JOURNAL OF ASTHMA
https://doi.org/10.1080/02770903.2025.2581018

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Tapering of inhaled corticosteroids in stable T2-low asthma: a randomized trial of symptom- and biomarker trajectories

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ABSTRACT

Objective: To investigate whether tapering of inhaled corticosteroids (ICSs) is non-inferior to standard of care (SoC) in asthma patients with a stable type 2 (T2)-low inflammatory profile, generally considered less responsive to ICS therapy, and to describe symptom and biomarker trajectories during tapering.

Methods: This randomized, controlled, open-label multicenter trial conducted across specialist centers between 2022 and 2024 recruited adult asthma patients with persistently low T2 biomarkers, defined as blood eosinophils $<0.15 \times 10^9$/L, fractional exhaled nitric oxide (FeNO) <25 ppb, and non-allergic phenotype. Patients' adherent to medium- or high-dose ICS were randomized 1:1 to either ICS tapering (50% reduction at randomization and withdrawal after 8 weeks) or continued SoC. The primary endpoint was change in Asthma Control Questionnaire (ACQ) score at 16 weeks. Secondary endpoints included changes in blood and sputum eosinophils, FeNO, periostin, and lung function.

Results: Recruitment proved challenging as only 20 of 2766 screened patients met eligibility criteria, leading to early study termination. Median ACQ remained stable in the tapering group (0 [–0.14; 0.5]) and improved modestly in the SoC group (–0.44 [–0.9; –0.11]; $p = 0.211$). FeNO ($p = 0.038$) and periostin ($p = 0.031$) increased with tapering but remained within the T2 low range. Minimal changes were observed in blood eosinophils ($p = 0.3$) and FEV_1 ($p = 0.7$).

Conclusions: Premature trial termination due to recruitment challenges reflects the rarity of stable T2-low asthma. ICS tapering was not associated with greater symptom deterioration compared to SoC, although non-inferiority was not demonstrated.

ARTICLE HISTORY
Received 3 July 2025
Revised 11 September 2025
Accepted 23 October 2025

KEYWORDS
T2-low asthma; biomarker guided therapy; individualized treatment; ICS withdrawal; asthma control

Introduction

Asthma is a common inflammatory airway disease that can be classified into endotypes, based on expression of biomarkers of type 2 (T2) inflammation. Elevated levels of sputum eosinophils, blood eosinophils, blood periostin and fractional exhaled nitric oxide (FeNO) are generally accepted as biomarkers of T2 inflammation (1), although the clinical utility of periostin remains uncertain. However, no specific biomarkers for T2-low asthma exist, thus T2-low asthma is defined as asthma with low levels of T2 biomarkers.

Inhaled corticosteroids (ICSs) are the cornerstone of asthma management, effectively reducing symptoms and exacerbations (2–4). It has been shown that ICS are less effective in patients with a low degree of T2 inflammation (5,6), and T2-low asthma patients may maintain asthma control with low doses of ICS (7). Furthermore, treatment with high dose ICS is associated with adverse effects, such as osteoporosis, type-2 diabetes, and cardiovascular disease (8).

Population-based studies indicate that T2-low asthma may account for less than 20% of asthma cases (9,10) whereas in severe asthma the prevalence is likely much

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Supplemental data for this article can be accessed online at https://doi.org/10.1080/02770903.2025.2581018.

lower, possibly less than 5% (11,12), a difference that could be explained by suppression of T2-inflammatory biomarkers by treatment with ICS or oral corticosteroids. Hence, in a severe asthma cohort attempting to assess the proportion of T2-low asthma, an approach incorporating historical biomarker measurements, has been suggested to avoid this corticosteroid-induced masking of T2-high inflammation (13).

Given the complexity of identifying "true" T2-low asthma and variation in efficacy of ICS, it is clinically important to determine whether ICS can be reduced or omitted in this subgroup without compromising asthma control. A safe reduction of ICS would minimize unnecessary corticosteroid exposure and potential side effects in patients with limited treatment response. Thus, the primary aim of this randomized controlled trial was to evaluate whether ICS tapering in a group of T2-low asthma patients was non-inferior to standard of care (SoC). Second, we wished to explore the trajectories of FeNO, blood periostin, blood eosinophils, sputum eosinophils, and lung function during tapering of ICS.

Methods

Setting, study participants and screening

The study was conducted across three respiratory outpatient clinics in Denmark: Copenhagen University Hospital – Hvidovre, Copenhagen University Hospital – Amager, and Copenhagen University Hospital – Glostrup. Eligible patients were adults (aged 18–65 years) with a confirmed asthma diagnosis. Asthma diagnosis required documented evidence of asthma based on at least one of the following: FEV1 reversibility ≥12% and ≥200 mL after bronchodilator or corticosteroid; a positive bronchial provocation test (mannitol or methacholine); peak-flow variation ≥20% over two weeks; or variability in FEV1 ≥ 12% and ≥200 mL over time. Patients were further required to have biomarkers suggesting T2-low asthma, defined as low blood eosinophils at screening (<0.15 × 10^9 cells/L), consistently low FeNO (<25 ppb at screening and no historical measurements > 25 ppb), and no allergy/atopy (negative skin prick test or specific immunoglobulin E (IgE) < 0.35 IU/mL, no prescription of systemic antihistamines or topical allergy medication for ocular/nasal use). Participants were required to be prescribed medium or high-dose ICS and demonstrate adequate adherence (medical possession ratio (MPR) ≥ 80%) in the preceding year. A detailed study protocol has been published previously, including a complete list of inclusion and exclusion criteria (14).

Patients were recruited from June 2022 to October 2023. Medical records were assessed for eligibility by going through the criteria listed in Figure Y, supplementary materials. Starting from the top, the first inclusion/exclusion criterion not met was registered as the reason for non-eligibility. Participants who met all eligibility criteria were invited to a screening visit. During this visit, written informed consent was obtained, and participants underwent clinical assessment including a clinical interview, measurement of T2 biomarkers (FeNO, blood eosinophils, blood periostin), spirometry, completion of the Asthma Control Questionnaire (ACQ), and adherence assessment.

The trial was terminated early due to slow recruitment, and fewer participants than originally planned were included.

The study was conducted in compliance with ethical standards and approved by the Ethics Committee of The Capital Region of Denmark (H-17017529), the Danish Medicines Agency (EudraCT no: 2017-14002244-33), and the Danish Data Protection Agency (P-2022-31).

Study design

This study was a multicenter, randomized, controlled, open-label, non-inferiority trial aimed at evaluating whether patients with T2-low asthma could maintain asthma control during ICS tapering compared to a group continuing usual treatment, randomized 1:1. Randomization was performed in electronic case-report forms: Research Electronic Data Capture (REDCap) with an allocation sequence generated by R statistical software 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria) in blocks of varying sizes to ensure balance between groups.

All participants were followed for a period of 12 months with seven planned follow-up visits for clinical assessments and biomarker evaluations. Table 1 in the published protocol paper describes the procedures in detail (14). Unscheduled visits were arranged if participants experienced worsening of asthma symptoms.

In the tapering group, the daily ICS dose was reduced at baseline by 50%, followed by complete discontinuation of ICS after 8 weeks. Throughout the study, participants continued their other asthma medications in fixed doses, including long-acting β_2-agonists (LABAs), leukotriene antagonists (LTRAs) and long-acting muscarinic antagonists (LAMAs). Participants in the SoC group continued their baseline ICS dose unchanged throughout the study.

Table 1. Patient characteristics at baseline of the ICS tapering and SoC group.

		ICS tapering	Standard of care	*p* Value
N		10	10	
Women, *n*		8 (80.0)	7 (70.0)	1.000
Age, years		54.5 [41.5; 60.5]	56 [50.5; 58.5]	1.000
BMI, kg/m^2		24.65 [22.33; 26.85]	29.15 [27.12; 31.85]	0.007
Smoking status	Never smoked, *n*	8 (80.0)	3 (30.0)	0.070
	Ex-smoker, *n*	2 (20.0)	7 (70.0)	
	Pack-years, years	14.5 [9.25; 19.75]	7.5 [4; 17.85]	0.889
ICS	Beclometasone dipropionate, *n*	5 (50.0)	7 (70.0)	
	Budesonide, *n*	1 (10.0)	1 (10.0)	
	Ciclesonide, *n*	0 (0.0)	1 (10.0)	
	Fluticasone furoate, *n*	4 (40.0)	0 (0.0)	
	Fluticasone propionate, *n*	0 (0.0)	1 (10.0)	
ICS dose (budesonide equivalent, µg/day)		400 [400; 800]	800 [800; 800]	0.016
LABA, *n*		10 (100.0)	9 (90.0)	1.000
LAMA, *n*		4 (40.0)	3 (30.0)	1.000
SABA prn, *n*		5 (50.0)	5 (50.0)	1.000
ICS/formoterol prn, *n*		5 (50.0)	5 (50.0)	1.000
ACQ		0.5 [0.32; 1.03]	1.5 [0.86; 1.82]	0.021
FeNO, ppb		9.98 [6.57; 12.35]	15.0 [10.65; 22.38]	0.143
Blood eosinophils, $\times 10^9$ cells/L		0.1 [0.06; 0.13]	0.12 [0.09; 0.14]	0.519
Periostin, ng/mL		69.71 [61.09; 81.29]	60.61 [47.63; 81.22]	0.631
Sputum eosinophils, %		0.3 [0.15; 0.35]	0.8 [0.35; 0.85]	0.169
FEV1, L		2.86 [2.18; 3.56]	2.36 [2.17; 2.89]	0.571

Note. Categorical variables are presented as counts (%) and continuous variables as medians [IQR]. Differences between groups were assessed using the Wilcoxon rank sum test for continuous variables and Fischer's exact test for categorical variables. *p* Values < 0.05 are considered statistically significant.

Outcomes

The primary endpoint was the change in ACQ-score (15) from baseline to week 16. The minimal clinically important difference (MCID) has been defined as ≥0.5 points (16), while an increase of ≥1.0 point resulted in participant withdrawal. Secondary endpoints were time to withdrawal due to worsened asthma control, and changes from baseline to week 16 in serum periostin, blood eosinophils, FeNO, sputum eosinophils, and forced expiratory volume in 1 second (FEV_1).

Study procedures

ACQ was evaluated at each visit to assess asthma symptom control (15). FeNO levels were measured with ECO MEDICS and Spiroware software following European Respiratory Society (ERS) guidelines (17). Spirometry was performed with Vitalograph Spirotrac IV at each study visit to assess lung function, according to the American Thoracic Society (ATS)/ERS guidelines (18).

EDTA-stabilized blood samples were centrifuged, and plasma samples were subsequently stored at −20 or −80 °C prior to batch-wise analysis. Periostin was quantified batch-wise employing an ELISA kit (Biomedica, Vienna, Austria; cat. no. BI-20433) according to the manufacturer's instructions (19). The inter-assay coefficient of variation (CV) was 14% as determined employing an in-house control (pooled plasma) and the intra-assay CV was never more than 10%.

Blood eosinophil counts were performed as routine analysis by the department of biochemistry, Copenhagen University Hospital – Hvidovre.

Sputum induction was done as previously described (20). Sputum samples were processed in the laboratory according to established methods (21). Cytospin slides were stained with May-Grünwald-Giemsa stain. The differential cell count was determined by a pathologist (ISC).

Adherence to ICS therapy was assessed during screening by evaluating redeemed prescriptions and calculating MPR as previously described (14). Throughout the study, adherence was tracked using inhaler dose counters when available or, alternatively, through participant self-reports.

Statistical analysis

To detect the MCID on the primary endpoint, a sample size of 110 participants was required, as outlined in the study protocol (14). Descriptive statistics was used to summarize data, with categorical variables presented as frequencies and percentages, and continuous data presented as median and interquartile range (IQR). The primary endpoint was analyzed using the Wilcoxon rank-sum test and distribution of data was tested using the Shapiro–Wilk test. The study outcomes were analyzed in an exploratory framework.

Measurements from unscheduled visits due to worsening of symptoms were recorded as the final data points for the withdrawn patients and were included in the analysis. Analyses were conducted using the complete dataset, incorporating all available data.

All analyses were performed using R version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Enrollment

A total of 2766 patients were assessed for eligibility (Figure 1), of these 884 patients were excluded because

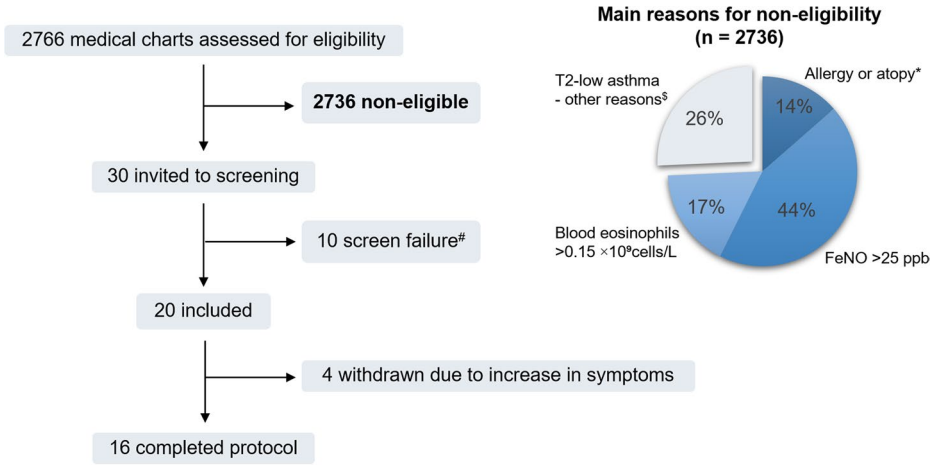

Figure 1. Patient flow through the study. *Allergy or atopy is confirmed with a positive skin prick test, allergen-specific IgE test, or by prescription of oral antihistamines or local allergy medication. $Other reasons for non-eligibility included age, smoking, poor adherence, or treatment with low-dose ICS/ICS–formoterol as needed. A complete list of criteria is provided in Figure Y in Supplementary materials. Each patient was assigned to the first non-eligibility criterion encountered, even if multiple criteria could apply. #Details on screen failures are presented in Figure Y in Supplementary materials.

of a prior blood eosinophil count of ≥0.15 × 10^9 cells/L, 214 based on a previous FeNO measurement >25 ppb, and 447 due to documented allergy or atopy. Further details regarding non-eligibility criteria are provided in Figure Y (Supplementary materials). Following this assessment, 30 patients attended a screening visit, and 20 were ultimately enrolled and randomized.

Baseline characteristics

Baseline characteristics are presented in Table 1 and Table X (Supplementary material). Patients in the tapering group had significantly lower ACQ scores, lower BMI, and were prescribed lower doses of ICS at baseline compared to the SoC group (Table 1). However, no significant differences were observed between patients who completed the study and those who were withdrawn due to worsening of asthma symptoms (Supplementary, Table X).

Primary outcome

Among patients who completed the study according to the protocol, median ACQ [IQR] remained stable in the tapering group (0 [−0.14; 0.5]) and decreased in the SoC group (−0.44 [−0.9; −0.11]). There was no significant difference between groups (p = 0.211), and the predefined criterion for non-inferiority of ICS tapering compared to SoC was not met.

Secondary outcomes

FeNO increased in the tapering group and decreased in the SoC group, with a significant difference between groups (p = 0.038). Periostin increased in both groups, though significantly more in the tapering group (p = 0.031). Blood eosinophils remained unchanged in the two groups (p = 0.307), whereas FEV_1 declined in the tapering group and remained unchanged in the SoC group (p = 0.677).

Overall, 45% of patients were able to produce adequate sputum samples. There was a tendency toward an increase in sputum eosinophils in the tapering group, vs. remaining stable or decline in the SoC group (p = 0.247).

Withdrawals

Four patients did not complete all follow-up visits during the study period: two in the tapering group and two in the SoC group. In the tapering group, one patient was withdrawn after 16 weeks due to loss of asthma control, accompanied by increase in FeNO, sputum and blood eosinophils, and periostin. The other patient withdrew consent but had stable biomarkers and lung function. In the SoC group, two patients were withdrawn due to an increase in ACQ score, both with unchanged biomarkers and lung function.

Discussion

The present randomized trial investigated whether ICS could be tapered without loss of asthma control in a group of asthma patients expressing low T2 biomarkers. During the 52 weeks study period, we observed no difference between the tapering group and the SoC group, most likely due to lack of power.

Despite access to large respiratory out-patient clinics, it was only possible to recruit very few participants, reflecting the difficulty of identifying patients who consistently fulfilled criteria for a T2-low phenotype. Upon evaluation of historical biomarker expression, 74% of the assessed asthma patients were found to be ineligible due to prior indications of T2 inflammation. This approach may have helped avoid the inclusion of patients with masked T2 asthma, yet it has evidently led to a substantial reduction in the number of eligible patients.

In this study, we found that 26% of the screened asthma patients (n = 2766) exhibited a T2-low inflammatory phenotype, a prevalence between earlier higher estimates (9) and more recent lower estimates (11,12). This discrepancy may reflect that our screened population included both mild-moderate and severe asthma patients. Of the 26% who expressed a T2-low phenotype, the majority were excluded due to age over 65 years, medication adherence below 80%, active smoking, or treatment with low-dose ICS and/or as-needed ICS-formoterol alone. While these criteria were important to properly test our hypothesis, the strict inclusion and exclusion criteria further complicated patient recruitment for the study. The difficulty in recruiting patients and the unexpectedly small number eligible for inclusion may reflect a clinical reality where true T2-low asthma is relatively uncommon.

This study utilized a triad of readily accessible biomarkers – FeNO, blood eosinophil count, and serum periostin – as a tool to identify patients with T2-low inflammation who might maintain asthma control after ICS withdrawal. The trajectories of the biomarkers during ICS tapering are illustrated in Figure 2 with additional details in Table 2. Notably, throughout the study, FeNO increased in the tapering group and decreased in the SoC group, with a significant difference between groups. However, despite this increase, median FeNO remained below 20 ppb at all study visits, remaining below the threshold typically associated with T2 inflammation (4). An increase in FeNO to >45 ppb has previously been associated with asthma exacerbations in patients undergoing ICS tapering (22). In contrast, other studies reported no significant difference in FeNO levels between patients with successful versus unsuccessful ICS dose reduction (7,23).

Blood eosinophil levels remained low, with no statistically significant difference between the two groups, though there was a trend toward an increase in the tapering group and a decrease in the SoC group, but again this may be due to the limited sample size in the present study. In a study including patients with blood eosinophil counts below 0.4×10^9 cells/L, unsuccessful ICS tapering was associated with relatively higher eosinophil levels at baseline and during tapering (7). In our study, blood eosinophil count remained largely unaffected by ICS tapering, suggesting that low eosinophil levels alone may be insufficient as a predictor of ICS withdrawal success.

The increase in periostin observed in both groups may reflect that periostin is only modestly affected

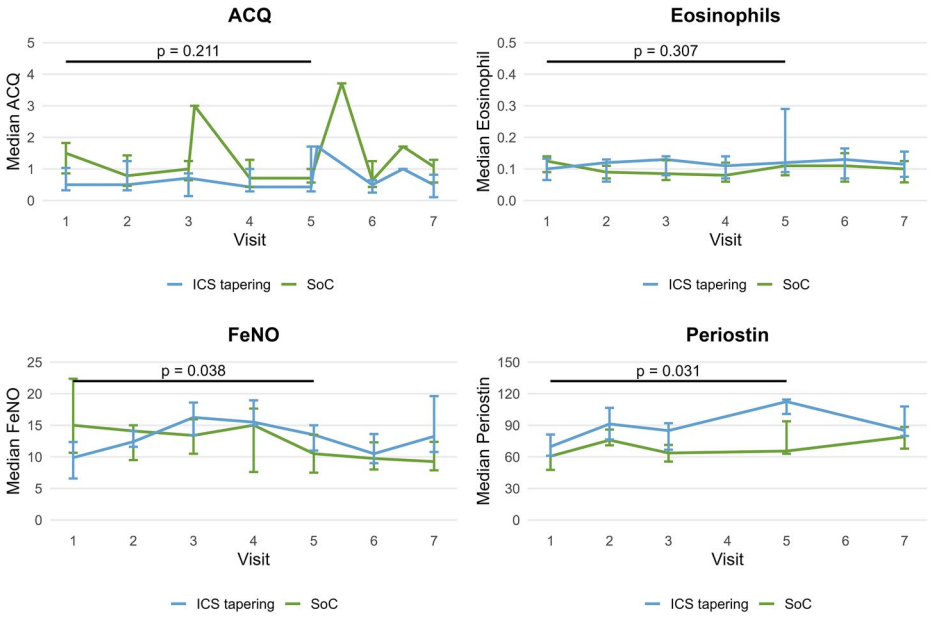

Figure 2. Change in ACQ, blood eosinophils, FeNO, and periostin from baseline to visit 7 (52 weeks) in participants receiving ICS tapering or SoC. p Values refer to the change from baseline to visit 5. Data are presented as medians with error bars indicating IQR.

Table 2. Change in outcomes from baseline to post-tapered ICS.

	ICS tapering			Standard of care			
	Completion of protocol (successful tapering) (N = 8)	Withdrawal due to increased symptoms (N = 2)		Completion of protocol (N = 8)	Withdrawal due to increased symptoms (N = 2)		
	Δ from baseline to week 16 (visit 5)	Δ from baseline to exclusion	p Value, completion vs. withdrawal	Δ from baseline to week 16 (visit 5)	Δ from baseline to exclusion	p Value, completion vs. withdrawal	p Value, ICS tapering vs. control group
ACQ	0 [−0.14; 0.5]	0.64 [0.39; 0.89]		−0.44 [−0.9; −0.11]	1.64 [1.53; 1.74]		0.211
FeNO, ppb	2.38 [0.52; 3.65]	17.35 [9.68; 25.03]	0.361	−4.5 [−9.78; 1]	−5.7 [−8.84; −2.55]	0.896	0.038
Periostin, ng/mL	39.96 [37.71; 51.98]	20.79 [6.79; 34.78]	0.513	14.17 [9.02; 23.49]	3.38 [−7.31; 14.06]	0.695	0.031
Blood eosinophils, $\times 10^9$ cells/L	0 [−0.01; 0.05]	0.15 [0.06; 0.23]	1	0 [−0.03; 0.01]	−0.01 [−0.03; 0.01]	1	0.307
Sputum eosinophils, %	0.3[a]	66.4[a]	1	0.1 [−0.2; 0.27]	NA	NA	0.247
Sputum neutrophils, %	−10.8[a]	−49.4[a]	1	−14.95 [−17.1; −2.67]	NA	NA	0.817
FEV1, L	−0.02 [−0.07; 0.08]	−0.09 [−0.14; −0.05]	0.514	0 [−0.05; 0.13]	0.02 [−0.06; 0.11]	0.896	0.677
FVC, L	0.09 [0.03; 0.2]	−0.19 [−0.28; −0.09]	0.151	0.28 [−0.04; 0.32]	−0.08 [−0.19; 0.03]	0.240	0.520
FEV1/FVC-ratio	−0.02 [−0.03; −0.01]	0 [0; 0]	0.090	−0.02 [−0.04; 0.01]	0.03 [0.03; 0.03]	0.050	0.678

Note. Data are presented as median [IQR]. The difference in change in primary and secondary outcomes, measured from baseline to week 16 or at exclusion due to worsening of asthma symptoms, is analyzed using the Wilcoxon rank-sum test. p Values < 0.05 are considered statistically significant.

[a]IQR is not reported as only one patient produced samples of acceptable quality at baseline and study end.

by ICS treatment (24). Periostin is not a lung-specific protein, but is also expressed in other tissues, such as bone and skin (19), and its role as a biomarker in asthma remains uncertain. Further studies are therefore needed to clarify its potential as a complementary biomarker in T2-low asthma. For now, however, the clinical applicability is limited, as periostin assays are not yet routinely available.

Interestingly, one patient in the tapering group turned out to have suppressed T2 inflammation despite initial classification as T2-low. This case illustrates the limitations of the biomarkers currently known, in that there is a risk of misclassification due to intra-individual variability and suppressed T2 inflammation caused by ICS treatment. Although combined biomarkers improve classification compared to a single-biomarker approach, clinical assessment including factors as BMI and exacerbation-rate should also guide selection of patients who may maintain asthma control without ICS (12,25).

One of the main strengths of this study is its randomized, controlled design across three clinical sites. The inclusion of several T2 biomarkers, FeNO, blood eosinophils, serum periostin, and sputum eosinophils, allows for a nuanced evaluation of the T2-low phenotype and its stability during ICS tapering. Furthermore, strict eligibility criteria as confirmed adherence to ICS prior to randomization minimize confounding by noncompliance or misclassification of inflammatory status. Another strength is that the study was conducted in a clinical care setting, which increases the relevance and applicability of the findings. While some biomarkers such as periostin and sputum eosinophils are not yet part of routine practice, their inclusion provided valuable insights into the T2-low phenotype. Additionally, participants were closely monitored for 12 months, allowing any changes in symptoms and biomarkers to be registered, which studies with shorter follow-up may not capture.

However, several limitations must be acknowledged. Most notably, the small sample size due to a very small number of eligible patients in the screening process limits the statistical power and generalizability of the findings. The limited number of participants did not allow valid statistics such as multivariate analyses that could have identified predictors of successful ICS tapering. Furthermore, the open-label design could potentially bias symptom reporting.

In conclusion, owing to the very limited sample size this randomized controlled trial could not determine whether tapering ICS is non-inferior to standard treatment in patients with T2-low asthma. Nevertheless, it provides preliminary indications that may guide the design of larger studies on the safety of ICS reduction and on refining patient selection in this subgroup.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

NSG reports personal fees for lectures and educational events during the last three years from AstraZeneca, Boehringer-Ingelheim and Chiesi. CSU reports personal fees for consulting or lectures from AstraZeneca, Berlin-Chemie Menarini, Boehringer Ingelheim, Chiesi, Covis Pharma, GlaxoSmithKline, Hikma Pharmaceuticals, IQVIA, Novartis, Novo Nordisk, Orion Pharma, Pfizer, Roche, Sanofi Genzyme, Takeda, TEVA and TFF Pharmaceuticals outside the submitted work.

CGW reports personal fees for lectures from Chiesi and GSK, a travel grant from Sanofi as well as consulting fees from GSK. CGW participated in voluntary activities with AstraZeneca and Sanofi and received no fees for these.

Funding

Study funding was received from P. Carl Pedersen's Foundation under Grant Number 20064, Helsefonden under Grant Number 20-B-0016, Skibsreder Per Henriksen, R. and Hustrus Foundation, Amager-Hvidovre Hospital Research Foundation, Mundipharma DK, Boehringer-Ingelheim DK, A.P. Møller Foundation under Grant Number L-2022-00050 and Danish Lung Association. The investigational medical products were provided by Orion Pharma, Espoo, Finland.

Data availability statement

The pseudonymized data from this study are not publicly available due to data protection regulations (GDPR). However, the data may be made available from the corresponding author upon reasonable request and with approval from relevant authorities.

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