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A Randomized Trial of a Composite T2-Biomarker Strategy Adjusting Corticosteroid Treatment in Severe Asthma: A *Post Hoc* Analysis by Sex



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What is already known about this topic? A female preponderance is present in adults with severe asthma who often have a high symptom burden but low biomarkers of T2 inflammation. Asthma guidelines recommend treatment escalation based on symptoms, which potentially leads to inappropriate corticosteroid (CS) dose escalation.

What does this article add to our knowledge? Compared with males, females with severe asthma derive greater benefit from biomarker-directed CS downtitration of treatment without worsening asthma control/increased exacerbation risk. Extrapulmonary comorbidities (obesity/anxiety and/or depression/anxiety) lead to increased symptom burden, which can expose females to excessive CS treatment.

How does this study impact current management guidelines? Clinicians should be aware of the dissociation between symptoms and inflammation and encouraged to measure T2 biomarkers, lung function, and other objective measures to inform precise treatment choices and prevent avoidable harm through inappropriate CS dose escalation.

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Abbreviations used

ACQ-7- 7-item Asthma Control Questionnaire

AQLQ- Asthma Quality of Life Questionnaire

BMI- body mass index

CS- corticosteroid

FENO- fractional exhaled nitric oxide

ICS- inhaled corticosteroid

LABA- long-acting β -agonist

NHS- National Health Service

OCS- oral corticosteroid

ppb- parts per billion

T2- type 2

BACKGROUND: Approximately 5% to 10% of patients with asthma have severe disease, with a consistent preponderance in females. Current asthma guidelines recommend stepwise treatment to achieve symptom control with no differential treatment considerations for either sex.

OBJECTIVE: To examine whether patient sex affects outcomes when using a composite T2-biomarker score to adjust corticosteroid (CS) treatment in patients with severe asthma compared with standard care.

METHODS: This is a *post hoc* analysis, stratifying patient outcomes by sex, of a 48-week, multicenter, randomized controlled clinical trial comparing a biomarker-defined treatment algorithm with standard care. The primary outcome was the proportion of patients with a reduction in CS treatment (inhaled and oral corticosteroids). Secondary outcomes included exacerbation rates, hospital admissions, and lung function.

RESULTS: Of the 301 patients randomized, 194 (64.5%) were females and 107 (35.5%) were males. The biomarker algorithm led to a greater proportion of females being on a lower CS dose versus standard care, which was not seen in males (effect estimate: females, 3.57; 95% CI, 1.14-11.18 vs males, 0.54; 95%

CI, 0.16-1.80). In T2-biomarker–low females, reducing CS dose was not associated with increased exacerbations. Females scored higher in all domains of the 7-item Asthma Control Questionnaire, apart from FEV₁, but with no difference when adjusted for body mass index/anxiety and/or depression. Dissociation between symptoms and T2 biomarkers were noted in both sexes, with a higher proportion of females being symptom high/T2-biomarker low (22.8% vs 15.6%; $P = .0002$), whereas males were symptom low/T2-biomarker high (22.3% vs 11.4%; $P < .0001$).

CONCLUSIONS: This exploratory *post hoc* analysis identified that females achieved a greater benefit from biomarker-directed CS optimization versus symptom-directed treatment. © 2023 The Authors. Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>). (J Allergy Clin Immunol Pract 2023;11:1233-42)

Key words: Severe asthma; Sex; Biomarkers; Extrapulmonary comorbidities

INTRODUCTION

Asthma affects more than 300 million people globally, with an estimated 5% to 10% having severe disease.¹ This is defined as asthma that remains uncontrolled despite adherence to maximal optimized therapy and management of contributory factors, or as asthma that becomes uncontrolled when high-dose treatment is decreased.¹ Severe asthma populations have a female preponderance, a phenomenon that is consistently well documented but remains largely unexplained.²⁻⁶ Catamenial asthma has previously been described in premenopausal women as a cause of

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asthma severity.⁷ However, the median age reported in cohorts with severe asthma is consistently more than 55 years, suggesting that catamenial asthma is not a major driver.²⁻⁶

Current asthma treatment guidelines recommend a stepwise increase in treatment with inhaled corticosteroids (ICSs) and adjunctive therapies to achieve symptom control and exacerbation reduction.¹ Guidelines recommend stepping down treatment after 3 months, when good asthma control is achieved.¹ However, symptoms in some patients with severe asthma may be due to both extrapulmonary comorbidities and non-corticosteroid-responsive pulmonary mechanisms. Consequently, symptom-driven treatment escalation can result in patients being maintained on inappropriately high corticosteroid (CS) doses, which is associated with an increased risk of CS-related adverse effects.⁸⁻¹⁰

Given that CS treatment provides minimal clinical benefit in the absence of type 2 (T2) cytokine-driven eosinophilic inflammation, we recently compared a management approach in which CS treatment decisions were guided by a composite T2-biomarker score (derived from fractional exhaled nitric oxide [FENO], peripheral blood eosinophil count, and serum periostin) versus standard care in patients with severe asthma who were T2-biomarker low at initial assessment.¹¹ Although the primary outcome of that study, the proportion of patients on lower CS dose at 48 weeks, was negative in the intention-to-treat population, it was positive in the per-protocol analysis. The main reason for this difference was patients choosing not to follow treatment advice, the reasons for which have been reported in a previous analysis.¹² However, in patients with uncontrolled asthma (with a score of ≥ 1.5 on the 7-item Asthma Control Questionnaire [ACQ-7]), we observed that biomarker-directed treatment adjustment resulted in a greater proportion of patients achieving lower CS doses, without loss of asthma control.¹¹ There was a marked female preponderance in both the overall clinical trial population and those with uncontrolled asthma (64% and 62%, respectively), suggesting that female preponderance seen in the general adult population with asthma also occurs in patients with a high symptom burden but with a low T2-biomarker score (biomarker low).¹¹ This symptom-high/biomarker-low discordance has been reported previously in a cluster analysis in patients with severe asthma and has been linked to female sex and obesity.¹³

Despite the consistent female preponderance in cohorts of patients with severe asthma and the observation that symptom burden is dissociated from T2 inflammation in a subset of females with severe asthma, asthma treatment guidelines do not suggest alternative treatment strategies for males and females. During the development of new asthma medicines, regulators require pharmaceutical companies to perform prespecified outcome analysis to ensure no sex difference is identified. However, evidence supporting different outcomes by sex is reported infrequently in other clinical trials.

In this *post hoc* analysis, stratifying patient outcome by sex, we report on CS adjustment using the composite T2-biomarker score in patients with severe asthma compared to standard care.

METHODS

Study design

We performed a *post hoc* secondary analysis on data from a 48-week, multicenter, randomized controlled clinical study comparing CS treatment optimization in patients with severe asthma using a

composite T2-biomarker strategy to a symptom/risk-based algorithm.¹¹

Important secondary outcomes of the study included comparison of exacerbation rates, asthma control, and asthma-related quality of life between the treatment arms (see this article's Online Repository at www.jaci-inpractice.org).¹¹ The study protocol (ClinicalTrials.gov NCT02717689)¹⁴ and the primary study outcome have been published previously.¹¹ The primary study protocol was approved by the Office for Research Ethics Committees Northern Ireland (NI0158) and individual National Health Service (NHS) Research and Development at participating centers. An independent Trial Steering Committee monitored conduct of the trial. All participants provided informed written consent.¹¹

Participants

Participants were recruited from 12 UK asthma centers between January 8, 2016, and July 12, 2018 (see this article's Online Repository at www.jaci-inpractice.org). All participants had severe asthma (Global Initiative for Asthma steps 4 and 5), were between 18 and 80 years old, and were enrolled in a nonselective manner. The full inclusion and exclusion criteria are given in this article's Online Repository at www.jaci-inpractice.org. However, as a core aim was to enrich for T2-biomarker-low participants, subjects had to have a FENO of less than 45 parts per billion (ppb) at screening.

Procedures

Following randomization, participants visited every 8 weeks for review of their asthma control and treatment.¹¹ After each study visit, patient ACQ-7 scores, postbronchodilator FEV₁, FENO, and blood eosinophil count (within 24 hours of collection) were recorded in the electronic case report form. Periostin values were entered automatically when available, usually within 3 to 5 days of sample collection by a central laboratory.

Participants in both trial arms received treatment instructions at each clinic visit, with strategies used to ensure patient blinding to their treatment arm, which were shown at the end of the study to have been effective¹¹; those in the biomarker arm and the standard care arm had treatment adjusted according to individual trial algorithms (see Tables E1 and E2 in this article's Online Repository at www.jaci-inpractice.org). Recommendations included therapeutic adjustment to decrease, maintain, or increase treatment (see Tables E3 and E4 in this article's Online Repository at www.jaci-inpractice.org). A default advisory to maintain treatment was provided when it was not possible to run the algorithm because of missing biomarker data (eg, unable to provide a blood sample or FENO measurement or logistical issue [sample leakage]). Asthma exacerbations were managed according to the participant's self-management plan, with no adjustment in background treatment, and any planned therapy adjustments were deferred until the next scheduled visit. Participants were seen by the clinical investigator if there was any concern regarding persistent poorly controlled asthma or treatment adjustments. Final assessments occurred at week 48.

Statistical analyses

Full statistical methods are provided in this article's Online Repository at www.jaci-inpractice.org. The primary outcome measure of the original study was the proportion of participants with a reduction in ICS or oral corticosteroid (OCS) dose from baseline to week 48. Secondary outcome measures included ICS dose at study end, cumulative dose of ICS, and proportion of participants on

TABLE 1. Demographic characteristics, medical history, lung function, biomarkers, CS treatment, and patient-reported outcomes in the randomized population by sex

Characteristics	Female (n = 194)*	Male (n = 107)*	P value†
Age (y), mean ± SD	54.3 ± 13.5	58.3 ± 12.1	.01
Ethnicity, n (%)			.70
Non-White	15 (7.7)	7 (6.5)	
White	179 (92.3)	100 (93.5)	
BMI (kg/m ²), mean ± SD	33.0 ± 8.0	29.2 ± 4.5	<.0001
<24.9, n (%)	25 (13.0)	17 (15.9)	
25-29.9, n (%)	49 (25.4)	50 (46.7)	
>30, n (%)	119 (61.7)	40 (37.4)	
Smoking status, n (%)			.32
Never smoked, n (%)	148 (76.3)	76 (71.0)	
Ex-smoker, n (%)	46 (23.7)	31 (29.0)	
Full-time working, n (%)	47 (24.4)	45 (42.1)	.001
Exacerbations (last year)‡	3 (1, 4)	2 (0, 3)	.0002
Asthma primary care visit (last year), n (%)	125 (64.4)	38 (35.5)	<.0001
Asthma ER attendance (last year), n (%)	46 (23.7)	20 (18.7)	.31
Asthma hospitalization (last year), n (%)	36 (18.6)	21 (19.6)	.82
Asthma ICU (ever), n (%)	43 (22.2)	21 (19.6)	.61
Ventilated (ever), n (%)	20 (47.6)	11 (52.4)	.72
Atopic disease, n (%)§	131 (67.9)	76 (71.0)	.57
History of rhinitis, n (%)	134 (69.1)	74 (69.2)	.99
History of eczema, n (%)	64 (33.0)	36 (33.6)	.91
History of nasal polyps, n (%)	34 (17.5)	39 (36.4)	.0002
History of nasal surgery, n (%)	32 (16.5)	38 (35.5)	.0002
History of esophageal reflux, n (%)	118 (60.8)	61 (57.0)	.52
History of aspirin sensitivity, n (%)	36 (18.6)	11 (10.3)	.06
Hypertension, n (%)	54 (27.8)	40 (37.4)	.09
Anxiety and/or depression, n (%)	74 (38.1)	18 (16.8)	.0001
Osteoarthritis, n (%)	58 (29.9)	20 (18.7)	.03
Osteoporosis/osteopenia, n (%)	45 (23.2)	21 (19.6)	.47
Hypercholesterolemia, n (%)	34 (17.5)	19 (17.8)	.96
Diabetes, n (%)	21 (10.8)	13 (12.1)	.73
Cataracts, n (%)	22 (11.3)	11 (10.3)	.78
% Predicted FEV ₁ §	77.0 ± 18.3	72.9 ± 20.8	.08
% Predicted FVC§	92.1 ± 17.0	89.3 ± 16.6	.16
FEV ₁ /FVC§	0.67 ± 0.12	0.63 ± 0.11	.003
PEFR (L/min)§	338.9 ± 98.7	442.9 ± 146.1	<.0001
ACQ-7 score§	2.1 ± 1.1	1.8 ± 1.2	.04
AQLQ total score§	4.7 ± 1.3	5.2 ± 1.4	.004
Sputum eosinophils (%)‡	1.3 (0.4, 13.1)	1.7 (0.3, 5.5)	.81
FENO (ppb)‡	19 (13, 28)	23 (14, 30)	.05
Blood eosinophils (10 ⁹ /L)‡	0.21 (0.11, 0.32)	0.22 (0.11, 0.36)	.44
Periostin (ng/mL)§	52.2 ± 15.9	54.3 ± 16.8	.29
Composite score, n (%)			.07
0	47 (24.4)	21 (20.0)	
1	116 (60.1)	56 (53.3)	
2	30 (15.5)	28 (26.7)	
Composite high (score 2), n (%)	30 (15.5)	28 (26.7)	.02
ICS dose (BDP) [μg]§	2253 ± 732	2207 ± 687	.59
OCS user, n (%)	73 (37.6)	41 (38.3)	.91
OCS dose (mg)‡	10 (7, 10)	10 (5, 10)	.97

BDP, Beclomethasone dipropionate; ER, emergency room; FVC, forced vital capacity; ICU, intensive care unit; PEFR, peak expiratory flow rate.

*The number of female and male participants is represented as a percentage in the text.

†P values for ethnicity, BMI, smoking status, and composite score are represented as combined figures.

‡Atopic disease was defined as a history of allergic rhinitis (seasonal or perennial allergen) or eczema.

§Figures presented as means (SD).

‖Figures presented as medians (Interquartile range).

OCSs. Asthma outcomes included rate of protocol-defined severe exacerbations per participant year, time to first severe exacerbation, hospital admissions for asthma and changes in lung function, ACQ-7 score, and Asthma Quality of Life Questionnaire (AQLQ) score from baseline to week 48. Separate analyses were conducted for females and males, with interaction tests used to formally test for differences between sexes¹⁵; sex was considered to be a binary variable. For the primary outcome, reductions in CS doses between the study start and end were analyzed using logistic regression models adjusted for age, smoking status, treatment center, courses of rescue steroids in the year before randomization (categorized as <2 or ≥ 2), and ACQ-7 score at baseline (categorized as <1.5 and ≥ 1.5).

Secondary outcomes were analyzed using linear (ACQ-7, AQLQ, FEV₁, log [FENO], log [blood eosinophils], periostin, ICS dose, and OCS dose), Poisson (protocol-defined exacerbations and hospitalizations), logistic (refusal to start OCS), and Cox (time to first exacerbation) regression models. All models were adjusted for age, smoking status, treatment center, rescue steroid use in the year before randomization (categorized as <2 or ≥ 2), and ACQ-7 score at baseline (categorized as <1.5 and ≥ 1.5). Data for outcomes measured at each study visit (ACQ-7, AQLQ, FEV₁, FENO, blood eosinophil count, periostin, ICS dose, and OCS dose) were further adjusted for the outcome baseline measurement.

RESULTS

Study population

Baseline demographic characteristics, medical history, comorbidities, lung function, and CS treatment in the randomized Refractory Asthma Stratification Programme (UK) population at baseline, stratified by sex, are presented in Table 1. Of the 301 participants randomized, 194 (64.5%) were female and 107 (35.5%) were male. Females were noted to be younger than males (54.3 ± 13.5 vs 58.3 ± 12.1 years). Female subjects also had a higher mean body mass index (BMI; 33.0 ± 8.0 vs 29.2 ± 4.5 kg/m²), with a larger proportion being obese (61.7% vs 37.4%). Females reported more exacerbations than males in the previous year (median, 3 vs 2), and a greater proportion had a primary care visit for asthma (64.4% vs 35.5%). The proportions of each sex visiting the emergency room (23.7% [females] vs 18.7% [males]) and being admitted to hospital for asthma in the year before randomization (18.6% [females] vs 19.6% [males]) were similar. Females had higher documented levels of anxiety and/or depression (38.1% vs 16.8%) (on the basis of patient health care records including medication use as well as a self-reported history of anxiety and/or depression requiring medical assessment) and osteoarthritis (29.9% vs 18.7%) compared with males, although they were less likely to have a history of nasal polyps (17.5% vs 36.4%) or nasal surgery (16.5% vs 35.5%). There was no difference in the reported incidence of prior atopic disease in females and males (67.9% and 71.0%, respectively). Females had more asthma symptoms at baseline as determined by ACQ-7 score (2.1 ± 1.1 vs 1.8 ± 1.2) and poorer asthma-related quality-of-life score (AQLQ; 4.7 ± 1.3 vs 5.2 ± 1.4), although they were less likely to be composite biomarker high when compared with males (15.5% vs 26.7%).

Effect on primary and secondary study outcomes by sex. Study outcomes, including CS use, lung function, asthma symptoms, asthma-related quality of life, and T2 biomarkers in a randomized population stratified by sex, are presented in Table II. For the primary end point, the biomarker algorithm led

to a substantially greater proportion of female participants versus males on lower doses of CS than the symptom-based algorithm (odds of being on a lower dose: 3.57 [95% CI, 1.14-11.18] in females and 0.54 [95% CI, 0.16-1.80] in males; interaction test, $P = .03$). The difference was driven by divergence in the symptom-based treatment arm, with females less likely than males to reduce CS treatment using a symptom-based algorithm. In terms of secondary outcomes, the difference in daily OCS dose and cumulative CS dose was greater in males compared with females, because of larger reductions in OCS using a symptom-based strategy in males (Table II). Despite a greater reduction in CS treatment in females, there was no suggestion of worsening asthma control, increased exacerbation rate, or difference in T2-biomarker levels between males and females.

Differences in asthma symptom score by sex (baseline).

The unadjusted difference between females and males in overall ACQ-7 score at baseline was 0.28 (95% CI, -0.55 to -0.01). Given the sex difference in the reporting of asthma symptoms (Table I; see Figure E1 in this article's Online Repository at www.jaci-inpractice.org), we explored mediation of the individual components of the ACQ-7 by baseline differences in demographic and clinical features between males and females (Figure 1). We observed higher symptom reporting among females in several areas of the subjectively reported constituent questions of the ACQ-7. Notably, when adjusted for BMI and anxiety and/or depression, the sex difference is largely attenuated in the constituent components of the ACQ-7 relating to "shortness of breath," "puffs of SABA," and "woken at night" as well as in the "overall score" (Figure 1). Adjustment for age and smoking history did not impact sex differences in the ACQ. Of note, lung function as the only objectively measured aspect of the ACQ; males experienced a greater burden in terms of FEV₁ compared with females, even after mediation was applied. We also observed a similar trend in quality of life, when assessed by AQLQ, and the individual domains within this questionnaire where differences in sex became less apparent after adjustment for BMI and anxiety and/or depression (see Figure E2 in this article's Online Repository at www.jaci-inpractice.org).

Relationship between symptoms and T2 biomarkers in males and females.

We observed distinct associations between T2 biomarkers and asthma symptom scores in females but not in males (Figure 2; $P = .004$). There was a strong positive relationship between the ACQ-7 score and the composite biomarker score in female participants ($P = .0002$), with higher symptom scores among those with a composite score of 2 (ACQ-7 score: 2.42; 95% CI, 2.19-2.65) when compared with those with a score of 0 (ACQ-7 score: 2.05; 95% CI, 1.83-2.28). Conversely, there was no evidence of any relationship between biomarkers and symptoms among males ($P = .47$), and symptom scores were similar between those with a composite score of 2 (ACQ-7 score: 1.89; 95% CI, 1.62-2.17) or 0 (ACQ-7 score: 1.99; 95% CI, 1.69-2.28). The mean difference between males and females among those with a composite score of 2 was 0.53 (95% CI, 0.22-0.84).

Concordant symptom and biomarker scores (where treatment adjustment using symptom and biomarker strategies would lead to similar treatment advice) were seen in 46% of females and 42% of males (Table III). However, a proportion of participants

TABLE II. Effects on CS treatment dose, lung function, asthma symptoms, asthma-related quality of life, and T2 biomarkers at the end of the study in the randomized population when stratified by sex

Result	Female			Male			P (interaction test)
	Symptom-based (n = 39)	Biomarker (n = 133)	Effect estimate (95% CI)	Symptom-based (n = 15)	Biomarker (n = 76)	Effect estimate (95% CI)	
Reduced CSs (%)	10.3 (2.9, 24.2)	28.8 (21.2, 37.3)	3.57 (1.14 to 11.18)	40.0 (16.3, 67.7)	27.6 (18.0, 39.1)	0.54 (0.16 to 1.80)	.03
ICS dose (BDP/ μ g)*	2067 (1937, 2197)	1938 (1765, 2110)	-123 (-347 to 100)	1867 (1593, 2140)	1986 (1767, 2204)	9 (-364 to 383)	.59
Total ICS dose (BDP/mg)†	729 (687, 770)	712 (657, 766)	-16 (-118 to 85)	715 (606, 823)	730 (664, 796)	28 (-126 to 182)	.73
OCS dose (mg)	7 (5, 10)	5 (4, 6)	-2 (-3 to 0)	3 (-0, 6)	6 (4,8)	1 (-1 to 4)	.03
Total OCS dose (mg)	1900 (1238,2561)	1450 (1125,1775)	-333 (-981 to 314)	913 (229,1596)	1947 (1329, 2566)	1006 (-434 to 2445)	.03
OCS usage (%)	64.1 (47.2, 78.8)	48.5 (39.7, 57.3)	0.47 (0.18 to 1.26)	33.3 (11.8, 61.6)	51.3 (39.6, 63.0)	2.42 (0.43 to 13.51)	.05
ACQ-7 score	2.3 (1.9, 2.7)	2.1 (1.8, 2.3)	-0.2 (-0.5 to 0.1)	2.0 (1.1, 2.8)	1.8 (1.5, 2.1)	0.2 (-0.2 to 0.6)	.15
AQLQ total score	4.4 (4.0, 4.9)	4.8 (4.6, 5.1)	0.2 (-0.3 to 0.6)	5.3 (4.3, 6.2)	5.3 (5.0, 5.7)	0.2 (-0.5 to 0.8)	.99
% Predicted FEV ₁	74.1 (68.1, 80.1)	74.3 (70.9, 77.6)	-0.0 (-4.0 to 4.0)	66.9 (53.0, 80.8)	71.3 (67.0, 75.6)	1.0 (-4.5 to 6.5)	.73
FENO (ppb)	20.0 (17.0, 27.0)	20.5 (19.0, 22.0)	0.93 (0.77 to 1.13)	19.0 (11.0, 26.0)	26.0 (22.0, 30.0)	1.24 (0.93 to 1.65)	.14
Blood eosinophils (10 ⁹ /L)	0.28 (0.18, 0.41)	0.19 (0.16, 0.22)	0.84 (0.62 to 1.13)	0.35 (0.27, 0.42)	0.25 (0.19, 0.29)	0.76 (0.46 to 1.26)	.66
Periostin (ng/mL)	50.4 (45.1, 55.8)	50.7 (48.3, 53.1)	-0.2 (-3.5 to 3.1)	63.3 (49.7, 76.8)	52.7 (49.3, 56.2)	-5.7 (-11.8 to 0.4)	.08
Annual exacerbation rate	1.92 (1.52, 2.43)	1.59 (1.38, 1.83)	0.76 (0.53 to 1.08)	1.00 (0.59, 1.69)	0.96 (0.76, 1.22)	1.02 (0.49 to 2.12)	.45
Annual hospitalization rate	0.16 (0.07,0.37)	0.11 (0.07,0.19)	0.70 (0.24 to 2.02)	0.14 (0.04,0.57)	0.07 (0.03,0.17)	0.52 (0.09 to 3.04)	.88
Refused OCS (%)	46.7 (21.3,73.4)	53.4 (39.9,66.7)	0.89 (0.23 to 3.47)	0.0 (0.0,97.5)	60.5 (44.4,75.0)		

BDP, Beclometasone dipropionate.

Data is represented as medians, interquartile ranges and effect estimates.

*BDP/ μ g equivalent.

†BDP/mg equivalent.

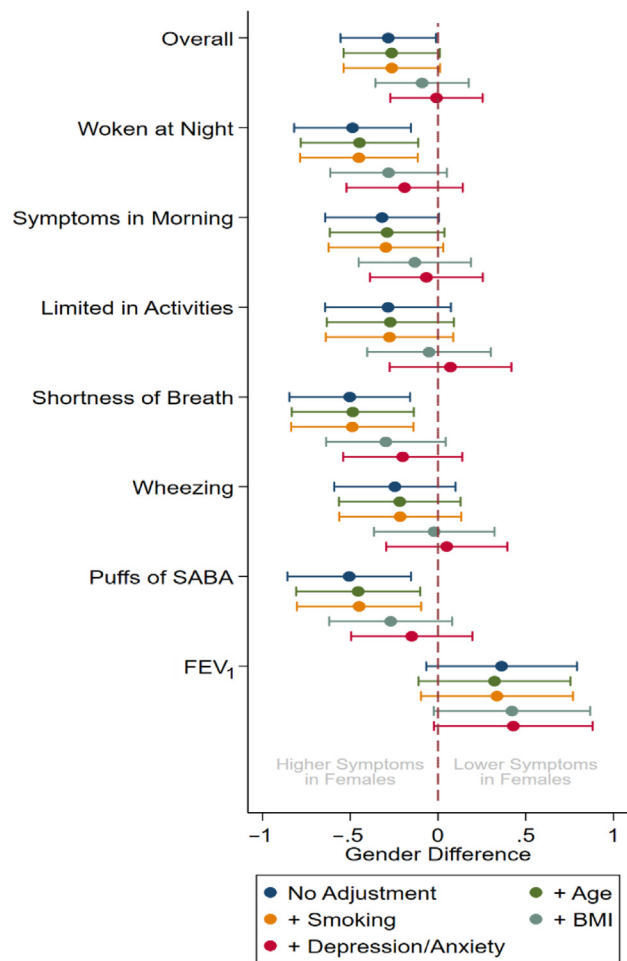


FIGURE 1. Mediation of sex differences in the overall ACQ-7 and the individual components of this questionnaire by demographic factors and comorbidities. *SABA*, Short-acting-Beta-agonist.

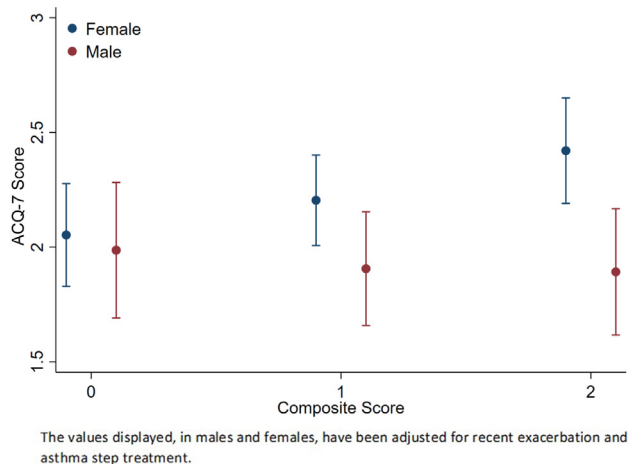


FIGURE 2. Relationship between composite T2-biomarker score and symptom score (ACQ-7), stratified by sex. The values displayed, in males and females, have been adjusted for recent exacerbation and asthma step treatment.

TABLE III. Biomarker and symptom concordance in males and females by composite scores*

Sex	Biomarkers		
Females	Score 0	Score 1	Score 2
Symptoms			
Score 0	31 (2.6%)	109 (9.1%)	28 (2.3%)
Score 1	131 (11.0%)	467 (39.1%)	101 (8.5%)
Score 2	76 (6.4%)	196 (16.4%)	54 (4.5%)
Males	Score 0	Score 1	Score 2
Symptoms			
Score 0	22 (3.4%)	93 (14.3%)	52 (8.0%)
Score 1	50 (7.7%)	230 (35.4%)	82 (12.6%)
Score 2	29 (4.5%)	72 (11.1%)	20 (3.1%)

Low symptoms with dissociated biomarkers are indicated by italicized text. High symptoms with dissociated biomarkers are indicated by bold text. *Females were more likely to be symptom high/biomarker low (22.8% vs 15.5%; $P = .0002$), whereas males were more likely to be symptom low/biomarker high (22.3% vs 11.5%; $P < .0001$).

had discordant symptom and biomarker scores, and the pattern of discordance was different between females and males, with a higher proportion of females being symptom high/biomarker low (ie, a symptom score of 2 and a combined biomarker score of 0-1) (22.8% vs 15.6%; $P = .0002$). More males were symptom low/biomarker high (ie, a symptom score of 0 and a combined biomarker score of 1-2) (22.3% vs 11.4%; $P < .0001$) (Table III). These dissociative patterns were also seen with FENO as a single biomarker and a composite score using FENO and blood eosinophil count (Table IV).

DISCUSSION

This *post hoc* analysis shows that females derive greater benefit than males from biomarker-directed CS optimization compared with a standard care-based approach, using symptom score and recent exacerbation history. A female preponderance was seen in both the overall study population (64.5% vs 35.5%) and those with uncontrolled asthma (ACQ-7 score ≥ 1.5 : 70.7% female, 29.3% male), which is consistently reported in cohorts with severe asthma.²⁻⁶ Our study population was observed to be symptom high/T2-biomarker low with a high prevalence of obesity, and this phenotype of female patients has been described in a previous cluster analysis of severe asthma.¹³

The beneficial reduction in CS dose in females, using a biomarker-directed strategy, was driven by differences in the proportion reducing treatment using a symptom-based approach. Overall reduction in CS dose in this female population with severe asthma was mainly driven by reduced OCS exposure in females, which is a potentially important driver of morbidity, including obesity and anxiety and/or depression, which was higher in our female study population.⁸⁻¹⁰ Despite the greater reduction in CS treatment seen in females with biomarker-directed treatment, there was no suggestion of worsening asthma control, increased exacerbation rate, or difference in T2-biomarker levels between males and females.

Our study confirmed that in this biomarker-low severe asthma population, females have higher ACQ scores, which represents a major barrier to treatment reduction using symptom-based strategies. Importantly, when looking at factors mediating the sex difference in the 6 self-reported questions in the ACQ,

TABLE IV. Predicted ACQ-7 score for each biomarker level, separately for females and males*

Biomarker	ACQ-7 score		Mean difference (95% CI)	P value	P (interaction test)
	Female	Male			
Composite score					.004
0	2.05 (1.83, 2.28)	1.99 (1.69, 2.28)	0.07 (−0.25 to 0.39)	.69	
1	2.20 (2.01, 2.40)	1.91 (1.66, 2.15)	0.30 (0.04 to 0.56)	.03	
2	2.42 (2.19, 2.65)	1.89 (1.62, 2.17)	0.53 (0.22 to 0.84)	.0007	
Blood eosinophil score					.10
0	2.15 (1.92, 2.37)	1.96 (1.68, 2.24)	0.19 (−0.10 to 0.47)	.20	
1	2.17 (1.95, 2.39)	1.95 (1.68, 2.22)	0.22 (−0.06 to 0.50)	.12	
2	2.33 (2.10, 2.56)	1.95 (1.66, 2.23)	0.39 (0.10 to 0.68)	.009	
FENO score					.04
0	2.13 (1.89, 2.36)	1.98 (1.69, 2.27)	0.14 (−0.15 to 0.44)	.34	
1	2.16 (1.94, 2.39)	1.94 (1.67, 2.21)	0.22 (−0.05 to 0.49)	.11	
2	2.37 (2.13, 2.61)	1.95 (1.66, 2.23)	0.42 (0.13 to 0.71)	.004	
Periostin score					.18
0	2.12 (1.91, 2.34)	1.96 (1.68, 2.23)	0.17 (−0.14 to 0.47)	.28	
1	2.28 (2.07, 2.48)	1.93 (1.67, 2.19)	0.35 (0.06 to 0.64)	.02	
2	2.22 (2.01, 2.43)	1.85 (1.59, 2.12)	0.37 (0.07 to 0.66)	.01	
Composite score (EOS/FENO)					.005
0	2.15 (1.91, 2.39)	1.96 (1.66, 2.26)	0.19 (−0.12 to 0.50)	.24	
1	2.13 (1.90, 2.35)	2.02 (1.75, 2.29)	0.11 (−0.17 to 0.38)	.44	
2	2.34 (2.11, 2.57)	1.88 (1.60, 2.15)	0.46 (0.19 to 0.74)	.0010	

EOS, Eosinophil.

Datan presented as medians and Interquartile ranges.

*Adjusted for recent exacerbation and asthma treatment step.

obesity and a history of anxiety and/or depression accounted for the sex difference in symptom burden, which are themselves worsened by OCS use. Previous studies have reported that confounding factors such as obesity, mental health issues, and socioeconomic status can have an impact on increased symptom reporting in older females.¹⁶

There was no “mediation effect” in terms of objectively measured lung function, suggesting that these comorbid factors contribute to the self-reported components of the ACQ in females, potentially capturing more than symptoms specifically due to asthma. Cross-sectional analysis in a national registry of adult patients with severe asthma also demonstrated that females had significantly better lung function compared with males, with similar symptom scores, again suggesting females are more likely to report a greater symptom burden with a lesser degree of lung function impairment.¹⁷

As we have demonstrated, high symptom reporting means that symptom-directed treatment reduction is challenging. It has been recognized for some time that multiple comorbidities are seen in patients with severe asthma and that characterizing this patient population using a systematic multidisciplinary approach is important.¹⁸⁻²⁰ In the absence of recognition that extrapulmonary comorbidities may drive ongoing respiratory symptoms, “chasing symptom control,” particularly in females who have obesity and anxiety and/or depression, could expose them to excessive CS treatment. This may further contribute to weight gain and psychological morbidity. Consequently, as anxiety and/or depression are known to influence patients’ perceptions of symptoms, a cycle of persistent symptoms and treatment escalation is established.²¹ This “overtreatment” hypothesis is supported by the absence of any evidence of worsening asthma symptoms, annual exacerbation

rate, or increased T2-biomarker levels in females who reduced treatment, using biomarker-directed care.

Interestingly, although females tended to consistently report higher levels of symptoms, there was a strong positive correlation between the ACQ-7 score and the composite T2-biomarker score for females, which was absent in males. This observation further supports a sex-specific dissociation in the relationship between T2-airway inflammation and self-reported symptoms, with males tending to report a lower symptom burden irrespective of their biomarker status, whereas females exhibited more concordance between symptom burden and T2-biomarker status. A similar relationship has been described in a previous cluster analysis of severe asthma, with description of a biomarker-high/symptom-low male population.¹³ Low levels of symptom reporting in males despite airway inflammation suggests that a symptom-based treatment strategy could potentially result in inadequate anti-inflammatory treatment and increased risk of exacerbation. A treatment strategy based on the measurement of T2 biomarkers to better target CS treatment allied with lung function measurement and appropriate use of additional bronchodilator treatment would potentially deliver more targeted and appropriate treatment in these patient groups in which T2 inflammation and symptoms are dissociated.^{22,23}

Other mechanisms for sex difference in asthma need to be considered in this study population. Hormonal differences are likely to play a significant role in symptoms and disease presentation between sexes. In adulthood, asthma prevalence and severity are notably higher in females than in males.¹⁶ Asthma control is reported to worsen in females during proandrogenic periods such as menopause, as evidenced by decreased lung function and increased symptom reporting.¹⁶ It has also been

suggested that estrogen may have a proinflammatory effect leading to increased T2 inflammation, airway hyper-responsiveness, and symptoms.^{16,17,24-26} However, it remains unclear as to why there is a greater representation of female patients with asthma within the sixth decade.^{16,17} In this study, we did not specifically relate hormonal levels in either sex to symptom level or exacerbation rate.

Our analysis benefits from the strengths of the original study, including detailed characterization of participants over serial study visits, high participant retention, detailed treatment adherence/adjustment records, and prospective follow-up. This study is a *post hoc* analysis and the findings should be considered exploratory. One limitation is that anxiety and/or depression have been presented as a combined diagnosis. The diagnosis of anxiety and/or depression was based on self-reporting by participants, and asking patients to distinguish anxiety from depression can be difficult, because these conditions often coexist. The complex and heterogeneous psychological profile of this population with severe asthma was previously demonstrated, when after formal psychiatric evaluation, half of the patients had a specific *International Classification of Diseases, Tenth Revision* diagnosis, with depression being the most common condition (59%).²⁷ Using a common screening tool (Hospital Anxiety and Depression Scale), anxiety scores (13.4 ± 0.8 vs 8.5 ± 0.7) and depression scores (10.2 ± 0.7 vs 4.8 ± 0.5) were significantly higher in subjects across all *International Classification of Diseases, Tenth Revision* diagnoses ($P < .001$).²⁷ Thus, “mood disorder” (anxiety and/or depression) is common within this patient group, but within a complex heterogeneous psychiatric case mix, however, our findings in this study support that mood disorder may act as a potential modifier of asthma symptoms and may lead to treatment escalation.

CONCLUSIONS

Data suggest that females derive greater benefit from biomarker-directed CS treatment adjustment, predominantly due to higher symptom burden, which is mediated by comorbid conditions such as obesity and mood dysfunction. Discordance between T2 inflammation and reported symptoms also seems to be different between sexes, and these groups may need different treatment approaches to ensure appropriate treatment. Further work is needed to determine the precise mechanism of persistent symptoms in T2-biomarker–low asthma, although extrapulmonary comorbid diseases, such as obesity and mood dysfunction, are likely to be contributory. Clinicians should be aware of dissociations between symptoms and inflammation and encouraged to measure T2 biomarkers, lung function, and other clinical features to inform precise treatment choices and prevent avoidable harm through inappropriate CS dose escalation.

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ONLINE REPOSITORY

PARTICIPATING CLINICAL CENTERS

The following is a list of NHS clinical centers with a dedicated tertiary care difficult asthma service that recruited patients for the study:

- Belfast Health and Social Care Trust
- Oxford University Hospitals NHS Trust
- Glenfield Hospital, University Hospitals of Leicester NHS Trust
- Wythenshawe Hospital, University Hospitals of South Manchester NHS Trust
- University Hospital Southampton NHS Foundation Trust
- Royal Brompton and Harefield NHS Foundation Hospital
- King's College Hospital NHS Foundation Trust
- Nottingham University Hospitals NHS Foundation Trust
- Sheffield Teaching Hospitals NHS Foundation Trust
- Gartnavel and Stobhill/Glasgow Royal Infirmary Hospitals, Greater Glasgow Health Board
- Heartlands Hospital, Heart of England NHS Foundation Trust
- Freeman Hospital, Newcastle upon Tyne NHS Foundation Trust

INCLUSION AND EXCLUSION CRITERIA OF STUDY SUBJECTS

The full study protocol has been previously published.^{E1}

Inclusion criteria

Patients must meet the following criteria at screening for study entry (patients can be rescreened for study entry up to 3 times):

1. Aged 18 to 80 years at screening visit;
2. Able and willing to provide written informed consent and to comply with the study protocol;
3. Baseline FENO less than 45 ppb at screening (FENO measured as per the Official American Thoracic Society Clinical Practice Guideline Interpretation of FENO for Clinical Applications 2011^{E2});
4. Severe asthma confirmed after assessment by an asthma specialist; diagnosed with asthma at least 12 months before screening;
5. Current asthma treatment with long-acting β -agonist (LABA) plus high doses of ICSs (≥ 1000 μg fluticasone propionate daily or equivalent);
6. Patients on an ICS/LABA single-inhaler strategy must be switched to fixed-dosing ICS/LABA for 4 weeks before screening; and
7. Documented history of reversibility of 12% or more change in FEV₁ within the past 24 months or during screening period, as demonstrated by
 - Documented airflow obstruction (FEV₁/FVC < 70%), where FEV₁ has varied by 12% or more either spontaneously or in response to OCS therapy or bronchodilators either between or during clinic visits; *or*
 - A 20% drop in FEV₁ (PC₂₀ FEV₁) to methacholine of less than 8 mg/mL or a 15% fall in FEV₁ (PD₁₅ FEV₁) after

inhaling a cumulative dose of mannitol of 635 mg or less, indicating the presence of airway hyperresponsiveness. If sites customarily use histamine to perform tests of airway responsiveness, this may be used in place of methacholine. (Spirometry was conducted according to the American Thoracic Society/European Respiratory Society guidelines, with Global Lung Function 2012 equations used to calculate FEV₁ and FVC predictive values.^{E3,E4})

Exclusion criteria

Patients who meet any of the following criteria to be excluded from study entry:

1. Acute exacerbation requiring OCSs in previous 4 weeks before screening (subjects were eligible for rescreening and inclusion);
2. If recently commenced on a leukotriene receptor antagonist or theophylline, stable on treatment for 4 weeks before screening;
3. Current self-reported history of smoking (including electronic inhaled nicotine products) or former smoker with a smoking history of more than 15 pack-years:
 - A current smoker is defined as someone who has smoked 1 or more cigarettes (or marijuana or pipe or cigar) per day for 30 days or more within the 24 months before the screening visit (day 14) and/or is cotinine-positive at screening;
 - Any individual who smokes (cigarettes, marijuana, pipe, or cigar) occasionally, even if for less than 30 days within the 24 months before the screening visit (day 14) must agree to abstain from all smoking from the time of consent through completion of study;
 - A former smoker is defined as someone who has smoked 1 or more cigarettes (or marijuana or pipe or cigar) per day for 30 days or more in his or her lifetime (as long as the 30-day total did not include the 24 months before the screening visit [day 14]);
 - A pack-year is defined as the average number of packs per day times the number of years of smoking.
4. Known current malignancy or current evaluation for a potential malignancy or history of malignancy within 5 years before baseline, with the exception of basal-cell and squamous-cell carcinomas of the skin and carcinoma *in situ* of the cervix uteri that have been excised and cured;
5. Known severe or clinically significant immunodeficiency, including, but not limited to, HIV infection or currently receiving or have historically received intravenous immunoglobulin for treatment for immunodeficiency;
6. Other clinically significant medical disease or uncontrolled concomitant disease despite treatment that is likely, in the opinion of the investigator, to require a change in therapy or impact the ability to participate in the study;
7. History of current alcohol, drug, or chemical abuse or past abuse that would impair or risk the subject's full participation in the study, in the opinion of the investigator;
8. Current use of an immunomodulatory/immunosuppressive therapy or past use within 3 months or 5 drug half-lives (whichever is longer) before the screening visit;
9. Use of a biologic therapy including omalizumab at any time during the 6 months before the screening visit;

10. Bronchial thermoplasty within 6 months before the screening visit;
11. Initiation of or change in allergen immunotherapy within 3 months before the screening visit;
12. Treatment with an investigational agent within 30 days of the screening visit (or 5 half-lives of the investigational agent, whichever is longer).
13. Female patients who are pregnant or lactating.

GENERATION OF THE COMPOSITE BIOMARKER SCORING SYSTEM

The predictive value of using FENO, blood eosinophils, and periostin as composite biomarkers to predict exacerbation risk was examined in the placebo arms of clinical trials with lebrikizumab and omalizumab in patients taking at least 500 µg of fluticasone propionate and a second controller.^{E5-E7} These studies were designed to prospectively collect data on exacerbation events. The analysis demonstrated that these biomarkers are all correlated with exacerbation risk, but by using the 3 biomarkers based on the tertile thresholds in these studies, the composite biomarker-low group (FENO < 15 ppb; blood eosinophil count < 150/µL; and periostin < 45 ng/mL) had a 4-fold lower risk of exacerbation compared with those with the maximum score of 6 (FENO > 30 ppb; blood eosinophil count > 300/µL; and periostin > 55 ng/mL). The scoring system was based on the average score of the sum of the 3 biomarkers (see Table I). This composite biomarker score was independent of symptom score, and the predictive value was identical in subjects on both OCSs and ICSs when compared with those on ICSs alone, allowing the scoring system to be used across the spectrum of severe asthma. In subjects with FENO less than 45 ppb (n = 314), in this analysis, 78 (24.8%), 187 (59.6%), and 49 (15.6%) had composite scores of 0, 1, and 2, respectively. This score was used to make a treatment advisory adjustment to CS treatment.

All treatment algorithms were automatically generated by the electronic case report form software. For *biomarker treatment adjustment* (see Table E1 and E3), FENO, blood eosinophil count, and serum periostin were measured at each study visit, with each biomarker assigned a score of 0, 1, or 2; the composite biomarker score was generated using the rounded average of the sum of all 3

biomarker scores. A composite biomarker score of 0 advised treatment reduction, a score of 1 advised maintenance of current treatment, and a score of 2 advised treatment increase; *symptom-/risk-based adjustment* was made using the algorithm (see Tables E2 and E4), and all therapeutic adjustments were automatically calculated and advised by the electronic case report form. This was considered essential because prestudy observations in the UK Severe Asthma Registry had identified “standard care,” and specifically CS treatment regimens differed substantially across clinical centers. A score of 0 advised treatment reduction, a score of 1 advised maintenance of current treatment, and a score of 2 advised treatment increase.

STATISTICAL METHODS

We used linear regression to examine potential disparities in asthma symptoms in relation to sex measured by the ACQ-7 and the mini-AQLQ. We investigated potential mediation by adjusting for age, smoking status, BMI, and depression/anxiety in a stepwise fashion. Factors were considered to be potential mediators if they substantially moderated the size of the sex disparity.

We investigated the longitudinal relationship between asthma symptoms and biomarkers separately for females and males. We used multilevel linear regression models, with the ACQ-7 score as the dependent variable and the composite biomarker score as the independent variable. Models included an interaction term between sex and composite biomarker score to formally test for sex differences in the magnitude of the linear association between biomarkers and symptoms. These models additionally included whether the patient had a recent exacerbation in the previous 8 weeks and their current asthma treatment step to account for potential confounding. Importantly, the longitudinal nature of our analysis, which used repeated measurements on the same patients over the course of the study, prevents confounding because of factors that are likely to be time-invariant, such as genetics, symptom perception, and attitude to medication adherence. Model coefficients were converted to adjusted predictions, which represent the mean ACQ-7 score for each sex, assuming all other variables in the model were fixed.^{E8} All analyses were conducted using the STATA 16 software package (StataCorp, College Station, Texas).

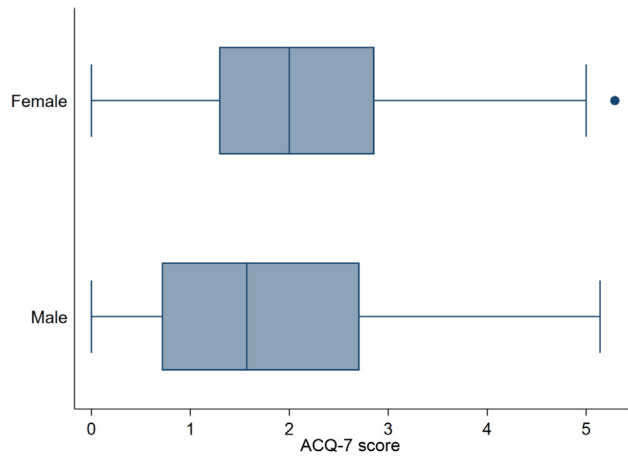


FIGURE E1. Box plot of ACQ-7 scores by sex at baseline.

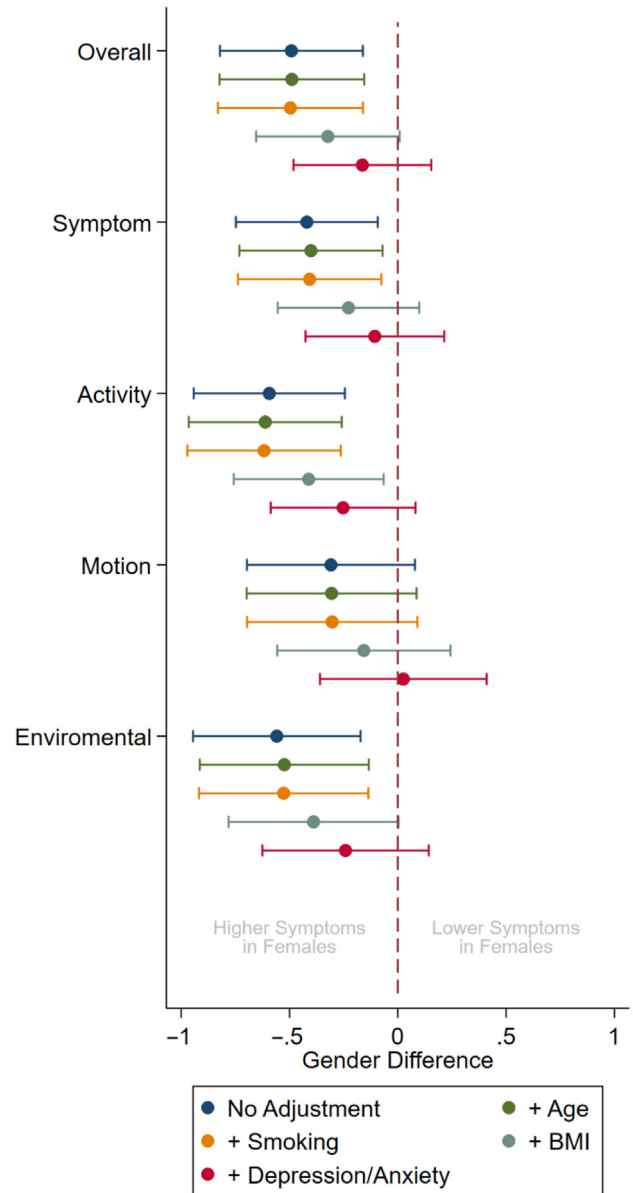


FIGURE E2. Mediation of sex differences in the overall AQLQ and the individual symptom domains of this questionnaire by demographic factors and comorbidities.

TABLE E1. Composite biomarker score derived from FeNO, Blood eosinophil count and Periostin to adjust treatment in the biomarker treatment adjustment arm

Scoring system	0	1	2
FeNO (ppb)	<15	15-30	>30
Blood eosinophil count (N/ μ L)	<150	150-300	>300
Periostin (ng/mL)	<45	45-55	>55

The composite biomarker score was generated using the rounded average of the sum of all 3 individual biomarker scores (eg, 0 + 1 + 1 = 2/3 = rounded score = 1).

TABLE E2. Composite score derived from symptoms AND/OR exacerbations to adjust treatment in the symptom-/risk-based treatment adjustment arm

ACQ-7	Score
ACQ-7 score is ≥ 1.5 and ≥ 1 change from baseline score <i>OR</i> a severe exacerbation since last visit (past 8 wk at baseline randomization visit)	2
ACQ-7 score is 1.0 to < 1.5 <i>OR</i> ACQ-7 score is ≥ 1.5 and < 1 change from baseline score <i>AND</i> no severe exacerbation since last study visit (past 8 wk at baseline randomization visit)	1
ACQ-7 score is < 1.0 <i>AND</i> no severe exacerbation since last study visit (before 8 wk at baseline randomization visit)	0

TABLE E3. Treatment adjustment table used to guide treatment changes in the biomarker treatment arm

Steroid therapy step	Seretide MDI	Seretide Accuhaler	Symbicort Turbohaler	Flutiform MDI	Relvar Ellipta	Other LABA/ICS combinations (FP equivalent dose per day)
Step 1	Seretide 50 2 bid	Seretide 100 1 bid	Symbicort 6/200 1 bid If ACQ score ≥ 1.5 , add OXIS 12 1 bid (or equivalent)	Flutiform 50 2 bid If ACQ score ≥ 1.5 , add OXIS 12 1 bid (or equivalent)	Seretide 100 Accuhaler 1 bd	LABA/FP equivalent 200 $\mu\text{g}/\text{d}$
Step 2	Seretide 125 2 bid	Seretide 250 1 bid	Symbicort 6/200 2 bid If ACQ score ≥ 1.5 , add OXIS 12 1 bid (or equivalent)	Flutiform 125 2 bid If ACQ score ≥ 1.5 , add OXIS 12 1 bid (or equivalent)	Relvar 22/92 1 mane	LABA/FP equivalent 500 $\mu\text{g}/\text{d}$
Step 3	Seretide 250 2 bid	Seretide 500 1 bid	Bud 12/400 2 bid	Flutiform 250 2 bid	Relvar 22/184 1 mane	LABA/FP equivalent 1000 $\mu\text{g}/\text{d}$
Step 4	Seretide 250 2 bid	Seretide 500 1 bid	Bud 12/400 2 bid	Flutiform 250 2 bid	Relvar 22/184 1 mane	LABA/FP equivalent 1000 $\mu\text{g}/\text{d}$
Step 5	Prednisolone 5 mg/d	Prednisolone 5 mg/d	Prednisolone 5 mg/d	Prednisolone 5 mg/d	Prednisolone 5 mg/d	Prednisolone: 5 mg/d
	Seretide 250 2 bid	Seretide 500 1 bid	Bud 12/400 2 bid	Flutiform 250 2 bid	Relvar 22/184 1 mane	LABA/FP equivalent 1000 $\mu\text{g}/\text{d}$
Step 6	Prednisolone 10 mg/d	Prednisolone 10 mg/d	Prednisolone 10 mg/d	Prednisolone 10 mg/d	Prednisolone 10 mg/d	Prednisolone 10 mg/d
	Seretide 250 2 bid	Seretide 500 1 bid plus	Bud 12/400 2 bid plus	Flutiform 250 2 bid	Relvar 22/184 1 mane plus	LABA/FP equivalent 1000 $\mu\text{g}/\text{d}$ plus
Step 7*	Prednisolone 15 mg/d	Prednisolone 15 mg/d	Prednisolone 15 mg/d	Prednisolone 15 mg/d	Prednisolone 15 mg/d	Prednisolone 15 mg/d
	Seretide 250 2 bid	Seretide 500 1 bid	Bud 12/400 2 bid	Flutiform 250 2 bid	Relvar 22/184 1 mane	LABA/FP equivalent 1000 $\mu\text{g}/\text{d}$ plus
	Prednisolone 20 mg/d	Prednisolone 20 mg/d	Prednisolone 20 mg/d	Prednisolone 20 mg/d	Prednisolone 20 mg/d	Prednisolone 20 mg/d

1 bid, 1 inhalation twice a day; 2 bid, 2 inhalations twice a day; Bud, budesonide; FP, fluticasone propionate; mane, morning; MDI, metered dose inhaler.

TABLE E4. Treatment adjustment table used to guide treatment changes in the system-based arm

Step 1	LABA/low-dose ICS (FP 200 µg or equivalent)
Step 2	LABA/moderate-dose ICS (500 µg FP equivalent)
Step 3	LABA/high-dose ICS (1000 µg FP equivalent)
Step 4	Add tiotropium
Step 5	Add regular oral steroids (starting dose 5-10 mg/d with increments of 5 mg)

FP, fluticasone propionate.

Treatment guidance in the biomarker treatment arm and symptom-based treatment arm

It is recognized that on some occasions, patients may require higher doses of systemic steroids beyond 20 mg prednisolone per day. As with all treatment steps, particular attention should be paid to adherence with prednisolone, but if required, prednisolone can be increased in further 5-mg increments.

The therapeutic adjustments are designed to reflect clinical practice and to be pragmatic and allow accommodation of currently used combination inhaler therapies in this population. Because of this, ICS will be adjusted in line with the patient's prescribed ICS/LABA inhaler device. This will mean that in some situations LABA is adjusted along with ICS, which would reflect usual clinical practice.

If patients are on theophylline, leukotriene receptor antagonist at baseline, these are not adjusted during study; they are not added during study.

In the symptom-based arm, if a patient has an ACQ-7 score of more than 1.5 and CS is not increased, tiotropium should be

added if there are no contraindications and if patient is not already on long-acting muscarinic antagonists (LAMA) therapy or nebulized short-acting antimuscarinic therapy.

If on inhaled steroid monotherapy (nebulized or inhaled) in addition to ICS/LABA combination therapy, the inhaled steroid monotherapy will be withdrawn initially.

If a patient is on oral steroids and reduces the dose to 5 mg/d, they should be advised to omit their prednisolone on the morning of their next study visit; at that visit, they should have a morning cortisol checked locally as part of routine clinical care:

- If cortisol is within normal range of local laboratory reference value, steroids can be stopped completely if indicated by study algorithm;
- If cortisol is present but is outside normal reference range of local laboratory, gradual oral steroid withdrawal in 1-mg increments is carried out;
- If cortisol is undetectable, prednisolone is maintained at 5 mg for study duration.

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