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ORIGINAL ARTICLE

Is Exhaled Nitric Oxide a Useful Adjunctive Test for Assessing Asthma?

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Rationale. To determine the general utility of clinical (Asthma Control Test) and physiologic (forced expiratory volume in the first second of exhalation [FEV₁] and fractionated exhaled nitric oxide level [FeNO]) parameters for characterizing asthma patients. **Methods.** Two cross-sectional independent studies simultaneously enrolled 100 patients in the US and 109 patients in Spain ≥ 18 years of age with a physician-diagnosis of asthma and confirmed by a ≥ 12% improvement in FEV₁ after bronchodilators or the presence of airway hyperresponsiveness, a central feature of asthma, as measured by methacholine challenge (PC₂₀ < 10 mg/mL). There was no restriction on asthma severity or treatment. Patients were excluded if they had a diagnosis of chronic obstructive pulmonary disease and/or were current cigarette smokers. Statistical analyses were performed to compare ACT, FeNO, and spirometry within and between sites. **Results.** Population characteristics revealed significant differences in distributions of age, percent-predicted FEV₁ (%FEV₁), FeNO, inhaled corticosteroid usage, and atopy between the two populations. The Spain site enrolled younger patients with milder asthma, based on higher %FEV₁ values and less frequent treatment with inhaled corticosteroids. At each site, mean FeNO levels decreased as asthma control categories increased, and means were lower in the US. There was a negative correlation between ACT and FeNO that was statistically significant for Spain patients *not* treated with inhaled corticosteroids. **Conclusions.** The results of this study support the use of FeNO as an adjunctive tool for assessing asthma primarily in mild inhaled corticosteroid (ICS)-naïve asthma patients. The lack of correlation of ACT with FeNO in this and other studies across the entire population appears to reflect the heterogeneity of asthma patients who have an admixture of asthma severity and treatment regimens making it very difficult to appreciate the nuances of sensitive tests like FeNO.

Keywords fractionated exhaled nitric oxide (FeNO); Asthma Control Test (ACT); forced expiratory volume in the first second of exhalation (FEV₁); percent predicted FEV₁ (%FEV₁); percent predicted FEV₁/FVC (%FEV₁/FVC); forced vital capacity (FVC); inhaled corticosteroid (ICS)

INTRODUCTION

The assessment of asthma is challenging, as phenotypes for this chronic obstructive lung disorder vary widely. The National Lung Health Blood Institute (NLHBI) guidelines for asthma management emphasize the importance of assessing patient impairment and risk to establish disease control (1). To achieve good asthma control, the guidelines emphasize the importance of utilizing patient-centric validated questionnaires and objective measurements of lung function (1). The Asthma Control Test (ACT) is a five-question patient-centric survey, scores ranging from 0 to 25 points, that parallels the current asthma management guidelines by focusing on asthma symptoms, use of rescue medications, and impact of asthma on daily function (2). In developing this questionnaire, stepwise logistic regression methods were used to identify those items that had the greatest validity in differentiating patients with different physician-described levels of asthma control (2). Based on this analysis, five items were incorporated into the ACT that were found to have an internal consistency reliability of 0.84 overall with a cut off score

of 19 demonstrating the highest overall agreement between the ACT and the asthma specialist's rating of asthma control ($r = 0.45$, $p = 0.0001$). (2) A score ≤ 19 had a sensitivity and specificity of 69.2% and 76.2%, respectively, for predicting poor asthma control based on the specialist's rating. There was a low but significant correlation between the ACT and FEV₁ ($r = 0.19$, $p = 0.0001$) (2).

Measurement of lung function parameters by spirometry is still considered the gold standard for asthma diagnosis for assessing the degree of airway obstruction and for monitoring response to treatment over time. However, quite often there is discordance between symptoms and lung function, which can confound the diagnosis of asthma. One investigation found that asthma patients with a poor perception of dyspnea were more often female and had more severe asthma over a longer duration (3). These individuals were also more prone to having severe asthma exacerbations that resulted in emergency room visits, hospitalizations, near fatal asthma episodes or death (3). Some studies have suggested that the current tools available for diagnosing asthma, assessing asthma control, and medication compliance are not sensitive enough to detect subclinical disease that could erupt in response to a specific or non-specific trigger at any time (4, 5).

The lack of a rapid detection method for the presence of airway inflammation, a central feature of asthma, has been a limitation in our ability to differentiate between asthma and other chronic obstructive lung disorders. Recently, fractionated

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exhaled nitric oxide (FeNO) devices have been approved by the FDA for use in the clinical setting. Exhaled nitric oxide is considered to be a useful non-invasive measurement of airway inflammation and is believed to directly correlate with asthma severity (4, 5). Smith et al. reported early on that FeNO had a significantly higher level of accuracy for diagnosing asthma with a sensitivity of 88% at a cut off of 20 ppb (flow rate of 50 mL/s) compared to conventional lung function tests such as spirometry and peak flow measurements, which exhibited sensitivity <47% (6). Furthermore, they and others demonstrated that FeNO is useful for guiding clinicians in stepping down or increasing inhaled corticosteroids to maximize asthma control over time (7–10). Investigators have also reported that a high baseline level of FeNO (>35–40 ppb at a flow rate of 50 mL/s) was much better at predicting a therapeutic response to inhaled corticosteroids than FEV₁ pre- and post-bronchodilators (7, 11, 12). However, subsequent studies have found that FeNO, by itself, does not appear to be useful for diagnosing asthma nor is it believed to be a good predictor of an asthma exacerbation (10). However, when coupled with other objective markers of lung function (i.e., FEV₁), FeNO was shown to have a much better positive and negative predictive value for this purpose (13). Therefore, FeNO may be useful as an adjunctive tool for assessing response to asthma therapy, asthma control, compliance with asthma medications, and as a screening tool for differentiating whether non-specific lower respiratory symptoms are associated with airway inflammation or secondary to some other clinical process.

Despite an increasing number of studies reporting asthma outcomes using FeNO measurements, its usefulness as an adjunctive test in clinical practice is still evolving. The purpose of this study was to further elucidate the general utility of clinical (Asthma Control Test) and physiologic (FEV₁ and FeNO) parameters for characterizing asthma patients. Results from two independent but similarly designed studies conducted in two different countries using these asthma parameters to phenotype their patients are reported.

METHODS

Subject Recruitment

Two cross-sectional studies simultaneously enrolled 100 asthma patients in the United States and 109 asthma patients in Spain. Subjects had to be 18 years of age or older and were included if they had a physician diagnosis of asthma confirmed by either a 12% improvement in FEV₁ post-bronchodilators or by the presence of airway hyper-responsiveness, measured by a positive methacholine challenge (PD₂₀ <10 mg/mL) according to international guidelines (NIH, Expert Panel Report 3 (EPR-3) (1). There was no evidence of restrictive lung disease defined as an FEV₁/FVC $\geq$ 1 by spirometry. Patients were excluded if they had chronic obstructive pulmonary disease from smoking and/or were active smokers, which was defined as ever having smoked in the past 5 years. Demographic information was collected for each patient, including atopic status. During the same visit, each patient completed an ACT and underwent an FeNO and spirometry. The University of Cincinnati and the Hospital Virgen del Camino from Pamplona Institutional Review Boards approved the protocols for each respective site.

MEASUREMENTS

Asthma Control Test

Patients from the US completed the English version of the ACT, whereas those from Spain completed the validated Spanish version (2,14). The ACT is an interactive patient-centric questionnaire designed as a quiz that includes five questions addressing an asthma patient's difficulty in performing daily activities due to asthma, frequency of shortness of breath, frequency of asthma symptoms (wheezing, cough, chest tightness), use of rescue medication, and subjective degree of asthma control over the past 4 weeks. Each question is graded from 1 to 5 with a total score ranging from 0 (not controlled at all) to 25 (completely controlled) points (2, 14).

Exhaled Nitric Oxide

Enrolled subjects were required to abstain from food and fluid intake as well as from strenuous exercise 2 hours before the FeNO measurement. Measurements were made using a chemiluminescence analyzer (Niox model, Aerocrine, Inc. Solna, Sweden) with a range of detection between less than 1 to 500,000 ppb at the US site and the NioxMino analyzer (MiNo, Aerocrine AB; Smidesvågen, Sweden) at the Spain site. Both methods have been shown to correlate well with each other (15). Measurements were made in accordance with the American Thoracic Society guidelines. FeNO measurements were obtained before spirometry as recommended by the American Thoracic Society (16, 17). For the US site, each subject was seated comfortably and instructed to inhale to total lung capacity and then exhale at a flow rate of 50 mL/s against fixed expiratory resistance to exclude nasopharyngeal NO from exhaled air (17). The plateau value was automatically recorded. The subject was asked to repeat the procedure a minimum of three times or until two consecutive values agreed within 10% of each other. The mean between the three values were calculated and recorded as avgFeNO. For the Spain site using a NioxMino only one test was recorded as repeated values are not required with this system. Subjects blew at a flow rate of 50 mL/s over at least 6 seconds at a pressure of 10 cm H₂O as recommended. A feedback signal of exhalation pressure and exhalation flow was used to control the flow rate.

Spirometry

Forced spirometry at the US site was performed using a Koko spirometer, following the guidelines of the American Thoracic Society (18). Forced spirometry was performed at the Spanish site using a Jaeger APS pro spirometer (Erich Jaeger, Germany). FEV₁, FVC, and peak expiratory flow rate (PEFR) were recorded for each subject using Crapo spirometric reference values in US and using Castellsague reference values in Spain (19, 20).

Statistical Analysis

Distributions of age (<, $\geq$ 45 years), gender, %FEV₁ (<, > 80), %FEV₁/FVC (<80, $\geq$ 80), FeNO (<40, > 40 ppb), inhaled corticosteroid (ICS) usage, atopy, and ACT scores (<20 = uncontrolled, 20–24 = well controlled, 25 = completely controlled) were obtained by site (USA, Spain). Differences between sites were tested by Pearson chi-square

tests of independence. Spearman rank correlation coefficients between ACT scores and FeNO, %FEV₁, %FEV₁/FVC%, and age were obtained for each site and combined sites. For each site, Student's *t* tests were performed to test mean differences between FeNO categories with respect to ACT, %FEV₁, %FEV₁/FVC, and age. In addition, chi square tests were performed to evaluate differences between percents of ICS usage and atopy between FeNO categories. These analyses were repeated testing differences between atopic and non-atopic patients at each site. Analyses of variance and post hoc comparisons were performed to compare means of FeNO and %FEV₁, across ACT categories <20, 20–24, and 25. The combined effects of FeNO level and ICS usage on mean differences among ACT scores between sites were investigated by multiple linear regression analysis, in which ACT was the dependent variable and the independent variables were site, FeNO category, ICS usage, and two-way interactions. These analyses allowed ACT scores within and between sites to be compared by levels of FeNO and ICS usage. A significance level of 5% was used, unless stated otherwise. Analyses were performed using SAS for Windows, version 9.1.3, SAS Institute, Cary, NC.

RESULTS

Patient Demographics

One hundred patients from the US site and 109 patients from the Spain site were recruited between August 2006 and July 2007. Characteristics of the two populations are summarized in Table 1. Subjects were predominantly Caucasians in both groups (79% for US; 100% for Spain). There was no significant gender difference between the two sites. However, there was a significant difference in the median values of age and ACT scores between the two sites ($p < 0.001$) (Table 1) and a significant difference between the distributions of ACT

TABLE 1.—Descriptive statistics of adult patients^a in USA (N = 100) and Spain (N = 109).

Variable	USA	Spain	<i>p</i> value
Age: median (IQR), yrs	50 (40–60)	37 (25–49)	
% < 45 yrs	37%	71%	< 0.001
Male, % N	45%	38%	0.28
FEV ₁ , median (IQR), pct predicted	72 (58–87.5)	103 (89–116)	
% < 80 pct predicted	61%	10%	< 0.001
FEV ₁ /FVC, median (IQR)%	80 (78–82)	75 (68–79)	
% < 80%	40%	75%	< 0.001
FeNO, median (IQR), ppb	28.8 (14.5–51.9)	42.0 (26.0–73.0)	
% < 40 ppb	65%	49%	0.02
Inhaled corticosteroid usage(ICS),% N	74%	50%	< 0.001
Atopy,% N	83%	62%	< 0.01
ACT ^b , median (IQR)	18 (13–22)	22 (19–24)	
% < 20	59%	28%	
% 20–24	35%	48%	
% 25	6%	24%	< 0.001
% Positive Atopy by ACT ^b			
< 20	87%	68%	
20–24	74%	60%	
25	100%	62%	0.46

^aNumbers vary slightly due to missing data.

IQR = Interquartile range.

^b< 20 = uncontrolled; 20–24 = well controlled; 25 = completely controlled.

Note: *p* values test between percent differences in USA and Spain for each variable or a pattern of percents for ACT and % positive atopy among ACT categories.

TABLE 2.—Mean values of ACT, %FEV₁, %FEV₁/FVC, Age, and %ICS Usage, %Atopy by Site and FeNO Categories.

	ACT	FEV ₁	FEV ₁ /FVC	Age (yr)	%ICS	%Atopy
USA (N = 100)						
FeNO <40 (N = 65)	17.6	75.3	80.4	49.9	75	79
FeNO ≥40 (N = 35)	16.6	69.9	80.1	49.0	71	91
Spain (N = 107)						
FeNO < 40 (N = 52)	22.6*	102.0	74.0	39.0	60**	60
FeNO ≥ 40 (N = 55)	20.2*	103.5	73.3	38.3	38**	65

*ACT means are significantly different between FeNO categories $p < 0.001$.

**ICS usage is significantly different between FeNO categories, $p < 0.05$.

Other results comparing FeNO categories at each site were not significant ($p > 0.05$).

categories between sites ($p < 0.001$). The US site had older patients and a greater proportion of patients with uncontrolled asthma. Similarly subjects from the US who site had a lower median %FEV₁, higher median % FeNO, were more likely to be atopic, and were more frequently treated with ICS (Table 1). Therefore, it was not possible to combine datasets from the two sites owing to these inherent differences between patient groups.

Mean Values of ACT, %FEV₁, %FEV₁/FVC, %ICS Use, and %Atopy by Site and FeNO Categories

Table 2 summarizes the mean values of ACT, %FEV₁, %FEV₁/FVC, and age, as well as distributions of ICS usage, and atopy for the US and Spain sites when FeNO was categorized as FeNO <40 ppb or ≥40 ppb. Subjects in the Spain group with a lower mean FeNO (< 40ppb) had a significantly higher mean ACT score (22.6) ($p < 0.001$). Fewer subjects with FeNO ≥ 40ppb at the Spain site were on ICS (38% versus 60%, $p < 0.05$). Otherwise, no significant differences in mean ACT, ICS use, or %FEV₁ were observed at the US or Spain sites for patients grouped as FeNO ≥ or < 40 ppb.

Mean Values of ACT, %FEV₁, %FEV₁/FVC, Age, Mean FeNO, and %ICS Use by Site and Atopy Status

No significant differences between atopic and non-atopic groups were observed for patients from the US or Spain site with respect to ACT, %FEV₁, and mean FeNO (Table 3). For the Spain site only, non-atopic patients were older (50.6 years versus 31.5 years, $p < 0.01$), had a significantly lower mean %FEV₁/FVC value (70.1% versus 75.9%, $p < 0.001$) and were more likely to be using ICS (76% versus 34%, $p < 0.001$) compared to the atopic group.

TABLE 3.—Mean values of ACT, %FEV₁, %FEV₁/FVC, Age, FeNO, and %ICS usage by site and atopy.

	ACT	%FEV ₁	%FEV ₁ /FVC	FeNO (ppb)	Age (yr)	%ICS
USA (N = 90)						
Atopy + (N = 75)	17.6	74.3	80.3	29.3	49.2	80
Atopy – (N = 15)	16.8	66.1	79.8	24.0	51.7	67
Spain (N = 109)						
Atopy + (N = 68)	21.2	104.8	75.9*	44.4	31.5**	34***
Atopy – (N = 41)	21.5	99.1	70.1*	46.3	50.6**	76***

*%FEV₁/FVC means are significantly different between atopy categories, $p < 0.001$.

**Age means are significantly different between atopy categories, $p < 0.01$.

***ICS usage is significantly different between atopy categories, $p < 0.001$.

Other results comparing atopy categories at each site were not significant ($p > 0.05$).

TABLE 4.—Comparisons of FeNO and %FEV₁ means among ACT categories within and between sites.

ACT Category	USA (N = 100)			Spain (N = 107)		
	<20 N = 59	20–24 N = 35	25 N = 6	<20 N = 30	20–24 N = 51	25 N = 26
Mean of FeNO (95% CI)	30.6 (24.0,38.8)	27.9 (20.4,38.1)	16.7 (7.9, 35.4)	65.8 ^{ab} (51.2,84.5)	41.0 ^b (33.8,49.7)	35.2 ^a (26.9,46.1)
	24.2 (18.9, 31.0) ^c			45.6 (38.8, 53.6) ^c		
Mean of %FEV ₁ (95%CI)	67.7 ^a (63.0,72.5)	82.5 ^a (76.3,88.6)	76.7 (61.8,91.5)	96.4 ^b (89.3,103.5)	104.5 (98.9,110.1)	107.2 ^b (99.0,115.5)
	75.6 (69.8,81.4) ^c			102.7 (98.8,106.6) ^c		

FeNO conclusion: There was no significant difference among FeNO means in ACT categories for the USA site ($p = 0.31$). In Spain, the FeNO mean for ACT <20 was significantly higher than the means for ACT 20–24 ($p < 0.01$)^b and ACT 25 ($p < 0.01$)^a. The FeNO mean value for Spain was significantly higher than USA ($p < 0.001$)^c.

%FEV₁ conclusion: %FEV₁ means differed significantly between ACT categories <20 and 20 to 24 ($p < 0.001$)^a in the USA; %FEV₁ means differed significantly between ACT categories <20 and 25 in Spain ($p = 0.05$)^b. The FEV₁ mean for Spain was significantly higher than USA ($p < 0.001$)^c.

Comparison of FeNO (ppb) and %FEV₁ Means by ACT Categories Within and Between Sites

There were no significant differences among FeNO means across ACT categories for patients from the US site ($p = 0.31$). However, for the Spain site, the FeNO mean for ACT <20 (65.8) was significantly higher than the means for ACT 20–24 (41.0, $p < 0.01$) and ACT 25 (35.2, $p < 0.01$). The FeNO mean value for the Spain site, 45.6, was significantly higher than the USA site, 24.2 ($p < 0.001$) (Table 4). For the Spain site, mean %FEV₁ values differed significantly between the ACT categories < 20 and 25 ($p = 0.05$), whereas for the USA site the mean % FEV₁ values differed significantly between the ACT categories <20 and 20–24 ($p < 0.001$) (Table 4). The mean %FEV₁ was significantly higher for the Spain site compared to the USA site ($p < 0.001$).

Spearman Rank Correlation Coefficients Between ACT and Each Variable: FeNO, %FEV₁, %FEV₁/FVC, and Age by Site and ICS Usage

For each site, ACT and FEV₁ were positively correlated when patients were dichotomized by ICS usage (Table 5). Significance was reached for all groups except Spain patients who did not use inhaled corticosteroids. The magnitudes of correlation were slightly higher at each site among patients using, versus not using, inhaled corticosteroids. Correlations were + 0.40 ($p < 0.001$) and + 0.39 ($p < 0.05$) at the USA site, and + 0.32 ($p < 0.05$) and + 0.26 ($p > 0.05$) at the Spain site, respectively. Negative correlations were obtained between ACT and FeNO at the Spain site only. ACT and FeNO were essentially uncorrelated at the US site. The absolute magnitudes of correlation were greater among Spain patients not using inhaled corticosteroids ($r = -0.48$, $p < 0.001$) than patients using inhaled corticosteroids ($r = -0.23$, $p > 0.05$). The ACT was positively correlated with %FEV₁/FVC

only among patients from the USA (+0.50) and Spain sites (+0.38) who were not using inhaled corticosteroids ($p < 0.01$) (Table 5).

ANOVA Testing Differences in Mean ACT Values Between Sites, FeNO Categories, and ICS Usage

The mean ACT score from the USA site (ACT = 17.4) was significantly lower compared to the Spain site (ACT = 20.5) ($p < 0.001$) when adjusted for FeNO categories and ICS usage. However, the mean ACT values from the USA site were not significantly different regardless of the FeNO and ICS category ($p = 0.90$) with the mean ACT values ranging from 17.1 to 18.0. For the Spain site, the mean ACT score for ICS naïve patients with high FeNO values was significantly lower (18.1) compared to all other categories. In particular, the mean ACT values were significantly different between ICS users (20.7) and non-users (18.1) for patients with a high FeNO (≥ 40 ppb) ($p < 0.01$), and means were significantly different between FeNO categories (high FeNO; ACT = 18.1: low FeNO; ACT = 21.9) among ICS naïve patients ($p < 0.001$). There were no significant differences between mean ACT values for FeNO values < 40 ppb regardless of whether subjects were on or off ICS.

DISCUSSION

The recommendation by the new National Asthma Education Prevention Program (NAEPP) 2007 asthma guidelines for achieving asthma control clearly reflects the current clinical shift away from merely classifying asthma severity on the basis of asthma symptoms and lung function (1). The importance of characterizing asthma patients in the clinical setting is highlighted by a recent study by Haldar et.al. who used cluster analysis to characterize asthma phenotypes in a primary care “mild” population and in a secondary care more “refractory” population (21). They identified three asthma phenotypes among patients being seen in a primary care setting and four phenotypic clusters in a specialty setting. The authors concluded from this analysis that to accurately identify multiple asthma phenotypes, it is important to use a variety of clinical, physiologic, inflammatory, and immunologic parameters to characterize illness (21). Therefore it is imperative that the clinician become adept at phenotyping asthma patients using a variety of subjective and objective parameters to establish an accurate diagnosis necessary for determining appropriate treatment interventions that will achieve asthma control.

TABLE 5.—Correlation coefficients between ACT and each variable: FeNO, %FEV₁, %FEV₁/FVC, and age by site and ICS usage.

	ACT-FeNO	ACT-FEV ₁	ACT - FEV ₁ /FVC	ACT-Age
USA (N = 100)				
ICS = yes (N = 74)	-0.08	+0.40***	-0.01	+0.03
ICS = no (N = 26)	+0.01	+0.39*	+0.50**	-0.34
Spain (N = 109)				
ICS = yes (N = 54)	-0.23	+0.32*	+0.20	+0.18
ICS = no (N = 55)	-0.48***	+0.26	+0.38**	-0.27*

*** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$.

The diagnosis of asthma should not be trivialized as it is often complicated by several factors, including the frequent disconnect between clinical symptoms and changes in lung function, the presence of concomitant diseases that mimic and/or aggravate asthma, patient compliance with medications, and the inability by the clinician to readily detect mild disease before it clinically manifests symptomatically or with decreased lung function. Testing currently used for this later purpose such as methacholine provocation and/or induced sputum for measurement of eosinophilia, while useful, can be very time-consuming and therefore is not practical for most clinicians to use in their office. For these reasons, FeNO measurement is being touted as an attractive adjunctive surrogate marker for further assessing asthma as it provides rapid information about the presence or absence of airway inflammation, a central feature of asthma.

Our study was unique in that two distinct populations were simultaneously evaluated using the ACT, %FEV₁, and FeNO. We found that ACT scores significantly correlated with %FEV₁ for both the USA and Spain sites (Tables 4 and 5), which is consistent with what has been reported in other studies (2, 22). However, the correlation between ACT and FeNO was only observed for the Spain site in ICS naïve patients (Table 5). Patients from the Spain site with lower FeNO values had significantly higher ACT scores. In contrast, for the USA site only, a lower %FEV₁ correlated with a lower ACT, but FeNO did not correlate well with either %FEV₁ or ACT. One explanation for the lack of correlation between ACT and FeNO for the USA site is that these patients had more moderate asthma severity and therefore were more likely taking ICS. Other demographic features such as atopic status and age had no impact on asthma control measured by ACT, FeNO, or lung function. These findings illustrate the limitations of FeNO as a diagnostic test for asthma but indicate that FeNO may be most useful as a surrogate marker for identifying the presence of airway inflammation in ICS-naïve asthma patients with mild to no lung function impairment. Therefore, FeNO levels may be primarily useful for assisting physicians indecisive on whether to initiate controller anti-inflammatory therapy in mild intermittent or persistent asthma patients using short-acting bronchodilators as needed or in patients presenting with new-onset symptoms suggestive of asthma that have normal lung function. The observation that FeNO correlated with ACT in ICS-naïve patients only also suggests a use for this test in assessing patient compliance with anti-inflammatory controller therapies.

Our findings contrast a recent study that found poor correlation between FeNO, ACT, and lung function parameters (23). In this study, 105 patients were serially enrolled without respect to asthma severity or treatment regimen. All patients enrolled were taking ICS and their average %FEV₁ was 89.4%, slightly higher than that of patients enrolled for our US site population. Interestingly, in their group considered totally controlled (ACT ≥25), the median FeNO levels was 53 ppb compared to those uncontrolled who had a median FeNO of 72 ppb. This is in contrast to our study where the US population manifested low ACT scores irrespective of the FeNO level (< or ≥40 ppb) and the Spain population, which demonstrated a strong correlation between ACT and FeNO only in milder ICS-naïve patients. Another recent

study that serially enrolled 100 asthma patients also found no correlation between FeNO and several different asthma control instruments including the ACT and the Asthma Control Questionnaire (24). The majority of their patients were on ICSs, but the severity of their lung function impairment was not reported. The FeNO levels for this population were quite low regardless of the asthma control scores (range 9 to 37 ppb for subjects reporting good control and 4 to 24 ppb for subjects reporting poor control) (24). Finally, Lopes et al. reported results on 174 consecutively enrolled patients, the majority of whom were on ICS (72%) (25). Using factor analysis, they also found no significant correlation between ACQ scores and FeNO levels but did see a weak but significant correlation between %FEV₁ and FeNO (25). Each of these studies concluded from their findings that optimal assessment of asthma control in patients would be enhanced by measurement of inflammatory surrogate markers in conjunction with lung function parameters and a standardized clinical history (23–25). However, the ambiguous findings of these studies emphasize the difficulty in drawing definitive conclusions regarding the utility of a specific test or combination of tests for assessing asthma across populations. Rather cluster analysis recommended by Haldar et al. to categorize homogenous subpopulations for assessing asthma phenotypes might be a more prudent approach for this purpose (21). In summary, the results of this study support the use of FeNO as an adjunctive tool for assessing asthma primarily in mild ICS naïve asthma patients. The lack of correlation of ACT with FeNO in this and other studies across the entire population appears to reflect the heterogeneity of asthma patients who have an admixture of asthma severity and treatment regimens making it very difficult to appreciate the nuances of sensitive tests like FeNO. The dilemma of whether to aggressively treat mild intermittent asthma patients and asymptomatic patients with high FeNO values or to take a more conservative approach and monitor for the onset of clinical symptoms in the presence or absence of the gradual deterioration of lung function warrants further discussion and investigation.

DECLARATION OF INTEREST

The first author is a speaker and clinical investigator for several pharmaceutical companies. He is a consultant for Dynova and Flint Hills Resources. He has received research funding from Dyax, Dynova and Meda pharmaceuticals and the NIH. This study was partially funded by a physician initiated proposal from GSK.

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