

Relationship of Inhaled Corticosteroid Adherence to Asthma Exacerbations in Patients with Moderate-to-Severe Asthma



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What is already known about this topic? Nonadherence to inhaled corticosteroid (ICS) therapy and elevated blood eosinophil levels are both associated with an increased risk of exacerbations in patients with asthma.

What does this article add to our knowledge? Using combined routine clinical and patient-reported data, we provide evidence that adherence to refill prescriptions for ICS therapy in patients with asthma with elevated blood eosinophils is not associated with a decrease in asthma exacerbations.

How does this study impact our current management guidelines? This study supports the requirement of additional therapy for patients with elevated blood eosinophil levels that continue to experience frequent asthma exacerbations, despite adherence to ICS.

BACKGROUND: Patients with asthma and elevated blood eosinophils are at increased risk of severe exacerbations. Management of these patients should consider nonadherence to inhaled corticosteroid (ICS) therapy as a factor for increased exacerbation risk.

OBJECTIVE: The objective of this study was to investigate whether poor adherence to ICS therapy explains the occurrence of asthma exacerbations in patients with elevated blood eosinophil levels.

METHODS: This historical cohort study identified patients within the Optimum Patient Care Research Database, aged 18 years or more, at Global Initiative for Asthma step 3 or 4, with 2 or more ICS prescriptions during the year before the clinical review. Patient characteristics and adherence (based on

prescription refills and patient self-report) for ICS therapy were analyzed for those with elevated (>400 cells/ μ L) or normal (≤ 400 cells/ μ L) blood eosinophils.

RESULTS: We studied 7195 patients (66% female, mean age 60 years) with median eosinophil count of 200 cells/ μ L and found 81% to be not fully adherent to ICS therapy. A total of 1031 patients (14%) had elevated blood eosinophil counts (58% female, mean age 60 years), 83% of whom were not fully adherent to ICS. An increased proportion of adherent patients in the elevated blood eosinophil group had 2 or more exacerbations (14.0% vs 7.2%; $P = .003$) and uncontrolled asthma (73% vs 60.8%; $P = .004$) as compared with non—fully adherent patients. **CONCLUSIONS:** Approximately 1 in 7 patients had elevated eosinophils. Adherence to ICS therapy was not associated with

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This study was funded by Teva Pharmaceuticals.

Conflicts of interest: A. Papi has received grants, personal fees, and nonfinancial support from AstraZeneca, Chiesi Farmaceutici, GlaxoSmithKline, Boehringer Ingelheim, Merck Sharp & Dohme, Menarini, Novartis, Zambon, TEVA, Pfizer, Takeda, and Mundipharma. D. Ryan, in the last 3 years, has received consultancy fees from TEVA, Chiesi, AstraZeneca, Novartis, Boehringer Ingelheim, and has spoken on behalf of AstraZeneca and TEVA and MEDA. J.B. Soriano has received pharmaceutical company grants from GSK in 2011 and Chiesi in 2012 via CIMERA, his former home institution, and from Linde via Hospital Universitario de La Princesa in 2014 and 2015; and participated in speaking activities, advisory committees, and consultancies during the period 2011–2016 sponsored by Almirall, AstraZeneca, Boehringer-Ingelheim, Chiesi, ERS, GEBRO, Grifols, GSK, Linde, Lipopharma, Mundipharma, Novartis, Pfizer, RiRL, Rovi, SEPAR, Takeda, and Teva. H. Chrystyn has no shares in any pharmaceutical companies. He has received sponsorship to carry out studies, together with board membership, consultant agreements, and honoraria for presentation, from several pharmaceutical companies that market inhaled products. These include Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Innovata Biomed, Meda,

decreased exacerbations for these patients. Additional therapy should be considered for these patients, such as biologics, which have been previously shown to improve control in severe uncontrolled eosinophilic asthma. © 2018 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2018;6:1989-98)

Key words: Adherence; Asthma control; Eosinophils; Asthma exacerbations; Inhaled corticosteroids; Severe asthma

Abbreviations used

COPD- Chronic obstructive pulmonary disease
ENCePP- European Network of Centres for
Pharmacoepidemiology and Pharmacovigilance
FeNO- Fraction of exhaled nitric oxide
GINA- Global Initiative for Asthma
ICS- Inhaled corticosteroid
iHARP- initiative Helping Asthma in Real People
IQR- Interquartile range
LABA- Long-acting β -agonist
MARS- Medication Adherence Rating Scale
MPR- Medication possession ratio
OPCRD- Optimum Patient Care Research Database
QOF- Quality and Outcomes Framework

The complex interrelationship between asthma control, exacerbation risk, blood eosinophil counts, and asthma treatment has been the subject of recent studies. In randomized controlled trials of severe asthma, blood eosinophil counts were associated with increased exacerbation risk.¹ In real-world studies, patients with asthma and blood eosinophil counts greater than 400 cells/ μ L similarly experienced more exacerbations,² coupled with poorer asthma control.³

The Global Initiative for Asthma (GINA) describes steps to maintain asthma control while reducing severe exacerbation risk.⁴ An observational database study showed that patients with blood eosinophil counts greater than 400 cells/ μ L were more likely to be on higher therapeutic steps (step 3 or 4) of the GINA management approach to control and risk.³ Blood eosinophil counts may therefore aid clinicians to establish GINA-based asthma management.

Nonadherence to prescribed medication is also an important risk factor for exacerbations, including asthma-related hospitalisations⁵⁻⁷ and death.⁸ Achievement of long-term asthma control is more likely when patients adhere to prescribed therapy,⁹ resulting in a significant reduction in the risk of death.¹⁰ However, patients may still remain with uncontrolled symptoms and at risk of exacerbation despite good adherence to prescription for inhaled corticosteroid (ICS).

We hypothesized that there would exist a population of patients with eosinophilic asthma, a common asthma phenotype characterized by elevated blood eosinophil counts,¹¹ who are still at risk of exacerbation despite good adherence to prescribed ICS treatment. This study aimed to identify and quantify the population of patients with asthma with elevated blood eosinophil levels, and to investigate whether poor adherence to ICS therapy explains the occurrence of exacerbations and poor asthma control in this subset of patients.

METHODS

This was a historical cohort study, using linked routine clinical and patient-reported data. The study period consisted of a baseline year for patient characterization and confounder definition, followed by a clinical review (questionnaire collection) for outcome evaluation (Figure 1). An independent steering committee was involved in all phases of the development of study design, review of analyses, and interpretation of results.¹² The study protocol is registered with the

Napp Pharmaceuticals, Mundipharma, NorPharma, Novartis, Orion, Sanofi, Teva, Trudell Medical International, UCB, and Zentiva. Research sponsorship has also been received from grant awarding bodies (EPSRC and MRC). He is the owner of Inhalation Consultancy Ltd. He is also an employee at Observational and Pragmatic Research Institute Pte Ltd, which conducted this study, with institutional support from Teva Pharmaceuticals Europe B.V., and has conducted paid research in respiratory disease on behalf of the following other organizations: UK National Health Service, British Lung Foundation, Aerocrine, AKL Research and Development Ltd, AstraZeneca, Boehringer Ingelheim, Chiesi, Meda, Mundipharma, Napp, Novartis, Pfizer, Respiratory Effectiveness Group, Takeda, Teva Pharmaceuticals, Theravance, and Zentiva. L. Bjermer has received fees over the past 3 years for speaking or participating in advisory boards for Aerocrine, Arsonette, Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Mundipharma, Novartis, Sandoz, Sanofi, Takeda and Teva. R. Rodríguez-Roisin has received personal fees from AstraZeneca, Boehringer Ingelheim, Pearl Therapeutics, TEVA, Menarini, and Novartis; and grants from Menarini. M.B. Dolovich is on an advisory board of Teva Pharmaceuticals and has received a research grant from Boehringer Ingelheim, Canada. M. Harris was an employee of Optimum Patient Care at the time of the study. L. Wood, M. Batsiou, and S.I. Thornhill were employees at the time of the study. Observational and Pragmatic Research Institute Pte Ltd conducted this study, with institutional support from Teva Pharmaceuticals Europe B.V., and has conducted paid research in respiratory disease on behalf of the following organizations: UK National Health Service, British Lung Foundation, Aerocrine, AKL Research and Development Ltd, AstraZeneca, Boehringer Ingelheim, Chiesi, Meda, Mundipharma, Napp, Novartis, Pfizer, Respiratory Effectiveness Group, Takeda, Teva Pharmaceuticals, Theravance, and Zentiva. D.B. Price has board membership with Aerocrine, Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, Mylan, Mundipharma, Napp, Novartis, and Teva Pharmaceuticals; consultancy agreements with Almirall, Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline,

Mylan, Mundipharma, Napp, Novartis, Pfizer, Teva Pharmaceuticals, and Theravance; grants and unrestricted funding for investigator-initiated studies (conducted through Observational and Pragmatic Research Institute Pte Ltd) from Aerocrine, AKL Research and Development Ltd, AstraZeneca, Boehringer Ingelheim, British Lung Foundation, Chiesi, Mylan, Mundipharma, Napp, Novartis, Pfizer, Respiratory Effectiveness Group, Teva Pharmaceuticals, Theravance, UK National Health Service, Zentiva; payment for lectures/speaking engagements from Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, GlaxoSmithKline, Kyorin, Mylan, Merck, Mundipharma, Novartis, Pfizer, Skyepharma, and Teva Pharmaceuticals; payment for manuscript preparation from Mundipharma and Teva Pharmaceuticals; payment for the development of educational materials from Mundipharma and Novartis; payment for travel/accommodation/meeting expenses from Aerocrine, AstraZeneca, Boehringer Ingelheim, Mundipharma, Napp, Novartis, and Teva Pharmaceuticals; funding for patient enrolment or completion of research from Chiesi, Novartis, Teva Pharmaceuticals, and Zentiva; stock/stock options from AKL Research and Development Ltd, which produces phytopharmaceuticals; owns 74% of the social enterprise Optimum Patient Care Ltd (Australia and UK) and 74% of Observational and Pragmatic Research Institute Pte Ltd (Singapore); and is peer reviewer for grant committees of the Efficacy and Mechanism Evaluation programme, and Health Technology Assessment.

Received for publication June 9, 2017; revised March 19, 2018; accepted for publication March 20, 2018.

Available online April 5, 2018.

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2213-2198

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<https://doi.org/10.1016/j.jaip.2018.03.008>

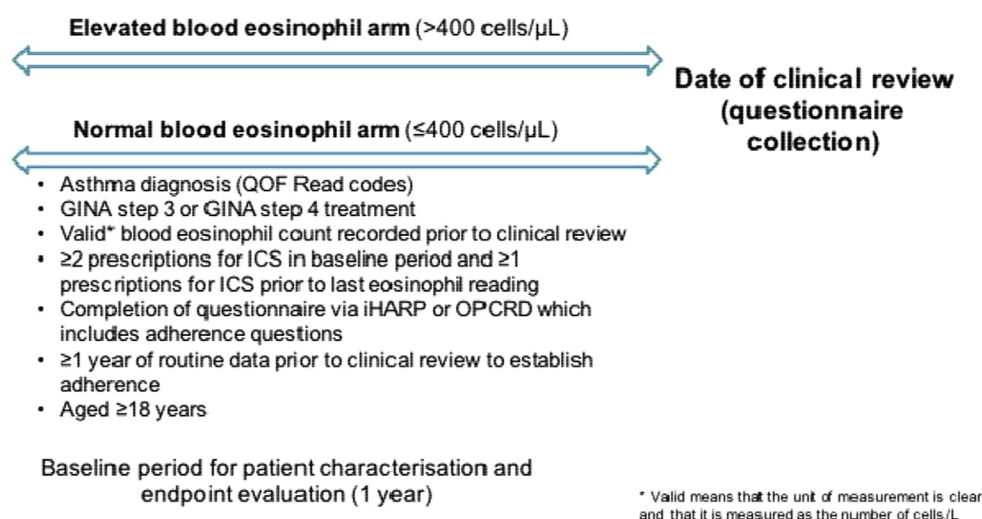


FIGURE 1. Study Design. Schematic illustrating the overall study design and patient inclusion criteria. *GINA*, Global Initiative for Asthma; *ICS*, inhaled corticosteroids; *iHARP*, initiative Helping Asthma in Real People; *OPCRD*, Optimum Patient Care Research Database; *QOF*, Quality and Outcomes Framework.

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) (ENCEPP/SDPP/11512) and was conducted in accordance with the ENCePP Code of Conduct.¹³

Data sources

Data were extracted from the Optimum Patient Care Research Database (OPCRD) and the initiative Helping Asthma in Real People (iHARP) database.

The OPCRD (www.opcrd.co.uk) is a quality-controlled research database containing fully anonymous, longitudinal, routinely collected electronic medical record data and patient-reported questionnaire data from more than 600 primary care practices across England, Scotland, Wales, and Northern Ireland. At the time of writing, the database encompassed more than 4.5 million patients from the United Kingdom (UK) population.¹⁴ The OPCRD is approved by the Health Research Authority of the UK National Health Service for clinical research use (Research Ethics Committee reference: 15/EM/0150).

The iHARP database is a global initiative that conducts thorough asthma review clinics according to asthma guidelines, recording parameters including inhaler technique and spirometry.^{15,16} The database currently comprises approximately 5000 patients from the UK, the Netherlands, Norway, Spain, Italy, Sweden, Australia, and France. UK patients who met all iHARP eligibility criteria (diagnosed with asthma, are receiving fixed dose combination ICS/long-acting β -agonist [LABA], are aged ≥18 years, and are at GINA step 3 or 4 during the iHARP review), ascertained from the OPCRD population, were invited for an iHARP review. To optimize the number of study patients and the evaluation of adherence, iHARP and OPCRD questionnaire data were combined into 1 dataset. Duplicate patients were removed.

Study population

The study population included adult patients, aged ≥18 years, with at least 1 year of continuous valid data before the date of the clinical review and with a prior diagnosis of asthma any time before the review based on the recorded Quality and Outcomes Framework (QOF) Read codes, the clinical coding system within the UK's

general practice for asthma. The presence of QOF Read codes indicates physician-diagnosed asthma; however, the criteria on which diagnosis had been made were not accessible. Patients were receiving GINA step 3 or 4 asthma management, as determined on the date of the clinical review using GINA criteria (2010-2012) for asthma control and risk (Table E1, available in this article's Online Repository at www.jaci-inpractice.org), had 2 or more ICS (fluticasone propionate-equivalent units) prescriptions during the baseline year, and had a valid blood eosinophil count recorded at any time before the clinical review (Figure 1). Patients with a diagnosis of chronic obstructive pulmonary disease (COPD; QOF Read codes), or who were prescribed either acute oral corticosteroids in the 4 weeks before eosinophil count or long-term systemic or maintenance oral corticosteroids for asthma, were excluded.

Eligible patients were divided into 2 groups according to blood eosinophil count of either ≤400 cells/μL (normal blood eosinophil count) or >400 cells/μL (elevated blood eosinophil count). A value of ≤400 cells/μL was selected *a priori* as this is the upper limit of the published normal blood eosinophil count range (0-400 cells/μL) in UK clinical practice.¹⁷ The last valid count before the date of the clinical review was used to stratify patients into elevated and normal blood eosinophil cohorts.

Measures of adherence

Adherence to ICS therapy was assessed from combined routine and questionnaire data. Routine data were based on the medication possession ratio (MPR), defined as the number of ICS prescriptions issued divided by the number of ICS prescriptions expected (based on prescribed ICS dose). An MPR of >80% was considered to be adherent to prescribed ICS therapy. Although a wide variety of cutoff values to define medication adherence have been used in the respiratory literature,¹⁸ a cutoff of >80% is the arbitrary standard threshold used.^{10,19-23} Patient-reported adherence was assessed using a 6-point (never, rarely, sometimes, regularly, often, and always) Medication Adherence Rating Scale (MARS), consisting of 5 questions on controller inhaler usage.²⁴ Patients were considered to be adherent if they had good adherence score across the 5 MARS questions, as well as an MPR of

>80%. More details are available in this article's [Online Repository](http://www.jaci-inpractice.org) at www.jaci-inpractice.org.

Clinical endpoints

The clinical outcomes of this study were the number of severe asthma exacerbations and asthma control. The number of severe asthma exacerbations was defined based on the American Thoracic Society/European Respiratory Society Task Force definition²⁵ to include asthma-related hospital admissions, accident and emergency attendances, or prescription for acute courses of oral corticosteroids. An asthma-related admission was defined as any definite asthma-related hospitalization or a generic hospitalization recorded on the same day as a lower respiratory consultation. Acute oral corticosteroid use associated with asthma exacerbation therapy was defined as all courses that were not maintenance therapy, and/or all courses where dosing instructions suggested exacerbation therapy based on the prescription strength or frequency. Asthma control was ascertained based on a composite measure of risk-domain asthma control and overall asthma control. Risk-domain asthma control was defined as the absence of asthma-related hospital admissions, accident and emergency attendances, outpatient attendances, antibiotics prescribed alongside a lower respiratory consultation, or prescription for acute courses of oral corticosteroids. Overall asthma control was defined as achieved risk-domain asthma control and an average daily dose of ≤ 200 μ g salbutamol or ≤ 500 μ g terbutaline. Questionnaire and routine data were combined and used to assess adherence, whereas routine data alone were used to assess all other variables. Further details on the outcomes can be found in this article's [Online Repository](http://www.jaci-inpractice.org) at www.jaci-inpractice.org.

Statistical analyses

The main analysis included patients with eosinophil counts recorded at any time before the date of questionnaire collection. All statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC).²⁶ Statistical evidence was determined if *P* values were less than .05.

Summary statistics were calculated for patient demographics and baseline characteristics, both overall, and by elevated and normal blood eosinophil cohorts. For continuous variables, either the mean and standard deviation or the median and interquartile range (IQR) were calculated. For categorical variables, the frequency and percentage of observed levels were calculated for the sample with nonmissing observations. Patient demographic and baseline characteristics were compared between the elevated and normal blood eosinophil cohorts using the χ^2 test, *t*-test, or Mann-Whitney *U* test, where appropriate.

Primary outcome analysis

The percentage of patients with 0, 1, or 2 or more exacerbations and the percentage of patients with controlled or uncontrolled asthma were compared between adherent and non-adherent patients within each blood eosinophil count group. Multinomial and binomial logistic regression were performed to compare exacerbations and asthma control, respectively, adjusting for age, smoking status, bronchiectasis, and active rhinitis.

Sensitivity analysis

Two sensitivity analyses were planned *a priori*. The primary outcome analysis was repeated for the following groups of patients and for the exacerbations outcome only:

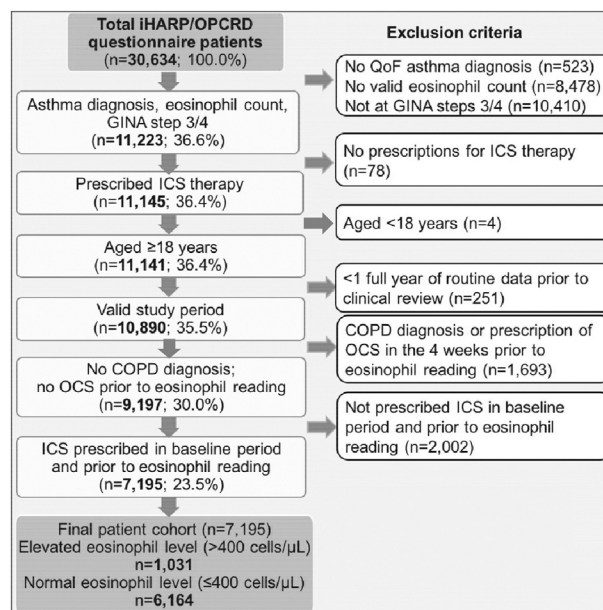


FIGURE 2. Patient flow chart. Flow chart showing the selection of the study population from the Optimum Patient Care Database (OPCRD) and the initiative Helping Asthma in Real People (iHARP) database. *COPD*, Chronic obstructive pulmonary disease; *GINA*, Global Initiative for Asthma; *ICS*, inhaled corticosteroids; *iHARP*, initiative Helping Asthma in Real People; *OCS*, oral corticosteroids; *OPCRD*, Optimum Patient Care Research Database; *QoF*, Quality and Outcomes Framework.

1. Patients with blood eosinophil counts recorded within 1 year from the date of questionnaire collection.
2. Patients with eosinophil counts recorded ever before questionnaire collection, where the cutoff for elevated eosinophil count was set *a priori* at >300 cells/ μ L.

RESULTS

Baseline demographic and clinical characteristics

The total iHARP/OPCRD population at the time of study initiation was 30,634 patients. After applying all inclusion and exclusion criteria, the final study population consisted of 7195 patients, 1119 from iHARP and 6076 from the OPCRD (Figure 2). Baseline characteristics of patients from both databases were similar apart from older patients in the OPCRD (mean age: 61.2 years vs 54.8 years) and more current (38.1% vs 10.7%), but fewer ex-smokers (7.1% vs 34.0%) in the OPCRD compared with iHARP. Patients had a mean age of 60 years, 66% were female, 72% were classified as overweight/obese, and 45% were current/former smokers (Table 1). Patients had a median eosinophil count of 200 cells/ μ L (IQR: 120-320 cells/ μ L) (Table E3, available in this article's [Online Repository](http://www.jaci-inpractice.org) at www.jaci-inpractice.org). During the baseline year, 22% received acute courses of oral corticosteroids with a respiratory consultation, and the majority were prescribed multiple respiratory medications.

Overall, 1031 of the 7195 patients (14%) had elevated blood eosinophil counts (>400 cells/ μ L). Compared with patients who had blood eosinophil counts of ≤ 400 cells/ μ L, patients with elevated blood eosinophils were more likely to be male (42% vs

TABLE I. Baseline demographic and clinical characteristics in patients with asthma with elevated versus normal eosinophil counts

Characteristics	Blood eosinophil count			P value*
	Overall population (n = 7195)	>400 cells/ μ L (n = 1031)	$\leq$ 400 cells/ μ L (n = 6164)	
Age (y)				
Mean (SD)	60.2 (15.1)	59.6 (15.8)	60.3 (15.0)	.194
Sex				
Male	2476 (34.4)	433 (42.0)	2043 (33.1)	<.001
Body mass index (BMI)				
Underweight	81 (1.1)	13 (1.3)	68 (1.1)	<.001
Normal	1897 (26.8)	304 (30.1)	1593 (26.2)	
Overweight	2565 (36.2)	396 (39.2)	2169 (35.7)	
Obese	2549 (35.9)	298 (29.5)	2251 (37.0)	
Smoking status				
Nonmissing	6953 (96.6)	999 (96.9)	5954 (96.6)	.107
Never	3815 (54.9)	573 (57.4)	3242 (54.5)	
Current	2345 (33.7)	329 (32.9)	2016 (33.9)	
Ex-smoker	793 (11.4)	97 (9.7)	696 (11.7)	
Categories of peak expiratory flow % predicted				
Nonmissing	6337 (88.1)	918 (89.0)	5419 (87.9)	.185
<50%	488 (7.7)	81 (8.8)	407 (7.5)	
50% to <70%	1527 (24.1)	237 (25.8)	1290 (23.8)	
70% to <80%	1287 (20.3)	186 (20.3)	1101 (20.3)	
$\geq$ 80	3035 (47.9)	414 (45.1)	2621 (48.4)	
Medication therapy $\pm$ SABA (or SAMA)				
ICS	921 (12.8)	105 (10.2)	816 (13.3)	.040
ICS+LABA (or LAMA)	5498 (76.6)	818 (79.6)	4680 (76.1)	
ICS+LTRA	77 (1.1)	9 (0.9)	68 (1.1)	
ICS+LTRA+LABA (or LAMA)	680 (9.5)	95 (9.3)	585 (9.5)	
Categories of ICS daily dose consumed (μ g) [†]				
>0-160	1733 (24.1)	274 (26.6)	1459 (23.7)	.218
>160-320	2356 (32.8)	321 (31.2)	2035 (33.0)	
>320-500	1795 (25.0)	248 (24.1)	1547 (25.1)	
>500	1306 (18.2)	187 (18.2)	1119 (18.2)	
SABA prescriptions				
Nonmissing	7178 (99.8)	1027 (99.6)	6151 (99.8)	.128
0	1356 (18.9)	211 (20.5)	1145 (18.6)	
1-3	2964 (41.3)	416 (40.5)	2548 (41.4)	
4-6	1516 (21.1)	199 (19.4)	1317 (21.4)	
7-9	679 (9.5)	107 (10.4)	572 (9.3)	
10-12	413 (5.8)	67 (6.5)	346 (5.6)	
>12	250 (3.5)	27 (2.6)	223 (3.6)	
Acute oral corticosteroid prescriptions [‡]				
0	5613 (78.0)	791 (76.7)	4822 (78.2)	.280
$\geq$ 1	1582 (22.0)	240 (23.3)	1342 (21.8)	
Antibiotic prescriptions [‡]				
0	5094 (70.8)	726 (70.4)	4368 (70.9)	.771
$\geq$ 1	2101 (29.2)	305 (29.6)	1796 (29.1)	
Bronchiectasis [§]	199 (2.8)	36 (3.5)	163 (2.6)	.124
Active rhinitis (diagnosis and/or nasal corticosteroids) [¶]	1431 (19.9)	229 (22.2)	1202 (19.5)	.043
Active oral thrush (diagnosis and/or antifungals) [¶]	276 (3.8)	39 (3.8)	237 (3.8)	.925
Eczema [§]	1955 (27.2)	320 (31.1)	1635 (26.5)	.003

ICS, Inhaled corticosteroid; LABA, long-acting β -agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; SABA, short-acting β -agonist; SAMA, short-acting muscarinic antagonist; SD, standard deviation.

Data are n (%) unless otherwise stated.

* χ^2 , t test, and Mann-Whitney U tests for categorical and interval/ratio variables, respectively.

[†]Fluticasone-equivalent units (based on prescriptions in the year before the index date).

[‡]Prescribed during a respiratory consultation.

[§]Diagnosis recorded in the year before the clinical review.

[¶] $\geq$ 1 prescription issued in the year before the questionnaire collection.

TABLE II. Baseline demographic and clinical characteristics in patients with asthma who were adherent and non–fully adherent to ICS therapy

Characteristics	Adherence*		P value†
	Adherent (n = 1392)	Nonfully (n = 5801)	
Age (y)			
Mean (SD)	61.4 (14.5)	59.9 (15.2)	.001
Sex			
Male	479 (34.4)	1996 (34.4)	1.00
Body mass index (BMI)			
Underweight	17 (1.2)	64 (1.1)	.13
Normal	395 (28.7)	1501 (26.3)	
Overweight	503 (36.6)	2062 (36.1)	
Obese	460 (33.5)	2088 (36.5)	
Smoking status			
Nonmissing	1342 (96.4)	5609 (96.7)	.010
Never	786 (58.6)	3028 (54.0)	
Current	413 (30.8)	1932 (34.4)	
Ex-smoker	143 (10.7)	649 (11.6)	
Peak expiratory flow % predicted			
Mean (SD)	78.3 (65.5, 90.6)	79.0 (65.4, 89.8)	.81
Medication therapy ± SABA (or SAMA)			
ICS	150 (10.8)	771 (13.3)	<.001
ICS+LABA (or LAMA)	1033 (74.5)	4465 (77.1)	
ICS+LTRA	14 (1.0)	63 (1.1)	
ICS+LTRA+LABA (or LAMA)	190 (13.7)	490 (8.5)	
Acute oral corticosteroid prescriptions‡			
0	1102 (79.2)	4610 (79.5)	.80
≥1	290 (20.8)	1191 (20.5)	
Bronchiectasis§	70 (5.0)	128 (2.2)	<.001
Active rhinitis (diagnosis and/or nasal corticosteroids)¶	474 (34.1)	1626 (28.0)	<.001
Active oral thrush (diagnosis and/or antifungals)¶	67 (4.8)	209 (3.6)	.035
Eczema§	364 (26.1)	1591 (27.4)	.33
Blood eosinophil count			
≤400 cells/μL#	1214 (87.2)	4948 (85.3)	.067
>400 cells/μL	178 (12.8)	853 (14.7)	

ICS, Inhaled corticosteroid; LABA, long-acting β -agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; SABA, short-acting β -agonist; SAMA, short-acting muscarinic antagonist; SD, standard deviation.

Data are n (%) unless otherwise stated.

*Based on the medication possession ratio (MPR) and 5 Medication Adherence Rating Scale (MARS). Adherent patients: >80% MPR and good adherence rating across MARS questionnaire items.

† χ^2 , *t*-test, and Mann-Whitney *U* tests for categorical and interval/ratio variables, respectively.

‡Prescribed during a respiratory consultation.

§Diagnosis recorded in the year before the clinical review.

¶≥1 prescription issued in the year before the questionnaire collection.

#Two patients in the ≤400 eosinophils/μL cohort had missing adherence data.

33%, $P < .001$) and a smaller proportion were obese (29.5% vs 37.0%) (Table I). Both the elevated and normal blood eosinophil cohorts were reasonably well balanced in terms of clinical variables and prescribed medication during the baseline year. No significant differences were observed between the groups in ICS daily dose or courses of oral corticosteroids; however, more patients with elevated blood eosinophils were treated with ICS+LABA (or long-acting muscarinic antagonist) (79.6%) compared with those with blood eosinophil counts ≤400 cells/μL (76.1%) (Table I). In terms of comorbidities, patients with elevated blood eosinophil counts had higher prevalence of active rhinitis ($P = .043$) and eczema ($P = .003$), and lower prevalence of hypertension ($P = .004$), compared with patients within the normal blood eosinophil cohort (Table I).

A breakdown of blood eosinophil counts for both cohorts, in terms of the average daily dose of ICS, can be seen in Table E2 (available in this article's Online Repository at www.jaci-inpractice.org). Approximately 80% of patients in both groups had eosinophil counts measured within 3 years before the questionnaire collection (Table E3, available in this article's Online Repository at www.jaci-inpractice.org).

Finally, only 19.4% patients studied had good adherence to ICS therapy (Table II). Significantly more adherent patients were older ($P = .001$), never smoked ($P = .010$), and had comorbid rhinitis ($P < .001$), bronchiectasis ($P < .001$), and oral thrush ($P = .035$). There were also significant differences in medication profile ($P < .001$) between adherence groups. However, there was no significant difference in the proportion of patients with

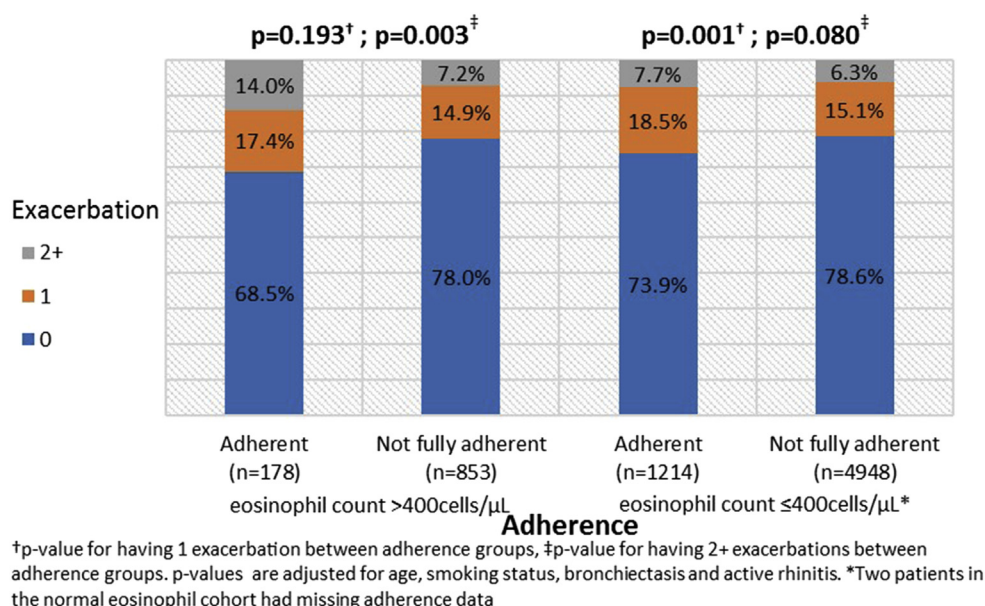


FIGURE 3. Percentage of patients with 0, 1, or 2+ exacerbations by adherence and eosinophil cohort. The proportions of patients within the elevated (>400 cells/μL) and normal blood eosinophil cohorts (≤400 cells/μL) that experienced asthma exacerbations during the baseline year, stratified by adherence to inhaled corticosteroids therapy. Severe exacerbations (from combined routine/questionnaire data): occurrence of hospital admissions/emergency department visits or prescriptions of acute courses of oral corticosteroids, in the year before the questionnaire collection. *P* values were generated by multinomial logistic regression for the risk of having 1 or 2+ exacerbations compared with having no exacerbation. Data are expressed as %.

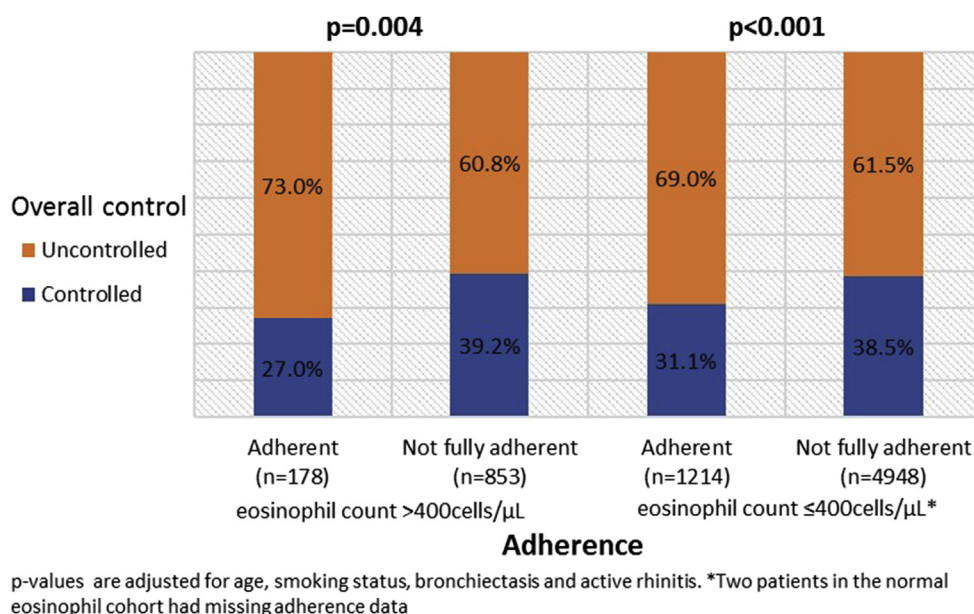


FIGURE 4. Percentage of patients with controlled/uncontrolled asthma by adherence and eosinophil cohort. The proportions of patients achieving asthma control, stratified by adherence to inhaled corticosteroids therapy, for both the normal (≤400 cells/μL) and elevated (>400 cells/μL) blood eosinophil cohorts are shown. *P* values were generated by binomial logistic regression. Data are expressed as %.

blood eosinophil count >400 cells/μL ($P = .067$) between patients who were adherent and patients who were not fully adherent to ICS therapy.

Primary outcome

The percentage of patients with 0, 1, or 2 or more exacerbations in each blood eosinophil cohort, stratified by adherence

to ICS therapy, is shown in Figure 3. The distribution of exacerbations differed significantly across adherence and eosinophil level groups, with the adherent patients in the elevated eosinophil group having the highest proportion of patients (14.0%) experiencing 2 or more exacerbations. Similar results were obtained in both sensitivity analyses (Tables E4 and E5, available in this article's Online Repository at www.jaci-inpractice.org).

The proportion of patients defined as having controlled asthma was also found to differ significantly between adherence groups; 73% of adherent patients in the elevated blood eosinophil cohort (>400 cells/ μ L) were found to have uncontrolled disease compared with 61% of patients not fully adherent to ICS treatment ($P = .004$) (Figure 4).

DISCUSSION

This is the first study to use routine clinical data to assess associations between adherence to ICS therapy, elevated blood eosinophil counts, and poor asthma control. In this novel, historical cohort study of more than 7000 patients with asthma and a clinically valid recorded blood eosinophil count, 14% had elevated blood eosinophils (>400 cells/ μ L). Within this group, 178 (17%) were adherent to ICS, of whom 25 (14%) experienced 2 or more exacerbations and 130 (73%) remained uncontrolled.

For patients with elevated blood eosinophils, the distribution of both exacerbations and asthma control differed significantly between the ICS adherence groups. A higher proportion of adherent patients had 2 or more exacerbations (14% vs 7%) and uncontrolled asthma (73% vs 61%) compared with non—fully adherent patients. A sensitivity analysis with a cutoff for high blood eosinophils of >300 eosinophils/ μ L demonstrated similar results, with an increased proportion of adherent patients experiencing severe asthma exacerbations during the baseline year (Table E5, available in this article's Online Repository at www.jaci-inpractice.org, $P = .017$ for 1 and $P = .022$ for 2 or more exacerbations). We also analyzed the relationship between adherence and exacerbation or symptom control in those with lower blood eosinophil counts, based on results from other studies that lower eosinophil group patients had worse response to ICS.^{27,28} In the current observational study, however, the relationship between adherence and the clinical outcomes was similar between the high and low eosinophil groups. There was also no significant statistical interaction between the adherence and eosinophil group (result not shown).

Differences in average daily ICS dose at baseline for elevated versus normal blood eosinophil counts were nonsignificant (median, 247 μ g/day [IQR, 137–427 μ g/day] vs 263 μ g/day [IQR 164–438 μ g/day] fluticasone equivalent; $P = .063$) and not clinically relevant. A dose-response effect of ICS on the reduction of blood eosinophil count for doses of up to 800 μ g/day (beclomethasone-equivalent) has been reported elsewhere.²⁹ Dose-response relationships between prescribed ICS and elevated blood eosinophil counts in patients with severe asthma should therefore be assessed in future studies.³⁰

One third of our study population prescribed medication within GINA steps 3 and 4 were current smokers, with more than 10% former smokers. Previous studies have reported that smoking hinders response to ICS treatment,^{31,32} and smoking status is therefore likely to confound the relationship between adherence to ICS treatment and symptom outcomes. We thus

adjusted for smoking status in the analysis of the relationship between adherence and asthma outcomes. Current and ex-smokers were found to be at significantly lower odds of having their asthma symptoms controlled than never smokers in the regression model (data not shown). This serves as a reminder for the requirement of continued efforts to offer smoking cessation to all respiratory patients.

Of note, 29% of patients with asthma included in this study received antibiotics during a respiratory consultation in the baseline year; it is unknown whether these prescriptions were clinically indicated or necessary. Although the signs and symptoms of an asthma exacerbation can be nonspecific, antibiotics should only be prescribed for patients with asthma when a bacterial infection is suspected; empirical or preventative use is not endorsed. This is a further call to strengthen government policy on the reduction of the unnecessary use of antibiotics to prevent side effects and thus avoid antimicrobial resistance.³³

In our study, patients with severe asthma and an elevated blood eosinophil count experienced frequent severe asthma exacerbations, despite evidence of adherence to refills for prescribed ICS therapy. This observation is in agreement with a previous retrospective study in which patients with asthma adherent to their controller therapy were not at a lower risk for symptom exacerbation.³⁴ Although this may indicate that a step-up in inhaled therapy is required for these patients, more than half of whom are on low-to-medium dose ICS treatment (≤ 320 μ g/day), it is likely that additional therapy, including the consideration of biologics, is needed. A total of 18% of patients within the elevated eosinophil cohort received an ICS daily dose of more than 500 μ g; this group of patients in particular may benefit from therapies specifically targeting eosinophilic airway inflammation, such as novel monoclonal antibodies, due to non-responsiveness to ICS therapy.³⁵

Blood eosinophil count is a useful biomarker for T2 profile asthma, but not all patients with asthma have a T2 profile.^{36,37} A study of adult-onset asthma found that increased blood neutrophil count was associated with disease severity.³⁸ Thus, blood neutrophil count would be an informative addition to further studies of this type to examine exacerbation risk.

Compared with the assessment of eosinophil counts in sputum, which is impractical in nonspecialized clinics,³⁹ simpler and less invasive clinical tests, such as peripheral blood eosinophil count or fraction of exhaled nitric oxide (FeNO),⁴⁰ may be more clinically feasible for assessing exacerbation risk and control. However, although there is a correlation between blood eosinophilia and FeNO, these biomarkers may be measuring differing inflammatory domains. Recent evidence suggests that blood eosinophils alone may not be sufficient to estimate lung inflammation; further research is needed to understand the dynamics of this relationship in routine clinical practice.⁴¹

A poor inhaler technique has been previously reported to be correlated with poor asthma control and asthma exacerbation and is frequently encountered.^{42,43} Thus, it is likely that the poor inhaler technique may have accounted for some of the poor asthma control and exacerbations observed within our adherent subjects. However, there is little to indicate differences in inhaler technique between compliant and noncompliant patients. This stresses the need for training and assessment of a proper inhalation technique to assist in controlling asthma symptoms and exacerbations.

The strengths of this study include the large sample size of patients with physician-diagnosed asthma and valid eosinophil readings. In addition, the study inclusion and exclusion criteria minimized potential confounding factors such as other asthma therapies, and the study identified patients prescribed ICS therapy from 2 large, well-described databases. To ensure that all potentially relevant variables for characterizing patients were included and that the key outcomes of interest could be evaluated, the statistical analysis plan, study population, and outcomes were all determined before any analyses.

However, there are potential limitations which are worth considering. This study aimed to represent real-life asthma care, but the study population might not be fully representative of the general UK asthma population. The proportion of patients with a Read code for physician-diagnosed asthma, who actually have asthma, is unknown.^{44,45} Patients diagnosed with other chronic respiratory diseases, such as COPD and asthma-COPD overlap syndrome, were excluded; these reportedly occur in 15% to 20% of patients with asthma, whereas their prevalence in some populations may be even higher.⁴⁶ Patients with features of both asthma and COPD often have frequent respiratory exacerbations⁴⁷; therefore, a similar study conducted using the identical databases and patient-reported data is needed to assess both asthma and COPD.

Adherence to ICS therapy was based on the MPR; however, it is not possible to determine whether the prescriptions for ICS were filled and taken by the patient. In addition, the higher proportion of adherent patients in the more severe outcome groups may conversely be a result of patients with more severe symptoms being more adherent to their treatment. The MARS questionnaire was included in this study as a measure of patient-reported adherence. However, patient self-reported adherence is known to be prone to inaccurate reporting by patients, either involuntarily (recall error) or voluntarily (over-reporting adherence to avoid negative feedback from healthcare providers).⁴⁸ This study used both medication dispensation measure and patient self-report, via questionnaire, to circumvent the weaknesses of each measure of adherence for a more accurate capture of patient medication consumption.

Given the observational nature of our research, reasons for the timing of venepuncture to determine eosinophil count and/or any other blood variable are unknown and cannot be formally interpreted here. Eosinophil count is not a routinely conducted clinical procedure in asthma management, and thus any eosinophilic measurement taken any time before the index date (usually recorded as part of a Full Blood Count or Complete Blood Count, drawn for other purposes) was included in this study to obtain a sufficiently large patient sample size. Only 53% of the patients in the current study had their eosinophils measured within a year before questionnaire collection (Table E3, available in this article's Online Repository at www.jaci-inpractice.org). However, sensitivity analysis in patients with eosinophil readings taken within 1 year from the index date showed similar results (Table E4, available in this article's Online Repository at www.jaci-inpractice.org). In addition, a recent publication using OPCR patient records showed eosinophilic counts to be relatively stable over a period of 1 year.⁴⁹

Lastly, it is possible that there are other potential confounders not currently taken into account, which could provide an alternate explanation for the results of this study. In the current study, adherence was assessed in the same period with asthma

outcome measures. Thus, it is not possible to determine the direction of causation between adherence and the heightened number of exacerbation and uncontrolled symptoms. The Ascertaining Barriers to Compliance taxonomy of adherence subdivides the traditional single act of medication adherence into separate acts of initiation, implementation, and persistence.⁵⁰ Future studies could therefore compare relationships among prescribed medications, asthma control, and the different temporal stages of adherence.

It is widely believed in respiratory medicine that patients with severe or uncontrolled asthma are poorly adherent to prescribed therapy.^{5,51} Contrarily, this study demonstrates that adherence rate to treatment was not lower among patients with more severe symptoms. Moreover, patients with elevated blood eosinophil levels who are nonresponsive to ICS therapy seem to constitute a higher proportion than previously suggested in the respiratory literature.^{5,35}

CONCLUSIONS

One in 7 patients in this study had elevated blood eosinophil counts; adherence to ICS therapy in these patients was not associated with better clinical outcomes. There exists a group of patients with asthma who are adherent with refill prescriptions to ICS therapy that still experience frequent exacerbations. This was also observed in patients with an elevated blood eosinophil level, which is usually indicative of better ICS responsiveness. Although it may be appropriate to increase inhaled therapy for those on lower doses of ICS, it is likely that additional treatment targeting other biological pathways apart from eosinophils may be required for these patients to achieve disease control. Among the considerations are interleukin suppressors such as anti-IL5 and other biologic therapies, which have been previously shown to reduce asthma exacerbation^{52,53} and improve asthma control⁵³ in patients with elevated blood eosinophil levels.

Acknowledgments

This study was conducted by the Observational and Pragmatic Research Institute Pte Ltd, in collaboration with the Respiratory Effectiveness Group (REG) and with institutional support from Teva Pharmaceuticals Europe B.V. The authors would like to thank Annabel Allison and Marcus Ngantcha for their assistance with analysis.

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ONLINE REPOSITORY STUDY POPULATION

Patients with elevated and normal blood eosinophil levels were characterized based on the demographic and clinical characteristics listed below obtained from the combined questionnaire initiative Helping Asthma in Real People (iHARP) and Optimum Patient Care Research Database datasets:

- Age and sex (at the time of the clinical review)
- Body mass index, at the time of, or closest to the clinical review, defined as the ratio of weight (kg) to squared height (m^2) and categorized as follows: underweight ($<18.5 \text{ kg}/m^2$); normal weight (≥ 18.5 and $<25 \text{ kg}/m^2$); overweight (≥ 25 and $<30 \text{ kg}/m^2$); obese ($\geq 30 \text{ kg}/m^2$)
- Smoking status (at the time of or closest to the clinical review): nonsmoker; current smoker; former smoker
- Comorbidities (also by the Charlson Comorbidity Index score) in the year before the clinical review included ischemic heart disease; heart failure; gastro-esophageal reflux disease; eosinophilic esophagitis; allergic and nonallergic rhinitis
- Side effects in the year before the clinical review included probable oral thrush; nasal polyps; anxiety/depression
- Lung function (peak expiratory flow [PEF], forced expiratory volume, PEF % predicted)
- Respiratory drugs usage (prescriptions and doses in the year before clinical review date)
- Number of inhaled corticosteroid (ICS) prescriptions, average ICS daily doses and device used in the year before eosinophil reading and in the year before the clinical review
- Number of prescriptions for acute courses of oral corticosteroids alongside a respiratory consultation
- Number of prescriptions and daily dose of reliever medication (short-acting β_2 agonists [SABA]) in the year before the clinical review
- Year of asthma diagnosis
- Date of eosinophil count and time from the date of the clinical review

Global Initiative for Asthma (GINA) evaluation and classification of asthma control

The level of GINA control (2010-2012 definition^{E1}) was evaluated based on questions regarding symptoms in the 4 weeks before the iHARP clinical review, and on PEF readings recorded closest to the date of the review, and categorized as follows:

- Controlled (no symptoms and PEF $>80\%$ of predicted)
- Partly controlled (1-2 asthma features and PEF $<80\%$ of predicted)
- Uncontrolled (partly controlled with ≥ 3 asthma features)

The percent predicted PEF values were calculated using Roberts' equations for male and female adults more than 18 years of age, as follows:

- Predicted PEF (liters/second) for males = $(5.317 \times (\text{height in meters})) - (0.062 \times (\text{age in years})) + 3.884$
- Predicted PEF (liters/second) for females = $(4.087 \times (\text{height in meters})) - (0.050 \times (\text{age in years})) + 2.945$

The GINA stepwise approach to asthma management is based on 5 "steps" that range from intermittent to severe chronic asthma. This classification of asthma is based on clinical characteristics that include frequency and control of asthma

symptoms, exacerbations or risks, poor inhaler technique, and adherence. At step 3, GINA advises 1 or 2 controllers and as-needed inhaled SABA; at step 4, 2 or more controllers and as-needed inhaled SABA.

ADHERENCE

Adherence to ICS therapy was inferred from patient-reported data and routine data, based on the medication possession ratio (MPR) and the Medication Adherence Rating Scale (MARS), respectively. Overall, adherence included the worse value of the 2 individual variables and was used for analysis in the current study.

ADHERENCE BASED ON ROUTINE DATA

Number of days per ICS pack = Number of actuations per ICS pack/Number of actuations per day

Total ICS pack days (for all prescribed ICS packs) = $\Sigma(\text{Number of days per ICS pack})$

$MPR \% = (\text{Total ICS pack days}/365) \times 100$

An MPR of $>80\%$ was used to group patients as adherent, and $\leq 80\%$ as non—fully adherent, to prescribed ICS therapy.

ADHERENCE BASED ON PATIENT-REPORTED DATA

Patient-reported adherence was measured based on MARS, which employs a 6-point scale (never, rarely, sometimes, regularly, often, and always) and the following 5 questions about controller inhalers:

1. I use it only when I feel breathless
2. I avoid using it if I can
3. I forget to take it
4. I decide to miss a dose
5. I choose to take it once a day

The responses to the above questions were categorized as follows:

- Poor adherence (respond to any of the questions with "often"/"always")
- Borderline (respond to more than 1 question with "sometimes")
- Good (none of above)

Patients with an MARS score of poor or borderline were classified as non—fully adherent.

Severe asthma exacerbations based on routine and patient-reported data

Severe asthma exacerbations (American Thoracic Society [ATS]/European Respiratory Society [ERS] definition) were inferred from patient-reported data and routine data, or a combination of patient-reported and routine data, where combined severe asthma exacerbations included the highest value of the 2 individual variables (main or sensitivity definitions only).

Severe asthma exacerbations based on patient-reported data

The number of severe asthma exacerbations (ATS/ERS definition) in the year preceding the clinical review period was defined from the number of acute oral corticosteroid courses reported by the patients when health care professionals asked

TABLE E1. Global Initiative for Asthma (GINA) criteria (2010-2012) for the assessment of current asthma control

Characteristics	Controlled (all the following)	Partly controlled (any present in any week)	Uncontrolled
Daytime symptoms	None (≤ 2 per week)	> 2 per week	≥ 3 or more features of partly controlled asthma
Limitation of activities	None	Any	
Nocturnal symptoms	None	Any	
Need for rescue/"reliever" medication	None (≤ 2 per week)	> 2 per week	
Lung function (PEF)	$> 80\%$ predicted	$< 80\%$ predicted or personal best	

PEF, Peak expiratory flow.

TABLE E2. Average daily inhaled corticosteroid doses of patients with elevated and normal eosinophil counts

		ICS average daily dose (µg fluticasone equivalent)*			
Eosinophil count (/µL)	No. of patients	>0-160	>160-320	>320-500	>500
Elevated eosinophil count (/µL)					
>400-500	436	123 (28)	138 (32)	93 (21)	82 (19)
>500-600	254	67 (26)	71 (28)	68 (27)	48 (19)
>600-700	129	30 (23)	45 (35)	30 (23)	24 (19)
>700-800	80	26 (33)	23 (29)	18 (23)	13 (16)
>800	131	28 (21)	44 (34)	39 (30)	20 (15)
Normal eosinophil count (/µL)					
0-100	1628	358 (22)	534 (33)	449 (28)	287 (18)
>100-200	2157	516 (24)	722 (33)	544 (25)	375 (17)
>200-300	1542	380 (25)	501 (32)	356 (23)	305 (20)
>300-400	833	205 (25)	278 (33)	198 (24)	152 (18)

ICS, Inhaled corticosteroid.

Data are n (%).

*Based on prescriptions issued in the year before questionnaire collection.

TABLE E3. Timing of blood eosinophil count from routine data

	Total (n = 7195)	Eosinophil groups	
		$> 400/\mu$ L (n = 1031)	$\leq 400/\mu$ L (n = 6164)
Last eosinophil count (/ μ L), median (IQR)	200 (120, 320)	540 (500, 700)	200 (100, 290)
Years between last eosinophil count reading and questionnaire collection			
≤ 1	3795 (53)	490 (48)	3305 (54)
$> 1-3$	2193 (30)	327 (32)	1866 (30)
$> 3-5$	705 (10)	110 (11)	595 (10)
> 5	502 (7)	104 (10)	398 (6)

IQR, Interquartile range.

Data are n (%) unless otherwise stated.

the following question: "How many courses of oral corticosteroids have you received in the last 12 months for worsening asthma?" Patients were classified as follows: higher risk (≥ 2

exacerbations in the previous year); moderate risk (1 exacerbation in the previous year); lower risk (0 exacerbations in the previous year).

TABLE E4. Sensitivity analysis of adherence by severe asthma exacerbations based on cutoff for elevated eosinophil levels at >400/ μ L recorded within 1 year from the date of questionnaire collection

	Eosinophil count >400/μL (n = 490)			Eosinophil count ≤400/μL (n = 3303)			Overall population (n = 3793)		
	Exacerbations*								
Adherence	0	1	2+	0	1	2+	0	1	2+
Adherent, n (%)	68 (71)	13 (14)	15 (16)	464 (73)	120 (19)	51 (8)	532 (73)	133 (18)	66 (9)
Non—fully adherent, n (%)	309 (78)	58 (15)	27 (7)	2071 (78)	430 (16)	167 (6)	2380 (78)	488 (16)	194 (6)
<i>P</i> value		.750			.044			.051	
1 exacerbation									
<i>P</i> value		.007			.157			.015	
2+ exacerbations									

Data presented as counts and percentages, n (%). *P* values were generated by multinomial logistic regression for the risk of having 1 or 2+ exacerbations compared with having no exacerbation.

*Severe exacerbations (combined routine/questionnaire data): occurrence of hospital admissions/emergency department visits or prescriptions of acute courses of oral corticosteroids, in the year before the questionnaire collection.

TABLE E5. Sensitivity analysis of adherence by severe asthma exacerbations based on cutoff for elevated eosinophil levels at >300/ μ L

	Eosinophil count >300/μL (n = 1865)			Eosinophil count ≤300/μL (n = 5328)			Overall population (n = 7193)		
	Exacerbations*								
Adherence	0	1	2+	0	1	2+	0	1	2+
Adherent, n (%)	232 (71)	56 (17)	38 (12)	787 (74)	199 (19)	80 (8)	1019 (73)	255 (18)	118 (8)
Non—fully adherent, n (%)	1205 (78)	224 (15)	110 (7)	3351 (79)	649 (15)	262 (6)	4556 (79)	873 (15)	372 (6)
P value		.017			.005			<.001	
1 exacerbation									
P value		.022			.075			.005	
2+ exacerbations									

Data are n (%). *P* values were generated by multinomial logistic regression for the risk of having 1 or 2+ exacerbations compared with having no exacerbation.

*Severe exacerbations (combined routine/questionnaire data): occurrence of hospital admissions/emergency department visits or prescriptions of acute courses of oral corticosteroids, in the year before the questionnaire collection.

REFERENCE

- E1. Global Initiative for Asthma (GINA). 2016 update: Global Strategy for Asthma Management and Prevention.