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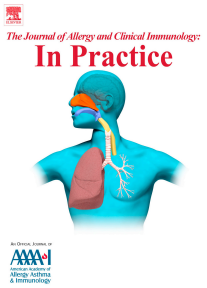

Relationship of inhaled corticosteroid adherence to asthma exacerbations in patients with moderate to severe asthma

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Relationship of inhaled corticosteroid adherence to asthma exacerbations in patients with moderate to severe asthma

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CONFLICT OF INTEREST DISCLOSURES

A Papi has received grants, personal fees and non-financial support from AstraZeneca, Chiesi Farmaceutici, GlaxoSmithKline, Boehringer Ingelheim, Merck Sharp & Dohme, Menarini, Novartis, Zambon, TEVA, Pfizer, Takeda, and Mundipharma.

D Ryan In the last three years DR has received Consultancy fees from TEVA, Chiesi, AstraZeneca, Novartis, Boehringer Ingelheim,and has spoken on behalf of AstraZeneca and TEVA and MEDA.

JB 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, Napp Pharmaceuticals, Mundipharma, NorPharma, Norvartis, Orion, Sanofi, Teva, Truddell 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 three years for speaking or participating in advisory boards for Aerocrine, Arsonette, Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Mundipharma, Novartis, Sandoz, Sanofi, Takeda and Teva.

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M Harris was an employee of Optimum Patient Care at the time of the study.

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DB Price has board membership with Aerocrine, Amgen, AstraZeneca, Boehringer

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Highlights Box:

What is already known about this topic? Non-adherence 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.

Abstract

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

Objective: 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, at Global Initiative for Asthma (GINA) steps 3 or 4, with ≥2 ICS prescriptions during the year prior to clinical review. Patient characteristics and adherence (based on prescription refills and patient self-report) for ICS therapy were analysed for those with elevated (>400 cells/μL) or normal (≤400 cells/μL) blood eosinophils.

Results: We studied 7,195 patients (66% female, mean age 60 years) with median eosinophil count of 200 cells/μL and found 81% to be non-fully adherent to ICS therapy. 1,031 patients (14%) had elevated blood eosinophil counts (58% female, mean age 60 years), 83% of whom were non-fully adherent to ICS. An increased proportion of adherent patients in the elevated blood eosinophil group had ≥2 exacerbations (14.0% vs 7.2%; p=0.003) and uncontrolled asthma (73% vs 60.8%; p=0.004) as compared to non-fully adherent patients.

Conclusions: Approximately one in seven patients had elevated eosinophils. Adherence to ICS therapy was not associated with 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.

Keywords: adherence; asthma control; eosinophils; asthma exacerbations; inhaled corticosteroids; severe asthma

Abbreviations:

ACO: Asthma-COPD Overlap

COPD: Chronic Obstructive Pulmonary Disease

ENCePP: European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

REC: Research Ethics Committee

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

LAMA = long-acting muscarinic antagonist

LTRA = leukotriene receptor antagonist

MARS: Medication Adherence Rating Scale

MPR: Medication Possession Ratio

OPCRD: Optimum Patient Care Research Database

QOF: Quality and Outcomes Framework

SABA = short-acting β-agonist

SAMA = short-acting muscarinic antagonist

SD: Standard Deviation

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INTRODUCTION

The complex interrelationship between asthma control, exacerbation risk, blood eosinophil counts and asthma treatment, has been the subject of recent studies. In randomised 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/μL 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/μL were more likely to be on higher therapeutic steps (steps 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.

Non-adherence to prescribed medication is also an important risk factor for exacerbations, including asthma-related hospitalisations[5-7] 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 hypothesised that there exists a population of patients with eosinophilic asthma, a common asthma phenotype characterised by elevated blood eosinophil counts, [11] 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 characterisation 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 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 over 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 [REC] 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 5,000 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/LABA, are aged ≥18years, and are at GINA step 3 or 4 during iHARP review), ascertained from the OPCRD population, were invited for an iHARP review. To optimise the

number of study patients and the evaluation of adherence, iHARP and OPCRD questionnaire data were combined in one 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 prior to the date of clinical review and with a prior diagnosis of asthma any time before review based on the recorded Quality and Outcomes Framework (QOF) Read codes, the clinical coding system within UK's general practice for asthma. Presence of QOF read codes indicate physician diagnosed asthma, however the criteria on which diagnosis had been made was not accessible. Patients were receiving GINA step 3 or 4 asthma management, as determined on the date of clinical review using GINA criteria (2010-2012) for asthma control and risk (**Table E1**), had ≥2 ICS (fluticasone propionate-equivalent units) prescriptions during the baseline year, and had a valid blood eosinophil count recorded at any time prior to 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 prior to eosinophil count or long-term systemic or maintenance oral corticosteroids for asthma, were excluded.

Eligible patients were divided into two 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 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 was 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 cut-off values to define medication adherence have been used in the respiratory literature,[18] a cut-off 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 the supplementary methods.

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 (ATS)/European Respiratory Society (ERS) Task Force definition[25] 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 hospitalisation or a generic hospitalisation 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, out-patient 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 average daily dose of ≤200µg salbutamol or ≤500µg terbutaline. Questionnaire and routine data were combined and used to assess adherence, while routine data alone was used to assess all other variables. Further details on the outcomes can be found in the supplementary data.

370

371 ***Statistical analyses***

372 The main analysis included patients with eosinophil counts recorded at any time prior
373 to the date of questionnaire collection. All statistical analyses were conducted using SAS
374 version 9.4 (SAS Institute, North Carolina, USA).[26] Statistical evidence was determined if P-
375 values were less than 0.05.

376 Summary statistics were calculated for patient demographics and baseline
377 characteristics, both overall, and by elevated and normal blood eosinophil cohorts. For
378 continuous variables either the mean and standard deviation (SD) or the median and
379 interquartile range (IQR) were calculated. For categorical variables, the frequency and
380 percentage of observed levels were calculated for the sample with non-missing
381 observations. Patient demographic and baseline characteristics were compared between the
382 elevated and normal blood eosinophil cohorts using the Chi-square test, t-test or Mann-
383 Whitney U test, where appropriate.

384

385 ***Primary outcome analysis***

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

391

392 ***Sensitivity analysis***

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

395 1. Patients with blood eosinophil counts recorded within 1 year from the date of
396 questionnaire collection

2. Patients with eosinophil counts recorded ever prior to questionnaire collection, where the cut-off for elevated eosinophil count was set *a priori* at >300 cells/µL

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 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 to 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/µL (IQR: 120-320 cells/µL) (**Table E3**). During the baseline year, 22% received acute courses of oral corticosteroids with a respiratory consultation, and the majority were prescribed multiple respiratory medications.

Overall, 1,031 of the 7,195 patients (14%) had elevated blood eosinophil counts (>400 cells/µL). Compared with patients who had blood eosinophil counts of ≤400 cells/µL, patients with elevated blood eosinophils were more likely to be male (42% vs 33%, p<0.001) and a smaller proportion were obese (29.5% vs 37.0%) (**Table 1**). 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 LAMA) (79.6%) compared with those with blood eosinophil counts ≤400 cells/µL (76.1%) (**Table 1**). In terms of comorbidities, patients with elevated blood eosinophil counts had higher prevalence of active rhinitis (p=0.043) and eczema (p=0.003), and lower prevalence of

hypertension (p=0.004), compared to patients within the normal blood eosinophil cohort (**Table 1**).

A breakdown of blood eosinophil counts for both cohorts, in terms of average daily dose of ICS, can be seen in **Table E2**. Approximately 80% of patients in both groups had eosinophil counts measured within 3 years prior to the questionnaire collection (**Table E3**).

Finally, only 19.4% patients studied had good adherence to ICS therapy (Table 2). Significantly more adherent patients were older (p=0.001), never smoked (p=0.010), and had co-morbid rhinitis (p<0.001), bronchiectasis (p<0.001), and oral thrush (p=0.035). There were also significant differences in medication profile (p<0.001) between adherence groups. However, there was no significant difference in the proportion of patients with blood eosinophil count >400 cells/μL (p=0.067) 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+ 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**).

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/μL) were found to have uncontrolled disease compared to 61% of patients non-fully adherent to ICS treatment (p=0.004) (**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 over 7,000 patients with asthma and a clinically valid recorded blood eosinophil count, 14% had elevated blood eosinophils (>400 cells/μL). Within this group, 178 (17%) were adherent to ICS, of which 25 (14%) experienced ≥2 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 exacerbations (14% versus 7%) and uncontrolled asthma (73% versus 61%) compared to non-fully adherent patients. A sensitivity analysis with a cut-off for high blood eosinophils of >300 eosinophils/μL demonstrated similar results, with an increased proportion of adherent patients experiencing severe asthma exacerbations during the baseline year (Table E5, p=0.017 for 1 and p=0.022 for ≥2 exacerbations). We also analysed 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 adherence and eosinophil group (result not shown).

Differences in average daily ICS dose at baseline for elevated versus normal blood eosinophil counts were non-significant (median, 247 μg/day [IQR, 137-427 μg/day] vs 263 μg/day [IQR 164-438 μg/day] fluticasone equivalent; p=0.063) and not clinically relevant. A dose–response effect of ICS on the reduction of blood eosinophil count for doses of up to 800 μg/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 non-specific, 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 asthma patients adherent to their controller therapy were not at lower risk for symptom exacerbation[34]. Whilst 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 µg/day), it is likely that additional therapy, including the consideration of biologics, is needed. 18% of patients within the elevated eosinophil cohort received an ICS daily dose of more than 500 µg; 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 non-specialised 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]

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 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 non-compliant patients. This stresses the need for training and assessment of proper inhalation technique to assist in controlling asthma symptoms and exacerbations.

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 minimised potential confounding factors such as other asthma therapies, and the study identified patients prescribed ICS therapy from two large, well-described databases. To ensure that all potentially relevant variables for characterising patients were included and that the key outcomes of interest could be evaluated, the statistical analysis plan, study population and outcomes were all determined prior to 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 (ACO) syndrome, were excluded; these reportedly occur in 15–20% of patients with

asthma, while their prevalence in some populations may be even higher.[46] Patients with features of both asthma and COPD often have frequent respiratory exacerbations;[47] 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 medication possession ratio; 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 utilised 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 prior to 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 (Supplementary Table E3). However, sensitivity analysis in patients with eosinophil readings taken within 1 year from the index date showed similar results (Supplementary Table E4). Additionally, a recent publication utilising OPCRD patient records showed eosinophilic counts to be relatively stable over a period of one 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 (ABC) 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 non-responsive to ICS therapy seem to constitute a higher proportion than previously suggested in the respiratory literature.[5,35]

CONCLUSIONS

One in seven 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. Whilst 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 control[53] in patients with elevated blood eosinophil levels.

ACKNOWLEDGEMENTS

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Tables and figures:

Table 1: Baseline demographic and clinical characteristics in patients with asthma with elevated versus normal eosinophil counts

Characteristics		Overall population (n=7195)	Blood eosinophil count		P value*
			>400 cells/µL (n=1031)	≤400 cells/µL (n=6164)	
Age (years)	Mean (SD)	60.2 (15.1)	59.6 (15.8)	60.3 (15.0)	0.194
Sex	Male	2476 (34.4)	433 (42.0)	2043 (33.1)	<0.001
Body Mass Index (BMI)	Underweight	81 (1.1)	13 (1.3)	68 (1.1)	<0.001
	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	Non-missing	6953 (96.6)	999 (96.9)	5954 (96.6)	0.107
	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	Non-missing	6337 (88.1)	918 (89.0)	5419 (87.9)	0.185
	<50%	488 (7.7)	81 (8.8)	407 (7.5)	

	50 - <70%	1527 (24.1)	237 (25.8)	1290 (23.8)	
	70 - <80%	1287 (20.3)	186 (20.3)	1101 (20.3)	
	≥80	3035 (47.9)	414 (45.1)	2621 (48.4)	
Medication therapy ±SABA (or SAMA)	ICS	921 (12.8)	105 (10.2)	816 (13.3)	0.040
	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 (µg)[†]	>0-160	1733 (24.1)	274 (26.6)	1459 (23.7)	0.218
	>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	Non-missing	7178 (99.8)	1,027 (99.6)	6151 (99.8)	0.128
	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)	0.280
	≥1	1582 (22.0)	240 (23.3)	1342 (21.8)	
Antibiotic prescriptions[¥]	0	5094 (70.8)	726 (70.4)	4368 (70.9)	0.771
	≥1	2101 (29.2)	305 (29.6)	1796 (29.1)	

Bronchiectasis[¶]	199 (2.8)	36 (3.5)	163 (2.6)	0.124
Active rhinitis (diagnosis and/or nasal corticosteroids)[#]	1431 (19.9)	229 (22.2)	1202 (19.5)	0.043
Active oral thrush (diagnosis and/or antifungals)[#]	276 (3.8)	39 (3.8)	237 (3.8)	0.925
Eczema[¶]	1955 (27.2)	320 (31.1)	1635 (26.5)	0.003

Data are n (%) unless otherwise stated. *Chi-square, t-test, and Mann-Whitney U tests for categorical and interval/ratio variables, respectively. [†]Fluticasone-equivalent units (based on prescriptions in the year prior to index date). [¶]Diagnosis recorded in the year prior to clinical review. [#]≥1 prescription issued in the year prior to the questionnaire collection. [¥]Prescribed during a respiratory consultation.

ICS = inhaled corticosteroid; IQR = interquartile range; 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.

615 **Table 2. Baseline demographic and clinical characteristics in patients with asthma**
616 **who were adherent and non-fully adherent to ICS therapy**

Characteristics		Adherence†		P value*
		Adherent (n=1392)	Non-fully (n=5801)	
Age (years)	Mean (SD)	61.4 (14.5)	59.9 (15.2)	0.001
Sex	Male	479 (34.4)	1996 (34.4)	1.00
Body Mass Index (BMI)	Underweight	17 (1.2)	64 (1.1)	0.13
	Normal	395 (28.7)	1501 (26.3)	
	Overweight	503 (36.6)	2062 (36.1)	
	Obese	460 (33.5)	2088 (36.5)	
Smoking status	Non-missing	1342 (96.4)	5609 (96.7)	0.010
	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)	0.81
Medication therapy ±SABA (or SAMA)	ICS	150 (10.8)	771 (13.3)	<0.001
	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)	0. 80
	≥1	290 (20.8)	1191 (20.5)	
Bronchiectasis¶		70 (5.0)	128 (2.2)	<0.001
Active rhinitis (diagnosis and/or nasal		474 (34.1)	1626 (28.0)	<0.001

corticosteroids)[#]				
Active oral thrush (diagnosis and/or antifungals)[#]		67 (4.8)	209 (3.6)	0.035
Eczema[¶]		364 (26.1)	1591 (27.4)	0.33
Blood eosinophil count	≤400 cells/μL[‡]	1214 (87.2)	4948 (85.3)	0.067
	>400 cells/μL	178 (12.8)	853 (14.7)	

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. *Chi-square, t-test, and Mann-Whitney U tests for categorical and interval/ratio variables, respectively. ¶Diagnosis recorded in the year prior to clinical review. #≥1 prescription issued in the year prior to the questionnaire collection. ¥Prescribed during a respiratory consultation. ‡Two patients in the ≤400 eosinophils /μL cohort had missing adherence data. ICS = inhaled corticosteroid; IQR = interquartile range; 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.

Figure Legends

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

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. Abbreviations: 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

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 ICS 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 prior to the questionnaire collection. P-values were generated by multinomial logistic regression for the risk of having 1 or 2+ exacerbations compared to having no exacerbation. Data is expressed as %.

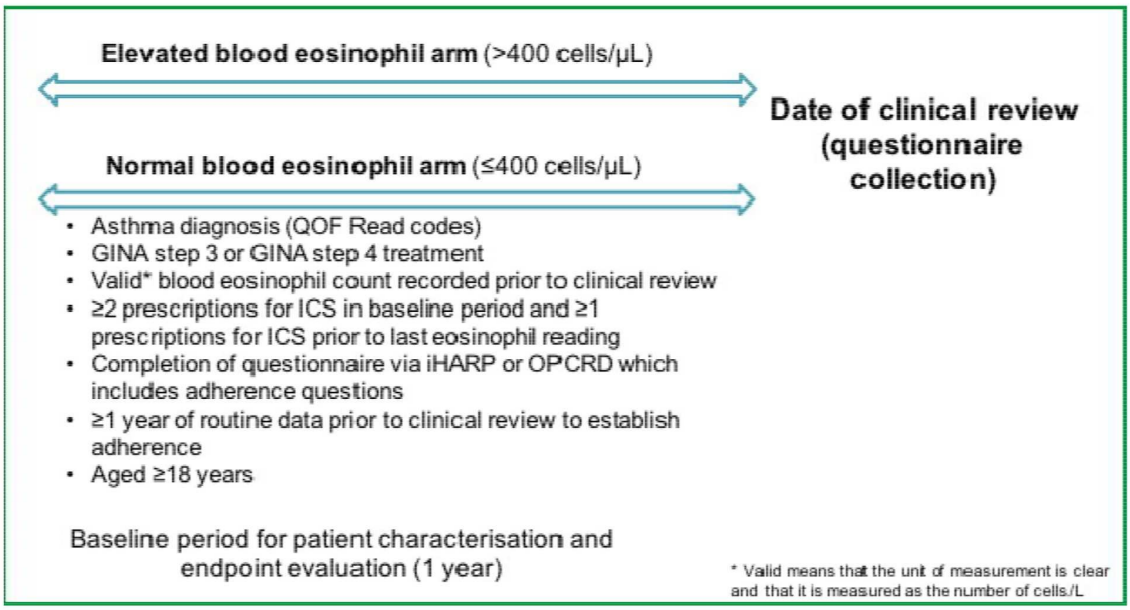
Figure 4: Percentage of patients with controlled/uncontrolled asthma by adherence and eosinophil cohort. The proportions of patients achieving asthma control, stratified by adherence to ICS therapy, for both the normal (≤400 cells/µL) and elevated (>400 cells/µL) blood eosinophil cohorts are shown. P-values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

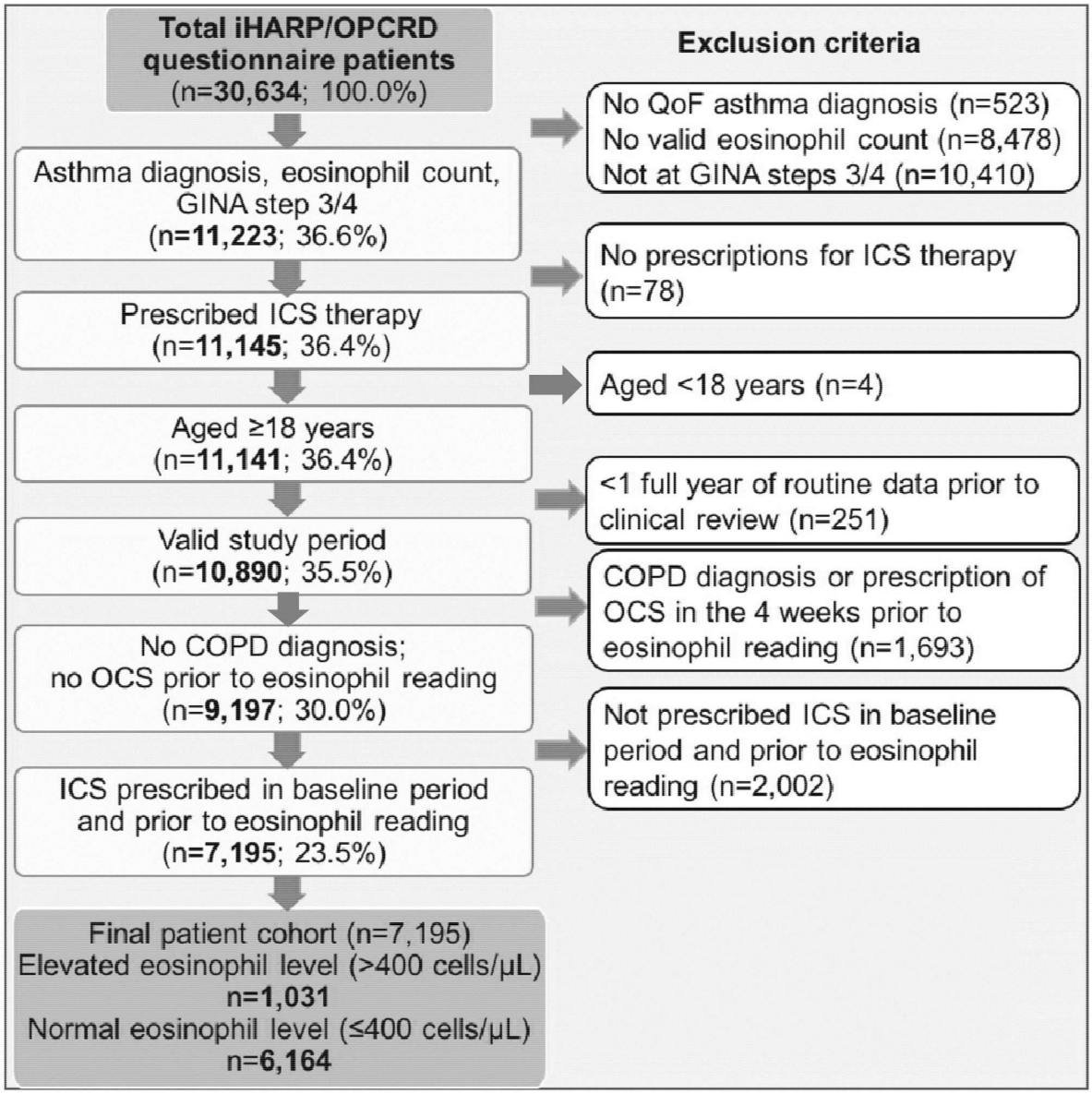
References

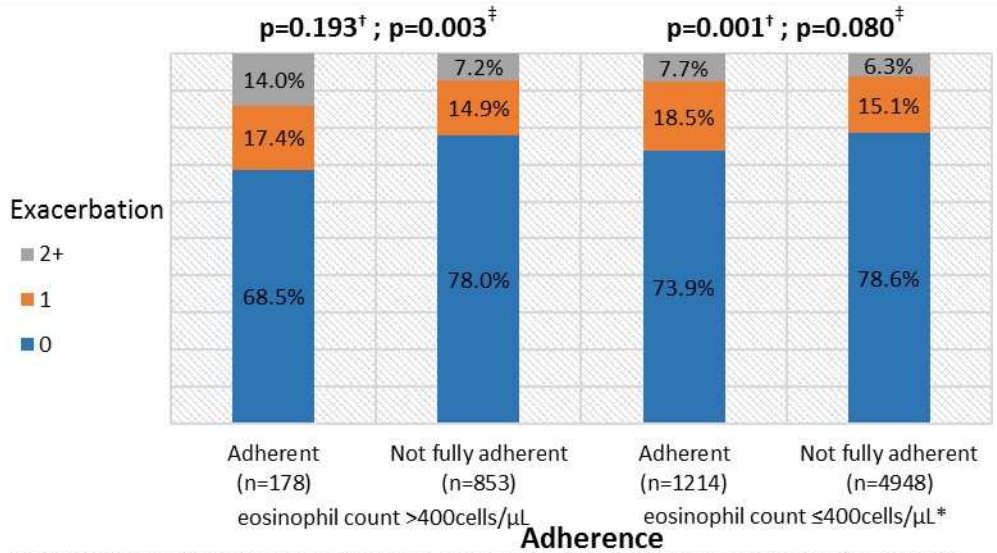
1. Pavord ID, Korn S, Howarth P, Bleecker ER, Buhl R, Keene ON, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. Lancet (London, England). 2012;380(9842):651-9.
2. Price D, Wilson AM, Chisholm A, Rigazio A, Burden A, Thomas M, et al. Predicting frequent asthma exacerbations using blood eosinophil count and other patient data routinely available in clinical practice. Journal of asthma and allergy. 2016;9:1-12.
3. 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. The Lancet Respiratory medicine. 2015;3(11):849-58.
4. Global Initiative for Asthma [Available from: http://ginasthma.org/.
5. Gamble J, Stevenson M, McClean E, Heaney LG. The prevalence of nonadherence in difficult asthma. Am J Respir Crit Care Med. 2009;180(9):817-22.
6. Sims EJ, Price D, Haughney J, Ryan D, Thomas M. Current control and future risk in asthma management. Allergy Asthma Immunol Res. 2011;3(4):217-25.
7. Suissa S, Ernst P, Kezouh A. Regular use of inhaled corticosteroids and the long term prevention of hospitalisation for asthma. Thorax. 2002;57(10):880-4.
8. Levy ML. The national review of asthma deaths: what did we learn and what needs to change? Breathe (Sheffield, England). 2015;11(1):14-24.
9. Bateman ED, Bousquet J, Busse WW, Clark TJ, Gul N, Gibbs M, et al. Stability of asthma control with regular treatment: an analysis of the Gaining Optimal Asthma controL (GOAL) study. Allergy. 2008;63(7):932-8.
10. Suissa S, Ernst P, Benayoun S, Baltzan M, Cai B. Low-dose inhaled corticosteroids and the prevention of death from asthma. N Engl J Med. 2000;343(5):332-6.
11. Gibson PG. Inflammatory phenotypes in adult asthma: clinical applications. Clin Respir J. 2009;3(4):198-206.
12. Roche N, Reddel H, Martin R, Brusselle G, Papi A, Thomas M, et al. Quality standards for real-world research. Focus on observational database studies of comparative effectiveness. Ann Am Thorac Soc. 2014;11 Suppl 2:S99-104.
13. European Network of Centres for Pharmacoepidemiology and Pharmacovigilance [Available from: http://www.encepp.eu/.
14. Optimum Patient Care Research Database (OPCRD) [Available from: http://www.optimumpatientcare.org/database-overview.
15. iHARP database [Available from: http://iharp.org/.
16. Haughney J, Sims E, Holohan J, Ryan D, Price D. Improving clinician-patient communication in asthma: the HARP project. Allergy. 2010;65(4):413-4.
17. NHS Foundation Trust, Salisbury. Eosinophilia - Causes and Investigations [Available from: http://www.icid.salisbury.nhs.uk/ClinicalManagement/Haematology/Pages/Eosinophilia-CausesandInvestigations.aspx.
18. Engelkes M, Janssens HM, de Jongste JC, Sturkenboom MC, Verhamme KM. Medication adherence and the risk of severe asthma exacerbations: a systematic review. Eur Respir J. 2015;45(2):396-407.
19. Erickson SR, Coombs JH, Kirking DM, Azimi AR. Compliance from self-reported versus pharmacy claims data with metered-dose inhalers. Ann Pharmacother. 2001;35(9):997-1003.
20. Guenette L, Moisan J, Preville M, Boyer R. Measures of adherence based on self-report exhibited poor agreement with those based on pharmacy records. J Clin Epidemiol. 2005;58(9):924-33.
21. Martin R, Price D, Krishnan J, Campbell JD, Bjermer L, McIvor A, et al. Poster presentation: Excess inhaled corticosteroid adherence may be a marker of uncontrolled asthma. European Respiratory Society Annual Congress; Barcelona2013.

22. Steiner JF, Prochazka AV. The assessment of refill compliance using pharmacy records: methods, validity, and applications. Journal of clinical epidemiology. 1997;50(1):105-16.
23. Van Steenis M, Driesenaar J, Bensing J, Van Hulten R, Souverein P, Van Dijk L, et al. Relationship between medication beliefs, self-reported and refill adherence, and symptoms in patients with asthma using inhaled corticosteroids. Patient Prefer Adherence. 2014;8:83-91.
24. Adherence in Asthma and COPD [Available from: http://advanceweb.com/web/AstraZeneca/focus_on_copd_issue11/focus_on_copd_issue11_Adherence_in_asthma_and_copd.html.
25. 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(2):343-73.
26. SAS statistical software [Available from: https://www.sas.com/en_gb/software/sas9.html.
27. Kitaguchi Y, Komatsu Y, Fujimoto K, Hanaoka M, Kubo K. Sputum eosinophilia can predict responsiveness to inhaled corticosteroid treatment in patients with overlap syndrome of COPD and asthma. International journal of chronic obstructive pulmonary disease. 2012;7:283-9.
28. Pascoe S, Locantore N, Dransfield MT, Barnes NC, Pavord ID. Blood eosinophil counts, exacerbations, and response to the addition of inhaled fluticasone furoate to vilanterol in patients with chronic obstructive pulmonary disease: a secondary analysis of data from two parallel randomised controlled trials. The Lancet Respiratory medicine. 2015;3(6):435-42.
29. Anderson WJ, Short PM, Williamson PA, Manoharan A, Lipworth BJ. The inverse agonist propranolol confers no corticosteroid-sparing activity in mild-to-moderate persistent asthma. Clin Sci (Lond). 2014;127(11):635-43.
30. Lipworth B, Jabbal S, Manoharan A, Anderson W, Short P. Inhaled corticosteroid dose-response on blood eosinophils in asthma. Lancet Respir Med. 2016;4(1):e1.
31. Shimoda T, Obase Y, Kishikawa R, Iwanaga T. Influence of cigarette smoking on airway inflammation and inhaled corticosteroid treatment in patients with asthma. Allergy and asthma proceedings. 2016;37(4):50-8.
32. Tomlinson JE, McMahon AD, Chaudhuri R, Thompson JM, Wood SF, Thomson NC. Efficacy of low and high dose inhaled corticosteroid in smokers versus non-smokers with mild asthma. Thorax. 2005;60(4):282-7.
33. Wise R. An overview of the Specialist Advisory Committee on Antimicrobial Resistance (SACAR). J Antimicrob Chemother. 2007;60 Suppl 1:i5-7.
34. Zeiger RS, Schatz M, Chen W, Li Q, Khatry DB, Tran TN. Adherent uncontrolled adult persistent asthma: Characteristics and asthma outcomes. The journal of allergy and clinical immunology In practice. 2015;3(6):986-90 e2.
35. Wardlaw AJ, Brightling C, Green R, Woltmann G, Pavord I. Eosinophils in asthma and other allergic diseases. Br Med Bull. 2000;56(4):985-1003.
36. Berry A, Busse WW. Biomarkers in asthmatic patients: Has their time come to direct treatment? J Allergy Clin Immunol. 2016;137(5):1317-24.
37. Wenzel SE. Asthma phenotypes: the evolution from clinical to molecular approaches. Nat Med. 2012;18(5):716-25.
38. Amelink M, de Groot JC, de Nijs SB, Lutter R, Zwinderman AH, Sterk PJ, et al. Severe adult-onset asthma: A distinct phenotype. J Allergy Clin Immunol. 2013;132(2):336-41.
39. Fulkerson PC, Rothenberg ME. Targeting eosinophils in allergy, inflammation and beyond. Nat Rev Drug Discov. 2013;12(2):117-29.
40. Price D, Ryan D, Burden A, Von Ziegenweidt J, Gould S, Freeman D, et al. Using fractional exhaled nitric oxide (FeNO) to diagnose steroid-responsive disease and guide asthma management in routine care. Clin Transl Allergy. 2013;3(1):37.

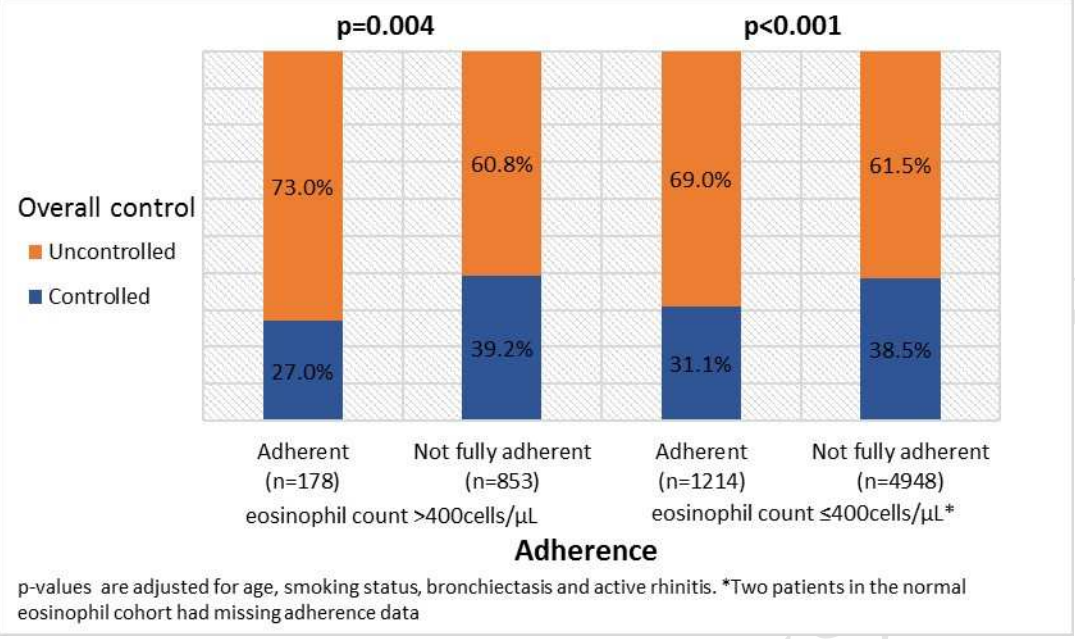
41. Malinovschi A, Fonseca JA, Jacinto T, Alving K, Janson C. Exhaled nitric oxide levels and blood eosinophil counts independently associate with wheeze and asthma events in National Health and Nutrition Examination Survey subjects. J Allergy Clin Immunol. 2013;132(4):821-7 e1-5.
42. Price DB, Roman-Rodriguez M, McQueen RB, Bosnic-Anticevich S, Carter V, Gruffydd-Jones K, et al. Inhaler Errors in the CRITIKAL Study: Type, Frequency, and Association with Asthma Outcomes. The journal of allergy and clinical immunology In practice. 2017;5(4):1071-81 e9.
43. Westerik JA, Carter V, Chrystyn H, Burden A, Thompson SL, Ryan D, et al. Characteristics of patients making serious inhaler errors with a dry powder inhaler and association with asthma-related events in a primary care setting. The Journal of asthma : official journal of the Association for the Care of Asthma. 2016;53(3):321-9.
44. Starren ES, Roberts NJ, Tahir M, O'Byrne L, Haffenden R, Patel IS, et al. A centralised respiratory diagnostic service for primary care: a 4-year audit. Prim Care Respir J. 2012;21(2):180-6.
45. Aaron SD, Vandemheen KL, FitzGerald JM, Ainslie M, Gupta S, Lemiere C, et al. Reevaluation of Diagnosis in Adults With Physician-Diagnosed Asthma. JAMA. 2017;317(3):269-79.
46. Barnes PJ. Asthma-COPD Overlap. Chest. 2016;149(1):7-8.
47. Gibson PG, Powell H, Coughlan J, Wilson AJ, Abramson M, Haywood P, et al. Self-management education and regular practitioner review for adults with asthma. Cochrane Database Syst Rev. 2003(1):CD001117.
48. Lam WY, Fresco P. Medication Adherence Measures: An Overview. Biomed Res Int. 2015;2015:217047.
49. Landis SH, Suruki R, Hilton E, Compton C, Galwey NW. Stability of Blood Eosinophil Count in Patients with COPD in the UK Clinical Practice Research Datalink. Copd. 2017;14(4):382-8.
50. Vrijens B, De Geest S, Hughes DA, Przemyslaw K, Demonceau J, Ruppar T, et al. A new taxonomy for describing and defining adherence to medications. British journal of clinical pharmacology. 2012;73(5):691-705.
51. Williams LK, Peterson EL, Wells K, Ahmedani BK, Kumar R, Burchard EG, et al. Quantifying the proportion of severe asthma exacerbations attributable to inhaled corticosteroid nonadherence. J Allergy Clin Immunol. 2011;128(6):1185-91 e2.
52. Katz LE, Gleich GJ, Hartley BF, Yancey SW, Ortega HG. Blood eosinophil count is a useful biomarker to identify patients with severe eosinophilic asthma. Ann Am Thorac Soc. 2014;11(4):531-6.
53. Bel EH, Wenzel SE, Thompson PJ, Prazma CM, Keene ON, Yancey SW, et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. The New England journal of medicine. 2014;371(13):1189-97.




Total iHARP/OPCRD questionnaire patients (n=30,634; 100.0%)
Exclusion criteria
Asthma diagnosis, eosinophil count, GINA step 3/4 (n=11,223; 36.6%)
No QoF asthma diagnosis (n=523)
No valid eosinophil count (n=8,478)
Not at GINA steps 3/4 (n=10,410)
Prescribed ICS therapy (n=11,145; 36.4%)
No prescriptions for ICS therapy (n=78)
Aged ≥18 years (n=11,141; 36.4%)
Aged <18 years (n=4)
Valid study period (n=10,890; 35.5%)
<1 full year of routine data prior to clinical review (n=251)
No COPD diagnosis; no OCS prior to eosinophil reading (n=9,197; 30.0%)
COPD diagnosis or prescription of OCS in the 4 weeks prior to eosinophil reading (n=1,693)
ICS prescribed in baseline period and prior to eosinophil reading (n=7,195; 23.5%)
Not prescribed ICS in baseline period and prior to eosinophil reading (n=2,002)
Final patient cohort (n=7,195)
Elevated eosinophil level (>400 cells/µL) n=1,031
Normal eosinophil level (≤400 cells/µL) n=6,164



†p-value for having 1 exacerbation between adherence groups, ‡p-value for having 2+ exacerbations between adherence groups. p-values are adjusted for age, smoking status, bronchiectasis and active rhinitis. *Two patients in the normal eosinophil cohort had missing adherence data



p-values are adjusted for age, smoking status, bronchiectasis and active rhinitis. *Two patients in the normal eosinophil cohort had missing adherence data

Online Supplement

Study Population

Patients with elevated and normal blood eosinophil levels were characterised based on the demographic and clinical characteristics listed below obtained from the combined questionnaire iHARP and OPCRD datasets:

- Age and sex (at the time of the clinical review)
- BMI (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 categorised as: Underweight (<18.5 kg/m^2); Normal weight (≥18.5 and <25 kg/m^2); Overweight (≥25 and <30 kg/m^2); Obese (≥30 kg/m^2)
- Smoking status (at the time of or closest to the clinical review): Non-smoker; Current smoker; Former smoker
- Comorbidities (also by Charlson Comorbidity Index score) in the year prior to the clinical review included ischaemic heart disease; heart failure; gastro-oesophageal reflux disease; eosinophilic esophagitis; allergic and non-allergic rhinitis
- Side effects in the year prior to the clinical review included probable oral thrush; nasal polyps; anxiety/depression
- Lung function (peak expiratory flow [PEF], forced expiratory volume [FEV_1], 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 prior to 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 prior to clinical review

- Year of asthma diagnosis
- Date of eosinophil count and time from the date of 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 prior to the iHARP clinical review, and on PEF readings recorded closest to the date of the review, and categorised as:

- 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 the Roberts' equations for male and female adults aged over 18 years of age, as follows:

- Predicted PEF (litres/sec) for males = (5.317 * (height in metres)) - (0.062* (age in years)) + 3.884
- Predicted PEF (litres/sec) for females = (4.087 * (height in metres)) - (0.050* (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 one or two controllers and as-needed inhaled short-acting $beta_2$-agonist; at Step 4, two or more controllers and as-needed inhaled short-acting $beta_2$-agonist.

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 two 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) = Σ (Number of days per ICS pack)

Medication Possession Ratio % = (Total ICS pack days/365) * 100

An MPR of >80% was used to group patients as adherent, and ≤80% as non-fully adherent, to prescribed ICS therapy.

Adherence based on patient-reported data

Patient-reported adherence was measured based on Medication Adherence Rating Scale (MARS) [1], 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 categorised as:

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

Patients with a 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 two 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 clinical review period was defined from the number of acute oral corticosteroid courses reported by the patients when health care professionals asked the following question: "How many courses of oral corticosteroids have you received in the last 12 months for worsening

asthma?" Patients were classified as: Higher risk (≥2 exacerbations in the previous year); Moderate risk (1 exacerbation in the previous year); Lower risk (0 exacerbations in the previous year).

References

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

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

Eosinophil count (/µL)		No. of patients	ICS average daily dose (µg fluticasone equivalent)*			
			>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	1,628	358 (22)	534 (33)	449 (28)	287 (18)
	>100-200	2,157	516 (24)	722 (33)	544 (25)	375 (17)
	>200-300	1,542	380 (25)	501 (32)	356 (23)	305 (20)
	>300-400	833	205 (25)	278 (33)	198 (24)	152 (18)

Data are n (%). *****Based on prescriptions issued in the year prior to questionnaire collection. ICS = inhaled corticosteroid.

Table E3: Timing of blood eosinophil count from routine data

		Total (n=7,195)	Eosinophil groups	
			>400/µL (n=1,031)	≤400/µL (n=6,164)
Last eosinophil count (/µL), 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)	3,305 (54)
	>1-3	2193 (30)	327 (32)	1,866 (30)
	>3-5	705 (10)	110 (11)	595 (10)
	>5	502 (7)	104 (10)	398 (6)

Data are n (%) unless otherwise stated. IQR = interquartile range.

Table E4: Sensitivity analysis of adherence by severe asthma exacerbations based on cut-off for elevated eosinophil levels at >400/µL recorded within 1 year from the date of questionnaire collection

Adherence	Eosinophil count >400/µL (n=490)			Eosinophil count ≤400/µL (n=3,303)			Overall population (n=3,793)		
	Exacerbations*								
	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)
Not fully adherent, n (%)	309 (78)	58 (15)	27 (7)	2071 (78)	430 (16)	167 (6)	2380 (78)	488 (16)	194 (6)
P-value 1 exacerbation	0.750			0.044			0.051		
P-value 2+ exacerbations	0.007			0.157			0.015		

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 to 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 prior to the questionnaire collection.

Table E5: Sensitivity analysis of adherence by severe asthma exacerbations based on cut-off for elevated eosinophil levels at >300/µL

Adherence	Eosinophil count >300/µL (n=1865)			Eosinophil count ≤300/µL (n=5328)			Overall population (n=7193)		
	Exacerbations*								
	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 1 exacerbation	0.017			0.005			<0.001		
P-value 2+ exacerbations	0.022			0.075			0.005		

Data are n (%). P-values were generated by multinomial logistic regression for the risk of having 1 or 2+ exacerbations compared to 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 prior to the questionnaire collection.