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Utility of exhaled nitric oxide to guide mild asthma treatment in atopic patients and its correlation with asthma control test score: a randomized controlled trial

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Abstract

Background Fractional exhaled nitric oxide (FeNO) is used for the diagnosis and monitoring of asthma, although its utility to guide treatment and its correlation with other tools is still under discussion. We study the possibility to withdraw inhaled corticosteroid treatment in atopic patients with mild asthma based on the FeNO level, as well as to study its correlation with other clinical control tools.

Methods Prospective and randomized study including atopic patients aged 18 to 65 with mild asthma, stable, on low-dose inhaled corticosteroid (ICS) treatment, who had their treatment withdrawn based on a FeNO level of 40 ppb. Patients were randomized into two groups: control group (treatment with ICS was withdrawn regardless of FeNO level) and experimental group (according to the FeNO levels, patients were assigned to one of two groups: FeNO > 40 ppb on treatment with budesonide 200 mcg every 12 h and SABA on demand; FeNO ≤ 40 ppb only with SABA on demand). Follow-up was conducted for one year, during which medical assessment was performed with FeNO measurements, asthma control test (ACT), lung function tests (FEV1, FEV1/FVC, PEF, and RV/TLC), and recording of the number of exacerbations.

Results Ninety-two patients were included, with a mean age of 39.92 years (SD 13.99); 46 patients were assigned to the control group, and 46 patients to the experimental group. The number of exacerbations was similar between the groups ($p = 0.301$), while the time to the first exacerbation was significantly shorter in the control group (30.86 vs. 99.00 days), $p < 0.001$, 95% CI (43.332—92.954). Lung function tests (FEV1, FEV1/FVC, PEF, and RV/TLC) showed no differences between the groups ($p > 0.05$). Both FeNO and ACT showed significant changes in the groups in which ICS was withdrawn ($p < 0.05$ for both parameters). A significant negative correlation was observed between FeNO and ACT ($r = -0.139$, $p = 0.008$).

Conclusions In atopic patients with mild asthma, withdrawal of ICS based on an FeNO of 40 ppb led to worsened symptoms but without changes in lung function tests or an increase in exacerbations. There was a negative correlation between FeNO values and symptomatic control measured by the ACT.

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Trial registration Clinical Trial Number: 2012–000372-42. Start Date: 2012–07-23. Trial registered prospectively (https://www.clinicaltrialsregister.eu/ctr-search/search?query=2012-000372-42). This study adheres to CONSORT guidelines of randomised control trials.

Keywords Fractional exhaled nitric oxide (FeNO), Atopy, Asthma, Asthma control test

Introduction

Bronchial asthma is a chronic inflammatory disease characterized by episodic symptoms of varying intensity associated with variable airway obstruction [1–3]. Bronchial hyperresponsiveness and airway mucosal inflammation are characteristic, and they are present in all severe forms of asthma [4, 5]. According to current guidelines, the primary goal in asthma management is to achieve and maintain clinical control of the disease [1, 2]. These guidelines recommend the use of indicators such as symptom assessment scales, the use of rescue medication and objective measurements of lung function [3]. Given that the pathophysiological mechanism of asthma is primarily based on inflammation, it would be logical to include an indicator of airway inflammation, such as fractional exhaled nitric oxide (FeNO). Due to its ease of use, low cost, and noninvasive nature, FeNO is currently the most commonly used biomarker for eosinophilic bronchial inflammation [6, 7].

Due to the established relationship between FeNO levels in the airway, eosinophilic bronchial inflammation, and the response to corticosteroid treatment [6, 8], many studies have attempted to find the optimal FeNO cutoff point for titrating corticosteroid treatment in asthmatic patients. According to the current American Thoracic Society (ATS) clinical practice guidelines [9], a FeNO level greater than 50 ppb in adult patients could be compatible with eosinophilic inflammation, whereas FeNO levels between 25 and 50 ppb should be interpreted cautiously and take into account the patient clinical context. Consequently, most studies use cutoff points within this latter range to adjust therapeutic decisions, complementing them with clinical or lung function parameters [10–12].

In this context, FeNO has been correlated with other inflammatory markers in the respiratory tract, including bronchial mucosal eosinophilia [13], bronchoalveolar lavage eosinophilia [14], bronchial hyperreactivity [15], sputum eosinophilia [15], and peripheral eosinophilia [16]. However, despite numerous studies, there is still discordance with other asthma control indicators (symptoms and lung function) in published research [17–19]. This is why, despite the existence of various tools for monitoring asthma control, none of them are considered the gold standard. Therefore, it is recommended to take a comprehensive approach, considering all these different parameters of symptom measurement, lung function, and airway inflammation together, rather than separately [1–3].

There are studies with algorithms to guide asthma treatment based on FeNO levels that use very variable cut-off points [12, 20–24]; some of them in which FeNO > 40 ppb produced high sensitivity and specificity to identify subjects with high variability in peak expiratory flow (PEF), suggesting greater variation in airway caliber among patients with stable asthma [25]. Due to this, we decided to opt for values already established in the main asthma guidelines that use a FeNO level > 40 ppb as a tool for asthma diagnosis. (British Thoracic Society [26], Scottish Consensus Statement on the Role of FeNO in Adult Asthma [27], the NICE guide for the management of asthma [28] and the Spanish Guide for the Management of Asthma [2]) since they consider that above this value the levels of FeNO are related to bronchial hyperreactivity, positive bronchodilator test, asthmatic symptoms and variability in the PEF, parameters that They could correspond to poor clinical control; wondering if this value could be useful not only for the diagnosis of asthma but also for titrating its treatment.

The purpose of this study was to determine whether, in atopic patients with mild asthma, stable from a clinical and pulmonary function point of view, it is possible to step down their therapy using 40 ppb as FeNO cut-off point without this implying a worsening of your symptoms or lung function; in addition to determining the relationship that exists between symptomatic control tools such as the ACT scale with FeNO levels in this type of patients.

Methods

Participants

Both male and female patients were included, all between the ages of 18 and 65, non-smokers, diagnosed with mild atopic bronchial asthma according to the Spanish Guidelines to Asthma Management (GEMA) criteria and who, due to both clinical and spirometric stability, were candidates for a reduction in their maintenance treatment.

Inclusion criteria

Patients who had previously signed informed consent for their participation in the study, between 18 and 65 years old, diagnosed with mild bronchial asthma according

to the definition included in the latest Spanish Asthma Management Guidelines (GEMA), well controlled with no exacerbations in the last month, with ACT≥20 and a normal spirometry with a negative bronchodilator test, and who had atopy (elevated total IgE and/or positive Allergy Tests to respiratory allergens (Prick Test), and/or peripheral eosinophilia) were included.

Exclusion criteria

Patients who did not meet the criteria defined by the GEMA for well-controlled mild atopic asthma, had an obstructive pattern in spirometry secondary to another pathology (COPD, tuberculosis sequelae, bronchiolitis, etc.), clinical instability in the inclusion period or with an exacerbation in the month before inclusion in the study, inability to correctly perform inhaled treatment, patients with muscular diseases (myasthenia gravis, Parkinson's, etc), smokers or former smokers, conditions that require essential treatment with potential bronchoconstriction effects (e.g., nonselective beta blockers), pregnancy or breastfeeding, history of allergy to glucocorticoids and patients included in any other research protocol.

Study design

Single-center, prospective, open-label, randomized, parallel-group, controlled clinical study. All patients who met the inclusion criteria and none of the exclusion ones were included, having signed the informed consent. At the beginning of the study, a treatment adjustment was made according to the recommendations of the GEMA guideline; In this way, there were patients on treatment only with ICS (budesonide) who were kept on the same regimen and other patients on treatment with ICS/LABA who were left on only ICS (budesonide). Patients included in the study were maintained on 200 mg of budesonide every 12 h for three months with subsequent medical visits to verify the clinical stability measured by spirometry (FEV1/FVC > 0.7 and FEV1 > 80%), the ACT symptom questionnaire (ACT ≥ 20), and the absence of exacerbations during this period. Only the patients who met these criteria were included in the study. Patients were randomized into two groups: Group A (Control): patients in whom the inhaled corticosteroid treatment was withdrawn regardless of the FeNO level, left with short-acting beta-2 agonists (SABA) as the only treatment that should be administered only in the case of symptom perception according to current guidelines; Group B (Experimental): Patients who were divided into two further groups according to the FeNO level: FeNO > 40 ppb: received budesonide 200 mcg in a pressurized cartridge 1 inhalation twice a day and SABA if needed; FeNO ≤ 40 ppb: received treatment only with short-acting beta-2 agonists as needed (SABA) (same as Group A).

The follow-up period was 12 months, with 5 scheduled visits (+1 month, +3 months, +6 months, +9 mont hs, +12 months) with a window of ± 30 days after which the visit was skipped. During these visits, lung function tests were performed (peak flow, spirometry with bronchodilator test and lung volumes), FeNO measurement, an ACT symptom questionnaire and medical examination to assess whether there was a reduction in symptoms (which is considered to be clinically significant when there is a decrease of more than 3 points on the ACT scale [29]), the number of exacerbations (defined as worsening of asthma symptoms leading to systemic corticosteroid use, emergency room visit or hospital admission), daily symptoms, activity limitations, nocturnal symptoms and the use of rescue medication. Patients in which exacerbations or worsening of symptoms measured by previous parameters that required a therapeutic step up according to asthma treatment guidelines were withdrawn from the study.

Procedures

Asthma Control Test (ACT): A standardized and simple questionnaire that is easy to complete and allows for self-administration. The validated version was used, adapted to Spanish [30]. It contains 5 questions related to the frequency of asthma symptoms and the requirement for rescue medication use in the last four weeks. The ACT score ranges from 5 (worst control) to 25 (total control), with the following ranges: ≥20: well-controlled asthma; 19–16: partially controlled asthma; and ≤15: poorly controlled asthma [31]. A 3-point variation between two groups or over time is considered clinically significant [29].

FeNO measurement: *On-line*measurements of FeNO were made with a constant flow rate of 50 mL/s using a previously calibrated device (NIOX MINO® Aerocrine AB, Solna, Sweden), the procedure was repeated until 2 acceptable measurements were obtained, following standardized procedures for FeNO measurement in accordance with ATS/ERS guidelines for adults in effect at the time of the study [9, 32, 33]. FeNO measurements were performed before the lung function tests. The ATS guidelines suggest the following cutoff points in adults: FeNO<25 ppb not suggestive of inflammation, FeNO>50 ppb suggestive of bronchial inflammation, and FeNO between 25 and 50 ppb where a cautious interpretation adapted to the clinical context of the patient is suggested [9, 33]. The mean of 2 acceptable measurements was used for analysis.

Lung function tests: Forced spirometry was performed using a previously calibrated spirometer (Datospir 110/120, Sibel S.A., Barcelona, Spain) following the standardized ATS/ERS guidelines [33]. The lung function variables measured included forced expiratory volume

in one second (FEV1), forced vital capacity (FVC), the FEV1/FVC ratio, peak expiratory flow (PEF), and the residual volume/total lung capacity ratio (RV/TLC). Lung function was considered to deteriorate when the FEV1 decreased to less than 80%. Bronchial hyperresponsiveness was determined by a positive bronchodilator test with an increase in FEV1 > 12% or > 200 mL [34]. Pulmonary hyperinflation or air trapping (defined as an RV/TLC ratio greater than 40% [35, 36]) was measured by measuring the lung volume via the helium dilution technique (dispositive Hyp'Air compact +, Medi-soft S.A. Sorinnes, Belgium).

Prick test: An intradermal puncture test was performed by trained nursing staff on all patients included. The most common respiratory allergens in the region were detected: dust mites (Dermatophagoides pteronyssinus, Dermatophagoides farina), epithelia (dog and cat), pollens (cypress, plane tree, olive, grass mix, ragweed, wall pellitory), and molds (Alternaria, Aspergillus). Histamine reagent (10 mg/ml) was used as a positive control, and 0.9% saline solution as a negative control. The reaction was read 15 minutes after the instillation and was considered positive if the resulting wheal was equal to or larger than the positive control or at least 3 mm in diameter.

Peripheral blood eosinophils and total IgE: Eosinophil levels were quantified using flow cytometry (Advia 2120, Siemens Healthcare Diagnostics Inc., Camberley, UK), considering peripheral eosinophilia when values were greater than 500 cells/mL. Total IgE was measured by chemiluminescent immunoenzymatic analysis in the solid phase (Immulite 2500, Siemens, Bad Nauheim, Germany). Values of total IgE > 100 kUI/L were considered high.

Randomization and masking

The initial sample size of 114 patients was calculated. As a precaution in case all the planned patients could not be recruited and to ensure a balanced sample size in both arms of the study, the sample was divided into 19 blocks of six patients each. Patients were assigned to one of the groups through a computerized generator of randomized assignment (statistical software SPSS 15.0 for Windows), with the Mersenne twister selected as the randomization algorithm. A variable ("Random number") with 114 random values, one for each patient, was created. The variable "Random number" was created randomly, following a normal distribution considering 0 as the minimum and 1 as the maximum, with 13 decimal positions. Inside each block of six subjects, the three patients with the lowest values of the variable "Random number" were assigned to group A, and the remaining three to group B. The ratio was 1:1 assigning to each patient assigned a number in increasing order as they were included in the study. The randomization numbers are the numbers of the patients. The investigators of the study knew to which randomization arm the patients were assigned.

Objectives

Our main objective was to determine if FeNO values can be used as a tool to optimize the treatment of atopic patients with stable mild asthma, allowing the withdrawal of inhaled corticosteroid treatment without this leading to clinical or spirometric worsening; for this, we measured symptomatic worsening measured by the ACT scale, the number of exacerbations and time to the first exacerbation, and pulmonary function tests (FEV1, FEV1/FVC, PEF and RV/TLC). As a secondary objective, we studied the correlation that exists between FeNO and other clinical asthma control tools such as the ACT symptom scale.

Sample size calculation

For the sample size calculation, a statistical confidence level (1-α) of 0.95 was adopted for all the statistical analyses, with a power (1-β) of 0.80. Finally, a total sample size of 102 patients was calculated (according to Cohen, d=0.5). Considering a 10% experimental mortality rate, the initial sample was composed of 114 patients.

Statistical analysis

The data were analyzed using SPSS statistical software, version 23.0 (IBM SPSS Statistics for Windows. Armonk, NY: IBM Corp.). Between group baseline analysis was performed using the Pearson chi-square test. For the assessment of categorical variables (symptomatic worsening measured by the ACT scale, exacerbations, lung function decline, and air trapping), the nonparametric Pearson chi-square test was used, and in the case of values lower than 5, Fisher's exact test was used. For the evaluation of the time to first exacerbation, Student's t test was used, first checking for homogeneity of variance with Levene's test. For the analysis of pulmonary function tests, FEV1 was analyzed using ANOVA as the statistical test for comparing measurements among three groups (control, FeNO>40 ppb, and FeNO<40 ppb), whereas for the comparison of the two main groups (control and experimental), Student's t test was used, assuming equal variances after Levene's test. For the analysis of FeNO and PEF, the nonparametric Kruskal–Wallis test was used for comparing three groups with numerical variables, while for the same type of variables but comparing only the two main groups, the Mann–Whitney U test was used. For these same variables, for the analysis of measurements between two samples taken at different times (comparison of measurements at follow-up visits with baseline),

the Wilcoxon signed-rank test was used. To evaluate the correlation between FeNO and ACT, the Spearman rank correlation coefficient was used. A p value <0.05 was considered to indicate statistical significance.

Ethical considerations

The trial was conducted rigorously following the international ethical recommendations for investigation and clinical trials in humans as collected in the Helsinki Declaration of 1964, the recommendations of the World Health Organization (WHO), the deontological code, regulations from the Spanish legislation on clinical trials (Law 29/2006 of July 26th, on guarantees and rational use of medicines and medicinal products, Royal Decree 223/2004 of February 6th, regulating clinical trials with medicines), and the International Conference on Harmonization (ICH) guidelines on Good Clinical Practice (GCP). The study protocol was approved by the Ethics Committee for Clinical Research of Fundación Sant Joan de Déu (Barcelona, Spain) (N.E. 2012-000372-42 - C.I. AC-06-12).

Results

Patient characteristics

A total of 92 patients aged between 18 and 65 years met the inclusion criteria and were therefore included in the selection visit; 46 of these patients were in the control group, and 46 in the experimental group (23 in the FeNO > 40 ppb group and 23 in the FeNO ≤ 40 ppb group). The analysis was conducted in patients who, after three months of follow-up, demonstrated good asthma control both by symptoms (ACT scale) and by spirometry at the clinical stability visit (Visit-0). Thirty-nine of these patients were in the control group, and 42 in the experimental group (21 in the FeNO > 40 ppb group and 21 in the FeNO ≤ 40 ppb group). A total of 41 patients did not complete the study (19 in the control group and 22 in the experimental group) for reasons detailed in Fig. 1.

The baseline characteristics of both groups are described in Table 1.

There were no statistically significant differences between the control and experimental groups regarding weight, height or BMI (Table 1). No significant differences were observed between the control and experimental groups in terms of age (mean of 36.74 vs 42.69; SD 10.78 vs 16.01, respectively). Female sex was predominant in both groups (58.97% vs 61.9%, respectively).

Both the control and experimental groups had similar characteristics regarding atopy: eosinophils (SD 0.17 vs. 0.15, respectively) and total IgE (median 188.50 vs. 155.0, respectively), and the rate of aeroallergens in the prick test was also similar ($p > 0.05$ in all cases). Respiratory

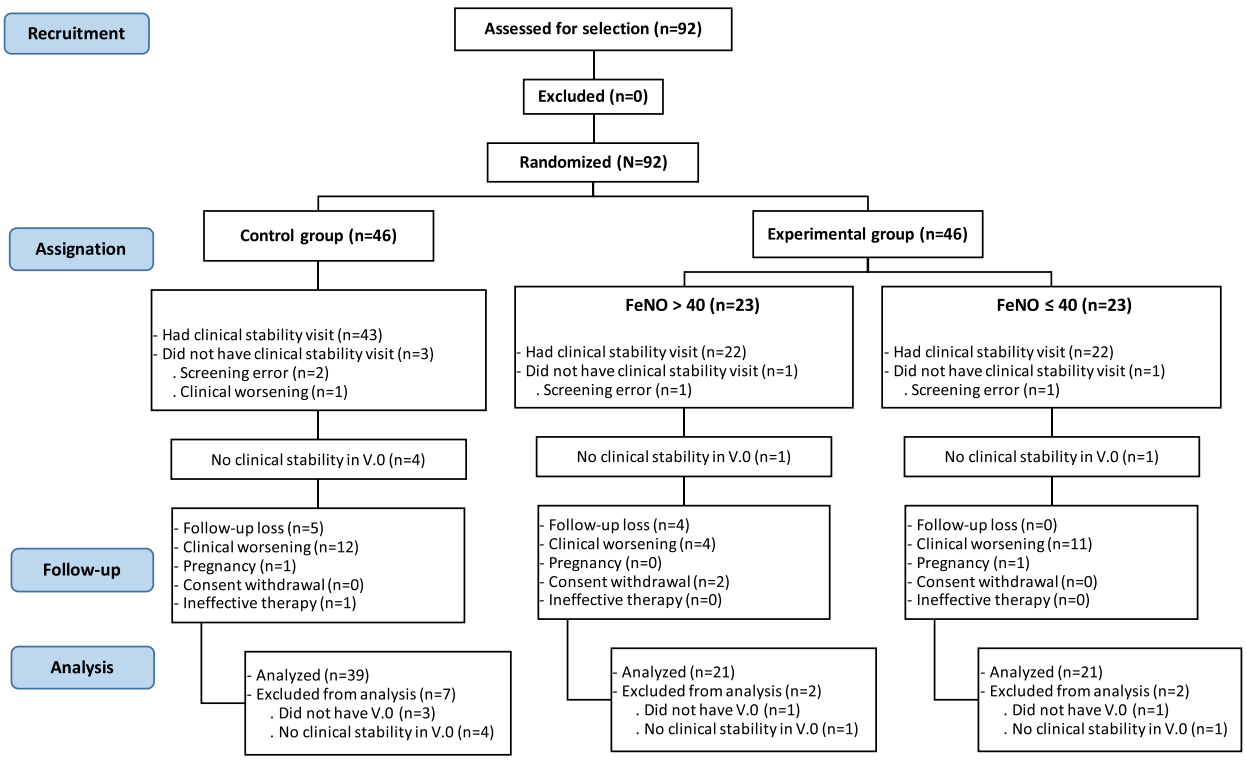

Fig. 1 Flowchart of patients. FeNO: fractional exhaled nitric oxide

Table 1 Baseline descriptive analyses at the beginning of the study

Baseline descriptive analyses at the beginning of the study			
Characteristics	**Control (*n* = 39)**	**Experimental (*n* = 42)**	***p*-value**
Sociodemographic data			
Sex: man/woman	16 (41.03%)/23 (58.97%)	16 (38.1%)/26 (61.9%)	0.79
Age	36.74 (SD: 10.78)	43.00 (SD: 16.01)	0.52
Race: cauc/ameri/asian	38 (97.44%)/1 (2.56%)/0	41 (97.62%)/0/1 (2.38%)	0.37
Vital signs	**Mean (SD)**		
Weight (Kg)	70.71 (12.45)	74.02 (14.79)	0.28
Height (cm)	166.77 (8.94)	165.26 (10.36)	0.49
Blood Pressure:			
SBD (mmHg)	121.75 (12.61)	125.07 (14.46)	0.27
DBP (mmHg)	75.74 (10.97)	76.41 (11.20)	0.79
Heart rate (bpm)	72.59 (11.26)	72.45 (8.83)	0.95
Complementary tests	**Mean (SD)**		
Blood count			
Hemoglobin (g/dl)	14.11 (1.15)	14.03 (1.49)	0.79
Platelets (Mil/mmcc)	254.34 (59.16)	262.85 (63.65)	0.54
Leukocytes (Mil/mmcc)	7.19 (2.01)	6.71 (1.32)	0.21
Eosinophils (Mil/mmcc)	0.27 (0.17)	0.30 (0.15)	0.39
Biochemistry			
Urea (mg/dl)	31.93 (10.09)	35.14 (13.38)	0.25
Creatinine (mg/dl)	0.78 (0.12)	0.79 (0.17)	0.72
GF (ml/min/1,73m2)	97.39 (14.06)	93.11 (17.07)	0.23
PCR (mg/L)	3.07 (4.32)	2.30 (2.49)	0.34
IgE (Kui/L) Median (IQR)	188.50 (365.00—120.25)	155.00 (336.50—111.00)	0.42
Respiratory test	**Mean (SD)**		
Forced Spirometry			
FVC (ml)(%) Pre-BD/Post-BD	4111 (95.80)/4130 (96.18)	3946 (94.19)/4002 (95.61)	0.44/0.54
FEV1 (ml)(%) Pre-BD/Post-BD	3319 (89.13)/3441 (99.77)	3181 (88.76)/3251 (98.51)	0.42/0.27
FEV1/FVC Pre-BD/Post-BD	80.91/83.60	80.70/81.60	0.97/0.22
FEV (25–75) (%) Pre-BD/Post-BD	94.64/105.23	99.86/106.51	0.44/0.84
Peak Flow (ml/sec)	423.56 (SD: 98.91)	420.69 (SD: 123.56)	0.61
FeNO (ppb) Median (IQR)	31.00 (52.00—19.00)	37.50 (79.50—21.75)	0.19
Prick test (n)(%)			
Mites	26 (66.70)	29 (69.00)	0.82
Epithelia	18 (46.2)	19 (45.20)	0.93
Pollen	22 (56.41)	26 (61.9)	0.45
Fungi	9 (23.1)	7 (16.67)	0.43
ACT Questionnarie Median (IQR)	24 (25—21)	21 (24—21)	0.006
Previous treatment (n)(%)			
ICS	30 (76.93)	26 (61.10)	0.78
ICS/LABA	9 (23.07)	16 (38.09)	0.14

SD standard deviation, *cauc* caucasian, *ameri* ameridian, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *IQR* interquartile range, *FVC* forced vital capacity, *FEV1* forced expiratory volume in the first second, *FeNO* fractional exhaled oxide nitric. *kg* kilograms, *mmHg* mercury millimeters, *bpm* beats per minute, *g/dL* grams per deciliter, *mg/L* milligrams per liter, kui/L: 1000 international units per liter, *ml* milliliter, *pre-BD* prebronchodilator, *post-BD* postbronchodilator, m*L/sec* milliliters per second, *ppb* particles per billion

function tests, including FEV1, FEV1/FVC, and PEF, showed no differences ($p > 0.05$ in all patients). Neither of the groups exhibited significant differences in their FeNO levels (median of 31 vs. 37.5, respectively). In the case of the ACT scale, although the means and SDs were very similar (23.26 for the control group vs. 22.24

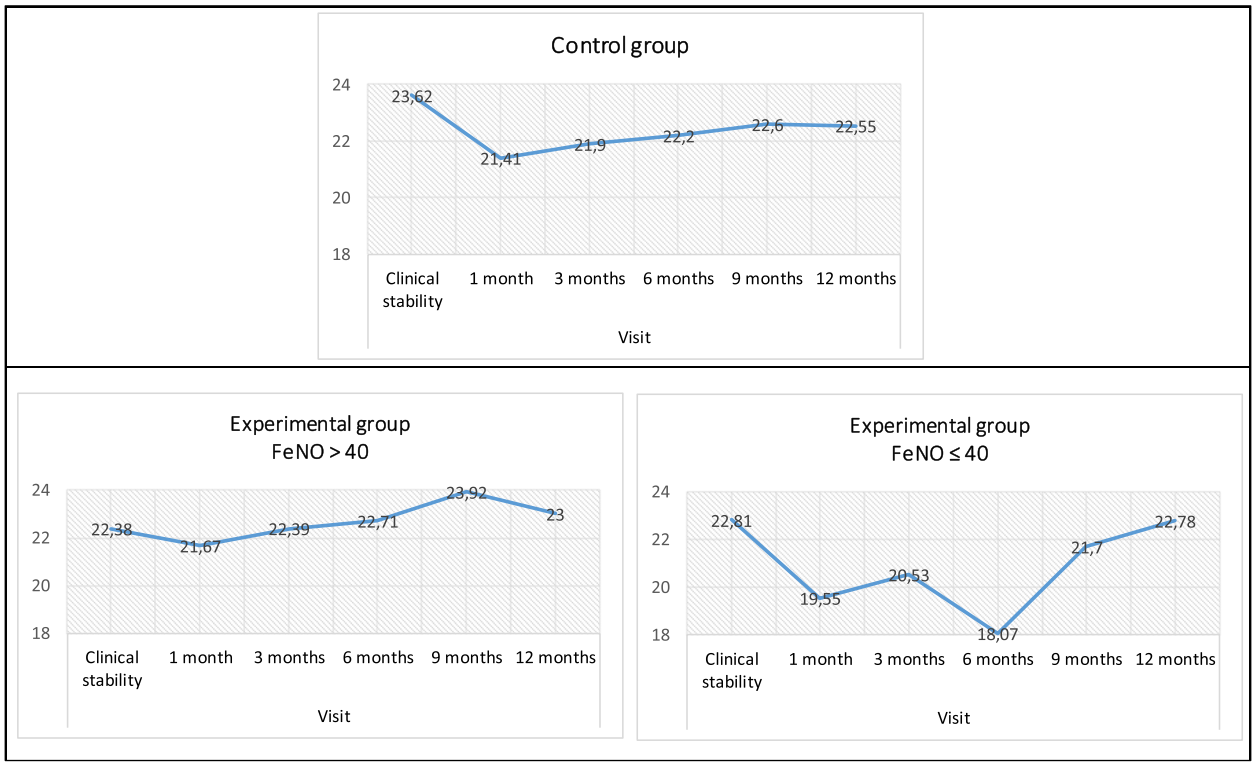

Fig. 2 Variation in the ACT scale at each visit during the study. FeNO: fractional exhaled nitric oxide. ACT: Asthma control test

for the experimental group), the Wilcoxon rank-sum test showed significant differences ($p=0.06$).

Symptom variation measured by the ACT

Cases that showed clinical worsening from visit-0 (clinical stability visit) measured by the ACT scale (qualitative analysis) were quantified; a reduction in said scale of 3 points or more was considered significant. Overall, 23 (59.0%) patients in the control group, 16 (80.0%) in the FeNO ≤ 40 ppb group and 8 (38.1%) in the FeNO > 40 ppb group experienced clinical worsening according to this tool. These differences were statistically significant ($\chi^2=7.424$, df = 2, $p=0.024$), and when comparing only the FeNO > 40 ppb and FeNO ≤ 40 ppb groups, the chi-square test revealed significant differences in the number of patients who presented worsening of their symptoms ($\chi^2=7.411$, df = 1; $p=0.006$) (Fig. 2 and Table 2).

In the analysis per visit, only visits 1 and 3 were significantly different between groups ($p=0.024$ in both cases). Table 2.

Exacerbations and time to first exacerbation

The number of exacerbations was very low, with the highest being 7 in the control group (19.95%), followed by the FeNO ≤ 40 ppb group with 2 (9.52%) and the FeNO > 40 ppb group with 1 (4.76%). Despite the differences in the absolute numbers and percentages of exacerbations between groups, the Pearson chi-square test revealed no statistically significant differences ($\chi^2=2.402$, df = 2, $p=0.301$). However, the time to first exacerbation, quantified in days, was significantly shorter in the control group than in the experimental group (30.86 vs 99.00 days, respectively; t = -6.333, df = 8, $p<0.001$, 95% CI (43.332—92.954)). Fig. 3.

According to the subgroup analysis within the experimental group, the mean number of days to the first exacerbation was similar between the FeNO > 40 ppb and FeNO ≤ 40 ppb groups (95 and 101 days, respectively) (Fig. 3).

Lung function tests

The number of patients who experienced lung function deterioration during the study, as measured by FEV1 < 80% and/or FEV1/FVC < 70%, was 22 (44%) in the control group, 16 (32%) in the FeNO ≤ 40 ppb group, and 12 (24%) in the FeNO > 40 ppb group. Both in the comparison between the control and experimental groups (2 groups) and in the comparison within the experimental subgroups (3 groups), the Pearson chi-square test did not reveal significant differences ($p>0.05$ at all visits) (Table 3). The same result was obtained when comparing FEV1 and FEV1/FVC values separately using ANOVA

Table 2 Number of patients who experienced clinical worsening according to the ACT scale score per visit

Number of clinical worsening cases according to ACT scale per visit							
Visit	**Group**	**ACT(Median)**	**SD**	**No worsening**	**Worsening**	**x^2**	***p*-value**
V1 +1 month	Control	21.41	3.477	25	14	7.489	0.024
	FeNO > 40	21.67	2.799	19	2		
	FeNO ≤ 40	19.55	4.148	11	10		
V2 +3 months	Control	21.90	3.229	21	10	1.453	0.484
	FeNO > 40	22.39	2.524	14	4		
	FeNO ≤ 40	20.53	2.718	10	7		
V3 +6 months	Control	22.20	3.317	18	7	7.469	0.024
	FeNO > 40	22.71	2.840	13	1		
	FeNO ≤ 40	18.07	5.077	7	8		
V4 +9 months	Control	22.60	2.280	15	5	4.369	0.113
	FeNO > 40	23.92	1.441	13	0		
	FeNO ≤ 40	21.70	4.473	7	3		
V5 +12 months	Control	22.55	3.170	18	2	0.455	0.797
	FeNO > 40	23,00	3.162	9	2		
	FeNO ≤ 40	22.78	2.224	8	1		

FeNO fractional exhaled nitric oxide, *ACT* asthma control test, *SD* standard deviation, χ^2 chi-square test. FeNO is expressed in particles per billion (ppb)

$p < 0.05$: statistically significant

(comparison between 3 groups) and Student's t test (comparison between 2 groups), with p values > 0.05 at all visits.

PEF values did not differ among the three groups during the study ($p > 0.05$ in all patients). The FeNO > 40 ppb group presented significant changes in PEF measurements at the end of the study compared to visit-0 and in comparison with the other groups (488 ± 184 L/min at V-5; + 39 ml compared to V-0) (z = -2.312, $p = 0.021$), while in other visits and the other groups, no significant changes in this variable were observed ($p > 0.05$ in all cases).

The number of cases with air trapping (RV/TLC > 40%) was 12 for the control group, 10 for the FeNO > 40 ppb group, and 11 for the FeNO ≤ 40 ppb group, with no differences observed at each visit where this parameter was measured ($p > 0.05$ in all cases).

Correlation between FeNO and ACT

During the follow-up visits, the Wilcoxon rank-sum test revealed significant changes in the FeNO levels in the control group and the FeNO ≤ 40 ppb group, with p values < 0.05 in all cases, with the results in the FeNO ≤ 40 ppb group being nearly significant ($p = 0.086$) only at V-5 (Table 4 and Fig. 4). Similarly, the ACT scale exhibited considerable variations predominantly in the control group and FeNO ≤ 40 ppb group, being significant at visits V-1 to V-3 for both groups ($p < 0.05$ for all of them) (Table 4).

According to the analysis per visit, negative correlation coefficients between the FeNO concentration and the ACT score existed only for visits 1 and 3 (Spearman -0.256, $p = 0.025$ and -0.324, $p = 0.017$, respectively). However, in the analysis of the totality of values of all visits, the statistical study revealed a significant negative correlation between FeNO and ACT (Spearman -0.139, $p = 0.008$). Table 5 and Fig. 5.

Discussion

FeNO has been established as the quintessential biomarker of bronchial eosinophilic inflammation due to its ease of use, noninvasive nature and low cost, and it is available both in hospitals and primary care settings. However, the value of measuring FeNO has yet to be defined as part of the clinical evaluation of asthma control [12, 24, 37].

We prospectively studied a population of mild asthmatic patients (according to the Spanish Guide for Asthma Management, which corresponds to its definition in the GINA guide), nonsmokers and those with atopy, with low-dose inhaled corticosteroid (ICS) treatment (step 2 of the GEMA guidelines and step 1 or 2 of the GINA guidelines), who were clinically stable (ACT ≥ 20) and spirometrically stable (FEV1 > 80% and FEV1/FVC > 70%), as opposed to most previous studies that included patients at different severity stages and only a percentage of whom were atopic individuals.

According to the main guidelines for asthma management [1, 2, 28], treatment can be reduced by one

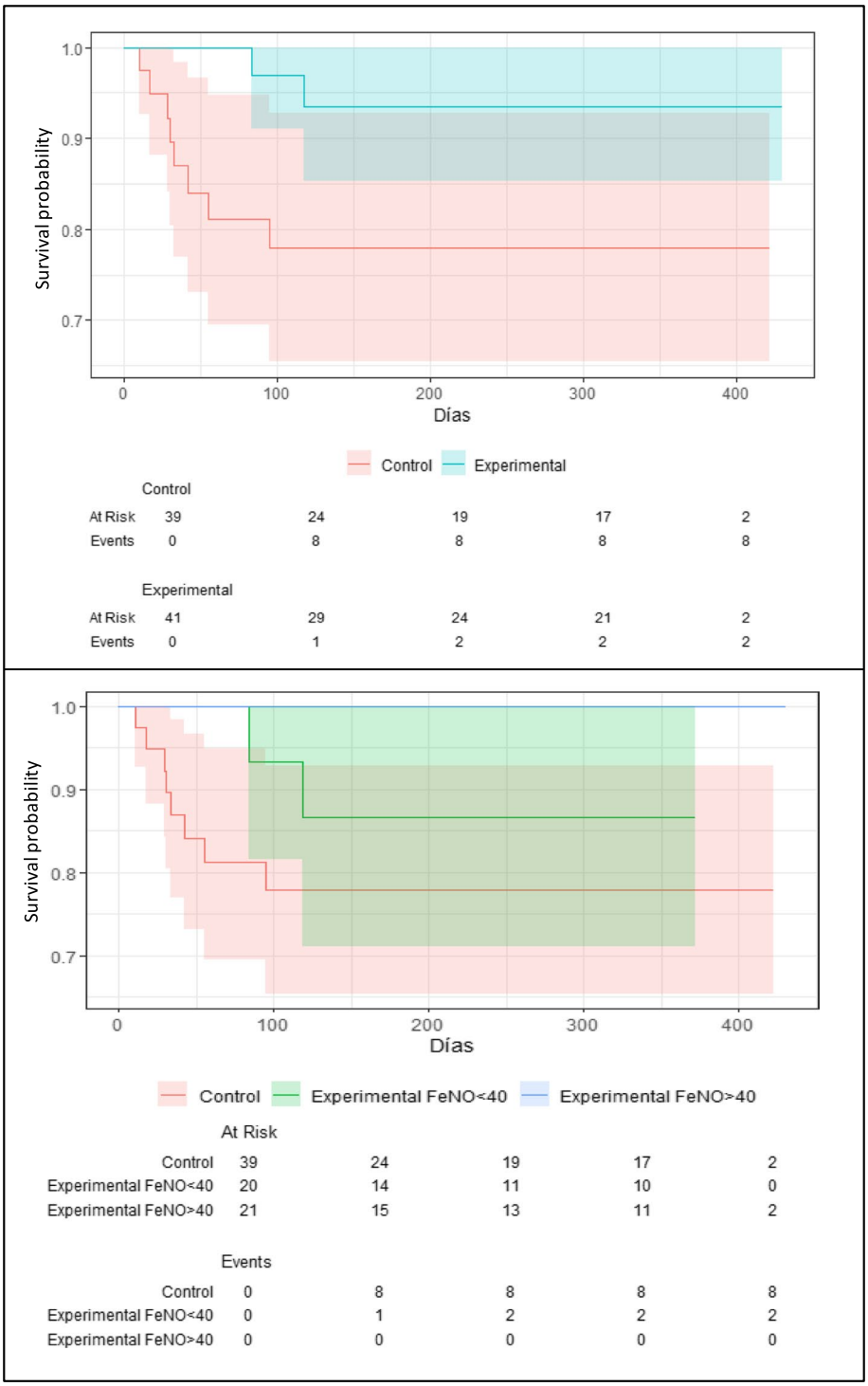

Fig. 3 Kaplan–Meier analysis. Time to first exacerbation

therapeutic step if the patient presents both clinical and spirometric stability. Based on the current ATS guidelines [9] at the time of this study's development, an FeNO level between 25 and 50 ppb should be cautiously interpreted, and according to the clinical context of the patient, we attempted to establish a cutoff point for the FeNO level that could allow for withdrawal of the ICS without resulting in worsening of the different asthma

Table 3 Lung function tests

Lung function tests												
		FEV1%			FEV1/FVC%			RV/TLC%			PEF(L/min)	
Visit	Group	Mean (SD)	< 80% (n)	*p*-value	Mean (SD)	< 70% (n)	*p*-value	Mean (SD)	> 40% (n)	*p*-value	Mean (SD)	*p*-value
V1 + 1 month	Control	91.19 ± 12.19	5	0.348	78.65 ± 7.40	4	0.527				430 ± 112	0.130
	FeNO > 40	96.71 ± 17.18	2		80.86 ± 7.89	3					455 ± 119	
	FeNO ≤ 40	94.33 ± 13.94	1		79.24 ± 5.44	1					386 ± 103	
V2 + 3 months	Control	94.84 ± 10.22	3	0.413	78.90 ± 7.35	5	0.252				433 ± 111	0.036
	FeNO > 40	92.83 ± 12.90	2		80.40 ± 8.43	2					450 ± 97	
	FeNO ≤ 40	90.41 ± 10.24	2		75.63 ± 10.75	4					367 ± 74	
V3 + 6 months	Control	92.68 ± 10.47	2	0.285	76.47 ± 6.38	3	0.682	35.76 ± 11.23	6	0.460	438 ± 120	0.377
	FeNO > 40	98.14 ± 15.48	1		77.56 ± 4.70	1		33.53 ± 13.50	6		454 ± 115	
	FeNO ≤ 40	100.50 ± 22.03	2		75.37 ± 6.69	3		34.95 ± 13.21	6		426 ± 162	
V4 + 9 months	Control	97.05 ± 9.69	0	0.239	82.14 ± 5.36	0	0.205				450 ± 109	0.107
	FeNO > 40	91.54 ± 11.99	1		79.18 ± 4.70	0					448 ± 111	
	FeNO ≤ 40	91.30 ± 10.77	1		78.63 ± 7.73	1					379 ± 85	
V5 + 12 months	Control	100.70 ± 20.21	2	0.904	77.79 ± 7.42	3	0.464	38.94 ± 13.56	6	0.470	461 ± 151	0.079
	FeNO > 40	100.55 ± 17.78	1		75.77 ± 5.14	1		35.96 ± 10.98	4		488 ± 184	
	FeNO ≤ 40	97.44 ± 16.46	0		74.29 ± 8.98	2		38.56 ± 13.58	5		348 ± 131	

SD standard deviation, *FEV1* forced expiratory volume in the first second, *FEV1/FVC* ratio of the forced expiratory volume in the first second/forced vital capacity, *RV/TLC* ratio residual volume/total lung capacity, *PEF* peak expiratory flow, *FeNO* fractional exhaled nitric oxide

RV/TLC was measured only for V0, V3 and V5

p value < 0.05: statistically significant

Table 4 Changes in FeNO and ACT at each visit

Changes in FeNO and ACT in each visit compared to visit-0							
	V0	**V1 (+1 month)**	**V2 (+3 months)**	**V3 (+6 months)**	**V4 (+9 months)**	**V5 (+12 months)**	***p-value*** [*] **(V1 -V5)**
FeNO (ppb)							
Control	35.59	56.14	49.01	49.08	50.65	50.20	0.000; 0.002; 0.010; 0.006; 0.004
FeNO > 40	61.23	72.25	60.11	62.71	67.92	60.55	0.277; 0.962; 0.944; 0.650; 0.894
FeNO ≤ 40	27.28	48.80	52.35	50.20	60.90	63.33	0.005; 0.029; 0.015; 0.036; 0.086
ACT							
Control	23.62	21.41	21.90	22.20	22.60	22.55	0.001; 0.012; 0.034; 0.081; 0.200
FeNO > 40	22.38	21.67	22.39	22.71	23.92	23.00	0.067; 0.899; 0.442; 0.009; 0.440
FeNO ≤ 40	22.81	19.55	20.53	18.07	21.70	22.78	0.001; 0.004; 0.003; 0.723; 0.833

[*] *p*-value at each visit compared to visit-0

$p < 0.05$ = statistically significant

FeNO fractional exhaled nitric oxide, *ACT* asthma control test, *ppb* particles per billion

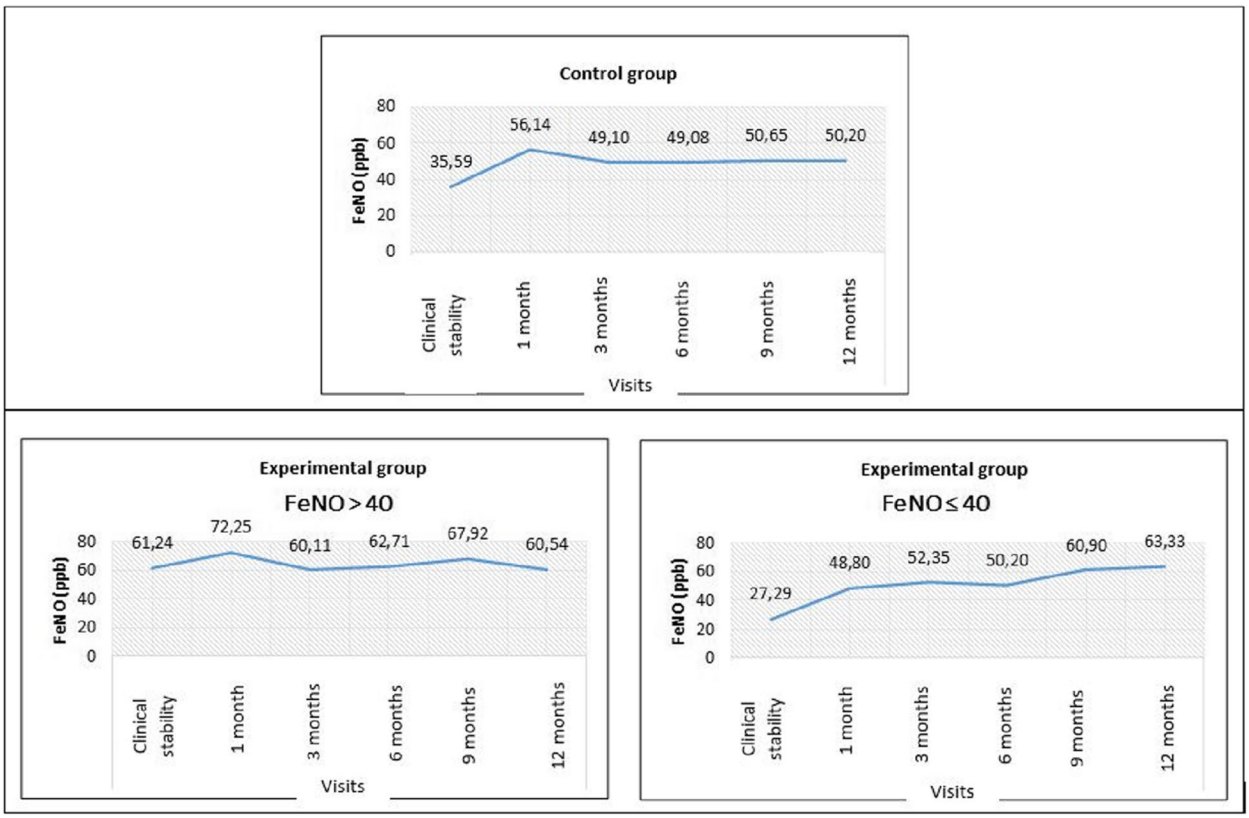

Fig. 4 Levels of FeNO per visit. The values are expressed in particles per billion (ppb). FeNO: fractional exhaled nitric oxide

control parameters. It should be taken into account that our population consisted of stable, mild asthmatic patients with a history of atopy, which in numerous studies has been linked to higher FeNO levels [38–41].

Our results showed a significant decrease in the symptomatology measured by the ACT scale in patients in whom the ICS treatment was withdrawn (control group and FeNO ≤ 40 ppb group) ($p = 0.024$), with a more pronounced reduction in visits 1 and 3, when there was a greater rate of abandonment of patients due to clinical worsening. However, this loss of clinical stability did not result in a statistically significant difference between

Table 5 Spearman correlation FeNO/ACT

Visit		ACT
0	FeNO	-0.067
	p-value	0.552
+1 month	FeNO	-0.256
	p-value	0.025
+3 months	FeNO	-0.670
	p-value	0.595
+6 months	FeNO	-0.324
	p-value	0.017
+9 months	FeNO	0.093
	p-value	0.555
+12 months	FeNO	0.026
	p-value	0.872

FeNO fractional exhaled nitric oxide, *ACT* Asthma control test

$p < 0.05$: statistically significant

groups regarding exacerbations ($p = 0.301$). Nevertheless, there was a significantly shorter time to first exacerbation in the control group than in the experimental group (30.86 vs 99.00 days, respectively, $p < 0.001$ CI 95% (43.332–92.954)), which was consistent with the results of the analysis of the experimental subgroups. Due to the limited number of events, it was not possible to apply a logistic regression model to analyze the prediction of possible exacerbations based on FeNO levels. Similar results were obtained in the study conducted by Kim et al. [42] in which Inhaled corticosteroid treatment was discontinued in patients with controlled mild asthma, and a loss of asthma control was observed in patients whose mean levels of FeNO were 37.7 ppb (very close to ours) at the beginning of the study, while the time to loss of asthma control was significantly shorter in the group without ICS (188 vs 872 days). In contrast, contradictory results to ours were reported by Hojo et al., [22] where the dose of ICS was reduced by 50% in adult mild asthmatic patients based on a level of FeNO ≤ 28 ppb. This study, similar to our study, showed an increase in the levels of FeNO, but this increase did not lead to significant changes in the symptomatology measured by the ACT. One possible reason for these discrepancies could be the severity of asthma in the populations included in our studies (moderate vs mild), but it mostly depends on the fact that their patients transitioned from a medium to a low dose of ICS/LABA; other concomitant treatments, such as antileukotrienes or theophylline, are also possible, but they are never totally discontinued, as was the case in our study. It should also be noted that we started with a relatively higher FeNO level (40 vs 28 ppb). Different studies and meta-analyses attempting to guide asthma treatment by titrating the dose of inhaled corticosteroid treatment based on FeNO levels have been previously performed. Each of them has described its own cutoff point but with contradictory results; some of them have shown benefits, while others have not [22, 43–45]. A meta-analysis has proven that management based on treatment adjustment guided by FeNO is associated with a significantly reduced risk of exacerbation [46], our study did not have the statistical power to confirm this relationship; however, our study detected a benefit in the experimental group, which suggests that there could be an association with a longer time to the onset of exacerbation. On the other hand, in a more recent systematic review and meta-analysis (7 RCTs with 384 patients over 12 years of age with mild to moderate asthma, non-smokers) [47] FeNO was classified as low (≤ 20 ppb), intermediate (20 to 50 ppb) and high (≥ 50 ppb) based on ATS recommendations. Using a logistic regression method, this meta-analysis concluded that reducing corticosteroid treatment based on a FeNO level < 50 ppb reduces the prescription of inhaled corticosteroids without increasing the number of exacerbations; results that are consistent with ours using a close FeNO level. Likewise, in this review a subgroup analysis is carried out in which it is reported that the risk of exacerbation was significantly higher in individuals with high versus intermediate FeNO ($p = 0.028$) (understanding as a limit between both a FeNO level of 50 ppb); but this did not happen in the subgroup of patients treated with an optimal dose of ICS defined as 150—200 mcg/day of fluticasone propionate and which is equivalent to the doses of ICS used in our study (budesonide 400 mcg/day), in this subgroup the exacerbation rate did not show significant differences between high vs intermediate FeNO levels (OR 1.56 95% CI 0.28 – 8.66; $p = 0.613$); results that are again consistent with ours, since the FeNO > 40 ppb and FeNO < 40 ppb groups showed similar exacerbation rates. On the other hand, this meta-analysis only evaluated exacerbations that occurred within 12 weeks after reducing ICS, which is why in its final comments it emphasizes that, to reinforce its results, future research should use longer follow-up periods and in relevant subgroups; this fact would add importance to our clinical trial taking into account the time and the population in which it was carried out (12 months of follow-up in mild asthmatic and atopic patients).

On the other hand, our study assessed lung function parameters measured by spirometry (FEV1, FEV1/FVC and PEF), including the RV/TLC ratio, to analyze the small airway since there are studies suggesting that inflammatory infiltration could be greater than that in central airways [48]. Moreover, the RV/TLC ratio could indicate the presence of a remodeling effect [49] and is an even better indicator of airway obstruction than usual parameters [50–53], with existing studies correlating the increase in residual volume (RV) with worse

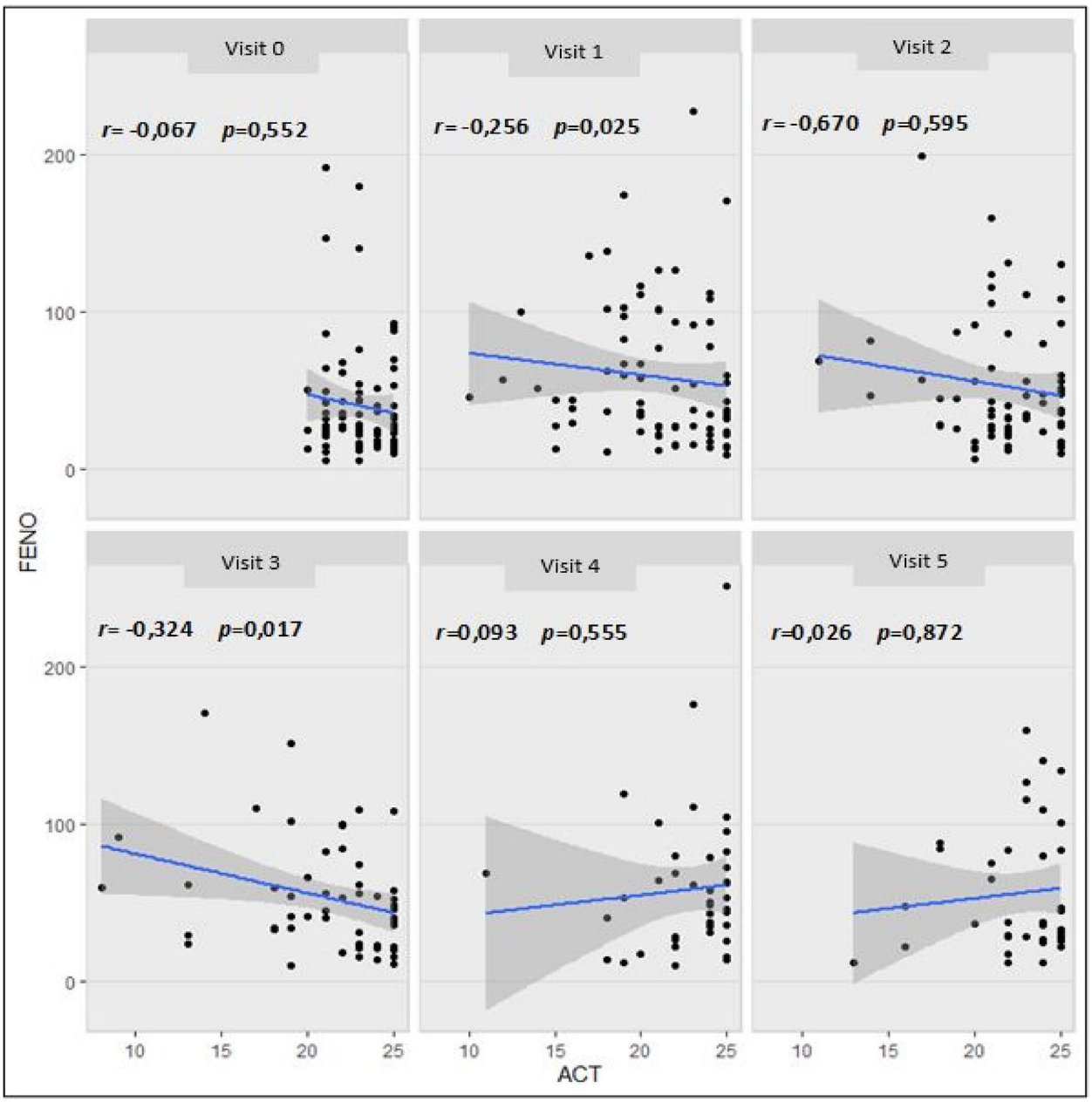

Fig. 5 Spearman correlation FeNO/ACT. FeNO: fractional exhaled nitric oxide. ACT: Asthma control test. Analysis of all the visits: $r = -0.139$, $p = 0.008$

clinical control and a greater number of exacerbations [54]. Our study revealed no significant differences in the deterioration of lung function (measured by FEV1 and FEV1/FVC), the PEF values or the RV/TLC ratio between the randomization groups and throughout the entire study ($p > 0.05$ in all cases). The group of patients in which ICS treatment was withdrawn due to a cut-off level of FeNO of 40 ppb did not show significant changes in lung function, as measured by FEV1, FEV1/FVC, or PEF, or in air trapping, as measured by lung volume (RV/TLC), in comparison to patients who kept such treatment.

Most previous studies that have attempted to guide asthma management based on FeNO levels have shown similar results to ours, although very different cutoff levels were used to discontinue or reduce inhaled corticosteroid treatment, which in all cases was lower than ours. For example, Malerba et al. (FeNO ≤ 10 ppb), [21] Prieto et al. (FeNO 15–20 ppb), [55] Hojo et al. (FeNO ≤ 28 ppb), [22] Syk et al. (FeNO < 21 ppb in men and < 19 ppb in

women), [43] Honkoop et al. (FeNO < 25 ppb), [44] and Calhoun et al. (FeNO < 22 ppb), [11] among others, did not find differences in lung function tests between study groups. These studies concluded that bronchial inflammation could not be related to lung function in this type of patients. To date, we have not found studies that have attempted to relate FeNO to air trapping. The study that comes closest to this aspect is the one conducted by Hojo et al. [22] reported spirometric results with values of mid-expiratory flows such as FEV25-75 (FeNO cut-off of ≤ 28 ppb) to assess small airway involvement in patients from whom inhaled corticosteroid treatment was withdrawn based on FeNO levels. In this study, the results did not show significant differences ($p > 0.05$). As mentioned above, our results are consistent with theirs despite having used a higher cutoff point that, consequently, could have led us to think that withdrawing the inhaled corticosteroid in an asthmatic patient based on a FeNO value of 40 ppb could cause a worsening in lung function tests in comparison to patients who did not undergo this intervention. However, it should be noted that our study was conducted in patients with mild stable asthma who had normal spirometry at the beginning of the study, suggesting that the changes in the spirometric values were not pronounced enough to reflect a relation in the bronchial inflammation measured by FeNO.

On the other hand, we consider of high relevant to know the relationship that exists between FeNO and one of the main assessment tools for asthma symptomatic control, the Asthma Control Test (ACT) scale; since in studies prior to the creation of this scale, the perception of symptoms had already been related to markers of bronchial inflation [56].

According to our results, the FeNO levels significantly changed over time in comparison to those at the initial visit and progressively increased in the groups in which ICS were withdrawn ($p < 0.05$). These changes corresponded to a progressive decrease in the ACT scores, indicating symptomatic worsening in these groups ($p < 0.05$). These findings are consistent with the fact that FeNO levels are linked to inhaled corticosteroid treatment, as evidenced in other studies [6, 8, 22, 23, 43]. The Spearman test revealed a significant negative correlation between FeNO and ACT, which was more pronounced at visits 1 and 3 but persisted in the combined analysis of all visits ($r = -0.139$, $p = 0.008$). The improvement in the FeNO and ACT values from this visit onward is likely secondary to the effect of the values of these parameters in patients who were not removed from the study due to clinical worsening, since most dropouts occurred at visit-3.

Previous studies with populations similar to ours showed similar results. In Spain, Bernstein et al. [57] conducted a study with 2 different populations (one in the USA and one in Spain). In the subanalysis of the Spanish population that included 55 mild asthmatic patients without ICS treatment, a strong correlation between FeNO and ACT ($r = -0.48$ $p < 0.001$) was shown, whereas the same correlation did not occur in patients receiving corticosteroid treatment ($r = -0.23$ $p > 0.05$). Similarly, Alvárez-Gutiérrez et al. [58] reported a weak negative correlation between ACT and FeNO levels greater than 35 ppb ($r = -0.16$, $p < 0.01$) in a population of patients with different severities of asthma, most of whom were treated with ICS/LABA, and 26% of whom had controlled asthma. In both studies, only a portion of the patients had atopic asthma (62% vs 74%, respectively), whereas the second included smokers. Previous studies by different authors worldwide involving patients without corticosteroid treatment obtained similar results. Indeed, Senna et al. [18] and Papakosta et al. [59] with a much smaller sample size ($n = 27$ and $n = 19$, respectively) showed a stronger correlation between both parameters ($r = 0.69$, $p = 0.001$ and $r = -0.76$, $p < 0.001$, respectively); moreover, Kavitha et al. [60] with a larger sample size showed a significant and strong correlation ($n = 151$, $r = -0.76$, $p < 0.001$).

On the other hand, the studies conducted by Shirai et al. [19] and Gutierrez et al. [58] reported a correlation between FeNO and ACT in a population of asthmatic patients treated with inhaled corticosteroids ($r = 0.31$, $p = 0.003$ and $r = -0.16$, $p < 0.01$, respectively). More recently, Gemicioglu et al. [61] and Nguyen et al. [62] with a larger sample size ($n = 416$ and $n = 410$, respectively) revealed a negative and weak relationship in these patients ($r = 0.31$, $p = 0.002$ and $r = -0.224$, $p < 0.001$, respectively).

Nonetheless, other studies have shown inconsistent findings with ours; Khalili et al., [17] Han et al. [63] and more recently, Katoch et al. [64] and Nguyen et al. [65] concluded that there was no relationship between FeNO and ACT ($p > 0.05$ in all cases) in populations that included adults and children. In addition to the sample size examined and the diversity of the population in these studies and their own ethnic and sociodemographic characteristics, which could explain these differences, another possible explanation for these discrepancies could be the heterogeneity of the population in terms of the severity of asthma. Moreover, in our study, we evaluated a population with well-controlled mild asthma. In the aforementioned studies, the population was affected by different severities of asthma, with a variable percentage of mild asthma ranging from 36.5% (Katoch et al. [64]) to 57.1% (Nguyen et al. [65]). Assuming that patients with moderate and severe asthma are under more adjusted treatment, with higher doses of inhaled corticosteroids,

long-acting beta-agonists (LABA) and/or antileucotrienes (ALT), we can suppose that the influence of ICS treatment on FeNO and that the influence of LABAs and ALT on the perception of clinical stability could result in the absence of significant changes in both parameters over time, leading to a correlation between them. If a subanalysis of the patients at the beginning of the study when all patients were receiving corticosteroid treatment was conducted, a significant correlation between FeNO and ACT would not be detected through the statistical Spearman test (r = -0.067, p = 0.552) (Table 5), which is consistent with previous data from those authors but would only be accurate for this specific visit.

In conclusion, in atopic patients with mild stable asthma, withdrawing inhaled corticosteroids based on FeNO levels could lead to symptomatic worsening, but without this impacting the rate of exacerbations or lung function tests; according to our results, there is a negative correlation between FeNO values and symptomatic control measured by the ACT scale. Our study would lead us to infer that in this type of patients there is an inflammatory component in the airways that affects them clinically, but without yet having an impact on lung function. Thus, FeNO could be considered a useful biomarker in decision making in atopic patients with stable mild asthma on inhaled corticosteroid treatment, but always in conjunction with other clinical asthma control tools. However, future studies with a larger population and longer follow-up time are necessary to confirm the findings obtained in our study.

Abbreviations

ACT	Asthma control test
ALT	Antileucotriens
ATS	American Thoracic Society
BMI	Body Mass Index
cells/mL	Cells per milliliter
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
ERS	European Respiratory Society
FEF_{25-75}	Forced expiratory flow at 25 and 75% of the pulmonary volumen
FeNO	Fractional exhaled nitric oxide
FEV1/FVC	Forced expiratory volume in one second/ forced vital capacity ratio
FEV1	Forced expiratory volume in one second
FVC	Forced vital capacity
GCP	Good Clinical Practice
GEMA	Spanish Guide for the Asthma Management
GINA	Global Initiative for Asthma
ICH	International Conference on Harmonisation
ICS	Inhaled corticosteroid
IgE	Immunoglobulin antibody E
kUI/L	1000 International units per liter
LABA	Long-acting beta agonist
mcg	Micrograms
mL/s	Milliliters per second
mL	Milliliter
PEF	Peak expiratory flow
ppb	Particles per billion
RV/TLC	Residual volume/total lung capacity ratio
RCT	Randomized controlled trial
SABA	Short-acting beta-2 agonists
SD	Standard deviation
USA	United States of America
WHO	World Health Organisation
χ^2	Chi-square

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Not aplicable

Authors' contributions
EP, RH, and LL were involved in study design, data analysis, and interpretation. JC, CL were involved in data collection, EA was involved in revising the manuscript. All authors contributed significantly to the review and approval of the final manuscript.

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Availability of data and materials
The datasets generated during the current study are available upon request from the corresponding author.

Declarations

Ethics approval and consent to participate
The study protocol was approved by the Ethics Committee for Clinical Research of Fundación Sant Joan de Déu (Barcelona, Spain) (N.E. 2012–000372-42—C.I. AC-06–12). Informed consent was obtained from all participants involved in the study or their legal guardians, and gave their voluntary consent to participate.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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