0 (3.0-16.9)	8 (3.0-14.6)	15.9 (7.3-45.7)	.365
Daily medication				
ICS in use before diagnosis	14 (7.5%)	1 (10.0%)	1 (25%)	.428
ICS starting dose (all, bud eq, μg)	991 (537)	1145 (573)	900 (503)	.610
Inflammatory parameters				
Blood eosinophils	0.29 (0.15-0.42)	0.22 (0.18-0.40)	0.40 (0.08-ND)	.976
Total IgE	84 (36-194)	61 (22-91)	182 (63-ND)	.196
Symptoms/quality of life				
AQ20 score	7 (4-9)	8 (5-13)	5 (4-11)	.475
Comorbidities				
Hypertension, n (%)	26 (13.8%)	3 (27.3%)	1 (25.0%)	.401
Diabetes, n (%)	2 (1.1%)	1 (9.1%)	0	.097
Coronary heart disease, n (%)	10 (5.3%)	0	0	.657
COPD	13 (7.1%)	1 (9.1%)	1 (25%)	.397

AQ20, Airways Questionnaire 20; *BD*, bronchodilator; *BMI*, body mass index; *COPD*, chronic obstructive pulmonary disease; *DL_{CO}/VA*, diffusing capacity adjusted by the alveolar volume; *FeNO*, fraction of exhaled nitric oxide; *FEV_1*, forced expiratory volume in 1 s; *FVC*, forced vital capacity; *ICS*, inhaled corticosteroid; *LABA*, long-acting β_2-agonist.

Bold indicates statistical significance ($P < .05$).

*Anti-IL-5 eligible patients refer to those who fulfill criteria for the primary endpoint of this study (daily use of medium-to-high ICS dose and LABA, ≥2 exacerbations per previous year before the 12-y follow-up visit, and blood eosinophil level ≥ 300 cells/μL or FeNO ≥ 50 ppb).

†Indicates $P < .05$ versus nonsevere group.

TABLE E2. Comorbidities of patients with nonsevere asthma, severe asthma, and those eligible* to anti-IL-5 therapy at 12-year follow-up visit

Characteristic	Nonsevere	Severe	Eligible to anti-IL-5	*P* value
No. of patients	188	11	4	
No. of comorbidities	1 (0-2)	2 (1-3)	0.5 (0-2.5)	.137
Hypertension	64 (34.0%)	4 (36.4%)	1 (25%)	.918
Diabetes	27 (14.4 %)	2 (18.2%)	0	.669
Obesity	63 (33.5%)	7 (63.6%)	1 (25%)	.115
Coronary heart disease	20 (10.6%)	1 (9.1%)	0	.780
Any psychiatric disease	24 (12.8%)	3 (27.3%)	0	.283
Depression	15 (8.0%)	2 (18.2%)	0	.410
Systemic rheumatic disease	4 (2.1%)	2 (18.2%)	0	**.009**
Thyroid disorder	12 (6.4%)	4 (36.4%)	0	**.001**
Painful condition	18 (9.6%)	1 (9.1%)	0	.809
Treated dyspepsia	13 (6.9%)	3 (27.3%)	0	**.043**
COPD (fulfills criteria $\geq$10 pack-years and post-BD $FEV_1/FVC < 0.7$)	30 (16.1%)	3 (27.3%)	1 (25%)	.575
Rhinitis (chronic/allergic)	126 (68.5%)	10 (90.9%)	4 (100%)	.121

BD, Bronchodilator; *COPD*, chronic obstructive pulmonary disease; *FeNO*, fraction of exhaled nitric oxide; FEV_1, forced expiratory volume in 1 s; *FVC*, forced vital capacity; *ICS*, inhaled corticosteroid; *LABA*, long-acting β_2-agonist.

*Anti-IL-5 eligible patients refer to those who fulfill criteria for the primary endpoint of this study (daily use of medium-to-high ICS dose and LABA, $\geq$2 exacerbations per previous year before the 12-year follow-up visit, and blood eosinophil level $\geq$ 300 cells/μL or FeNO $\geq$ 50 ppb).

REFERENCES

E1. Viljanen AA, Halttunen PK, Kreus KE, Viljanen BC. Spirometric studies in non-smoking, healthy adults. Scand J Clin Lab Invest Suppl 1982;159:5-20.

E2. American Thoracic Society, European Respiratory Society. ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, 2005. Am J Respir Crit Care Med 2005;171:912-30.

E3. Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. Lancet 2012;380:37-43.

E4. Ilmarinen P, Tuomisto LE, Niemelä O, Danielsson J, Haanpää J, Kankaanranta T, et al. Co-morbidities and elevated IL-6 associate with negative outcome in adult-onset asthma. Eur Respir J 2016;48:1052-62.

E5. Barley EA, Quirk FH, Jones PW. Asthma health status measurement in clinical practice: validity of a new short and simple instrument. Respir Med 1998;92:1207-14.

E6. Global Initiative for Asthma. From the global strategy for asthma management and prevention. Last updated 2010. Available from: http://www.ginasthma.org/. October 27, 2014.

E7. Mantalos P, Zografos K. Interval estimation for a binomial proportion: a bootstrap approach. J Stat Comput Simul 2008;78:1251-65.