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Original Article

Relationship of the Asthma Control Test (ACT) with Lung Function, Levels of Exhaled Nitric Oxide and Control According to the Global Initiative for Asthma (GINA)

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ABSTRACT

Introduction: The current goal of asthma treatment is to achieve and maintain control. This study aimed to explore the relationship between the ACT (Asthma Control Test) questionnaire and the levels of control according to GINA (Global Initiative for Asthma) to establish the cut-off points for the ACT and evaluate its relationship with lung function and fractionated exhaled nitric oxide level (FeNO).
Patients and methods: A multi-centre prospective study including 441 patients followed up in an outpatient Chest Clinic. A clinical protocol was followed, and FeNO, spirometry and ACT performed. Disease was classified according to levels of control using GINA. The study analysed sensitivity, specificity and area under the curve (ROC), and the ACT cut-off points. We studied the differences between the functional parameters and FeNO between levels of control.
Results: For controlled asthma the cut-off obtained was ACT≥ 21 (area under the curve 0.791) and for uncontrolled ≤ 18 (AUC 0.774). We found significant differences in FeNO levels and pulmonary function among ACT≥ 21 and ACT ≤ 18, although only 26.3% of patients with ACT≤ 18 had a FEV1 <80% and 40% higher FeNO (≥ 35 ppb). We found a correlation between baseline FEV1 and ACT (r = 0.19, P < 0.01) and between ACT and FeNO (r = −0.16, P < 0.01).
Conclusions: The cut-off points would be, for controlled asthma ACT≥ 21, partly controlled asthma ACT = 19-20 and uncontrolled asthma ACT ≤ 18. A more complete assessment would require including monitoring operating parameters and FeNO.

Relación del test de control del asma (ACT) con la función pulmonar, niveles de óxido nítrico exhalado y grados de control según la Iniciativa Global para el Asma (GINA)

Palabras clave:
Asma
Asthma Control Test (ACT)
Control
Cuestionarios
GINA (Global Initiative for Asthma)
Óxido nítrico exhalado (FeNO)

RESUMEN

Introducción: El objetivo actual en el tratamiento del asma es conseguir y mantener el control. Este estudio tiene como objetivos estudiar la relación entre el cuestionario ACT (Asthma Control Test) y los niveles de control según Global Initiative for Asthma para establecer los puntos de corte del ACT y evaluar su relación con la función pulmonar y la Fracción exhalada de óxido nítrico (FeNO).
Pacientes y métodos: Estudio prospectivo multicéntrico con inclusión de 441 pacientes seguidos en consultas externas de neumología. Se realizó protocolo clínico, FeNO, espirometría forzada y ACT. Se clasificó la

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enfermedad según los niveles de control de la Global Initiative for Asthma. Se realizó estudio de sensibilidad, especificidad y área bajo la curva (ROC), estimándose los puntos de corte de ACT. Se estudiaron las diferencias entre los parámetros funcionales y FeNO entre los niveles de control.
Resultados: Para el asma controlada el punto de corte obtenido fue ACT ≥ 21 (área bajo la curva 0,791) y para el no controlada fue ≤ 18 (área bajo la curva 0,774). Encontramos diferencias significativas en niveles de FeNO y función pulmonar entre ACT ≥ 21 y ACT ≤ 18, aunque solo el 26,3% de pacientes con ACT ≤ 18 presentaron un FEV1 < 80% y el 40% FeNO elevado (≥ 35 ppb). Encontramos correlación entre FEV1 basal y ACT (r = 0,19, p < 0,01), así como entre ACT y FeNO (r = –0,16, p < 0,01).
Conclusiones: Los puntos de corte para el asma controlada serían ACT ≥ 21, para el asma parcialmente controlada ACT = 19-20 y para el asma no controlada ACT ≤ 18. Una valoración más completa del control requeriría incluir parámetros funcionales y FeNO.

Introduction

Asthma is a chronic inflammatory disease of the airways with multiple dimensions and phenotype expressions. As from a few years ago treatment guides for this disease have emphasised the concept of control. According to this scheme the most important aspect in the management of this disease is to carry out the best control of each patient, modifying their treatment according to this objective. Since the year 2006 in the Global Initiative for Asthma (GINA[1]), the term control includes, for all practical purposes, the clinical characteristics of the disease (symptoms and exacerbations), limitation of activities and lung function tests (basically forced expiratory volume (FEV1) and peak expiratory flow (PEF). According to this data, there have arbitrarily been established, 3 levels of control (controlled asthma, partially controlled asthma and non-controlled asthma). This classification has not been validated from the clinical point of view and is established by the physician at the time of assessing the patient.

Recently self-administered questionnaires have been developed, which are simple and easily completed by the patients to make it easier to assess the degree of control in everyday clinical practice. In 2004 Nathan et al.[2] developed a questionnaire known as ACT (Asthma Control Test), which contained 5 questions related to frequency of asthma symptoms and use of rescue medication needed by the patient during the previous 4 weeks, with scores that could go from 5 (worse control) to 25 (total control). This questionnaire has been recently validated in Spanish.[3,4] The relationship of this questionnaire with degrees of control has been studied according to GINA and other criteria determined in each study, to establish the respective cut-off points. Therefore, for controlled asthma ACT≥ 20 have been chosen,[5] whereas for non-controlled asthma values of ACT between ≤ 15[6,7], ≤ 17[5], ≤ 19[2,3,8,9] or ≤ 20[10] have been suggested. These cut-off points are dependent, in great measure, on the criteria applied to define disease control, since very few studies so far have applied the levels chosen by GINA as criteria for control.

On the other hand, it has been pointed out that measurement of the exhaled nitric oxide fraction (FeNO) as a marker of airway inflammation can be useful given the positive correlation seen between the degrees of eosinophilia in blood,[11] sputum,[12] bronchoalveolar lavage[13] or bronchial mucosa.[14] However, only in the last few years has the relationship between clinical control parameters been examined, either according to GINA or ACT and degree of inflammation, measured by FeNO,[15-18] and there are still very few studies that have assessed their possible usefulness in everyday clinical practice.

As a result, this study has as its aim the assessment of the relationship between ACT score and levels of control according to GINA in a group of patients followed by means of external pneumological consultations, to establish cut-off points for ACT that possess a better correlation with these levels. We will also assess the relationship of these cut-off points with lung function and degree of inflammation measured by FeNO.

Patients and methods

Multicentric prospective study, carried out during 4 external asthma consultations in the Pneumology Service, from March 2007 to March 2009. This study included a broad baseline study visit with a one year follow-up visit "FUSION" that has the main purpose of analysing the evolution of the ACT test, FeNO, and reversibility of FEV1, their relationship with disease evolution and the design of a multidimensional control index that includes the 3 variables.

Patients

All patients diagnosed with bronchial asthma according to clinical and functional criteria established by GINA 2006[1] and over 12 years of age were included. The patients had not received any treatment with oral steroids during the month prior to their inclusion. Specifically, patients had to have a clinical history of symptoms compatible with the disease and a history of reversible obstruction or this had to be determined by spirometry performed on the day of inclusion (bronchodilator test with FEV1 ≥ 12% and ≥ 200ml). They could have a history as current or former smokers, but accumulated consumption had to be less than 10 pack years. Nor were patients included who had very severe asthma, multiple exacerbations or frequent use of oral steroids. They could use treatment with fluticasone of 200 to 2000mcg a day or equivalent doses of budesonide, alone or associated with long lasting B2, with/ without montelukast 10mg every 24 hours. They could not have a history of other respiratory diseases (COPD, bronchiectasia, interstitial or tumour diseases, etc.)

Methodology

The investigating physician drew up the initial protocol on the day of inclusion, and this included the epidemiological and clinical variables of the study. Once the patient had been examined during a medical consultation they were handed over to a registered nurse for ACT, FeNO, forced spirometry and the allergic sensitisation test if this

had not been performed previously. Patients with continued treatment were told to suspend the last dose prior to undergoing functional tests. FeNO was measured by means of an electrochemical technique (NIOX MINO aerocrine. Solna, Sweden). The patient inspires deeply from the interior of the equipment through a filter and until total lung capacity is reached. Subsequently a spirometry is performed into the interior of the equipment maintaining a flow of 50ml/s, controlled by a light and sound sensor to ensure and facilitate flow. This procedure, following the manufacturer's recommendations, requires a single measurement and the result is show on the equipment's digital screen. Forced spirometry is carried out using Master Scope PC Viasys Healthcare spirometers and JLab, Lab Manager, V 5.3.0, software, following ATS/ERS[19] recommendations. A baseline test and one after 200mcg of salbutamol (postbronchodilator) were performed. FEV1 was expressed in absolute values and % of theoretical value, as also basal and postbronchodilator FEV1/FVC.

The ACT questionnaire with 5 questions related to asthma symptoms and use of asthma medication during the 4 previous weeks was administered. Patients self-administer this questionnaire in Spanish, writing in each question box the number of their answer on a scale that goes from 1 (worst scenario) to 5 (best scenario), therefore the score ranges from 5-25.

The allergic sensitisation test was carried out using the allergen prick test which is common in our environment.[20] Histamine dihydrochloride (10mg/ml) and saline solution at 0.9% served as positive and negative controls, respectively. The test was considered positive if after 15min the resulting wheal measured a minimum of 3mm in diameter or was equal to or greater in size than the positive control. Atopy was defined by the positive result of this test.

According to the results of the clinical interview and the functional tests, patients were classified according to different levels of severity (intermittent, persistent mild, moderate or severe) and the degree of control was established according to GINA 2006[1] (controlled, partially controlled, non-controlled). The investigating physician did not know on this visit what the FeNO level was nor the ACT score.

Written informed consent was requested for clinical data inclusion in the database. No personal data (name, address, telephone number, clinical history number, etc.) was included in this database and only a key reference number, related to the patient's clinical history, was included on a separate record card, which was kept by the investigators. The study was approved by the clinical investigation ethics committee of the principal investigator's hospital.

Statistical Analysis

Data was analysed using the SPSS v. 16 statistical package. Data on qualitative variables data was presented in percentages and on quantitative variables in mean and standard deviation (SD).

Values of sensitivity, specificity, positive and negative predictive values and Youden Index were established (sensitivity+specificity-1) and the (ROC) analysis was performed, estimating an area under the curve for each ACT cut-off point in relation to controlled and non-controlled asthma according to GINA. ACT cut-off points were established for controlled and non-controlled asthma, according to the best ratio for sensitivity, specificity and greater area under the curve. Once ACT cut-off points were established for controlled and non-controlled, and by elimination, partially controlled asthma, we studied the relationship of these points with lung function and FeNO data, as also the differences for classification according to GINA.

Table 1
Patient characteristics

N = 441	
Age (years)	
Range	14-78
Mean (SD)	39 (17)*
Sex	
Male	151 (34.2%)
Female	290 (65.8%)
Smoking	
Smoker	58 (13.2%)
Former smoker	117 (26.5%)
Passive	11 (2.5%)
Non-smoker	255 (57.8%)
Asthma Severity	
Intermittent	10.2%
Persistent mild	34.6%
Persistent moderate	46.3%
Persistent severe	8.9%
Degree of Control	
Controlled	121 (27,4%)
Partially controlled	151 (34,2%)
Not controlled	169 (38,3%)
Atopy	
Yes	327 (74.1%)
No	96 (21.8%)
NA+	18 (4.1%)
*ACT**	18 (4.8)
*FeNO**	36.8 (33.6)
Eosinophils in peripheral blood(n/ml N = 345)*	355 (517)
FEV1 prebronchodilator (cc)(N = 434)*	2845 (947)
FEV1 pre(%)(N = 434)*	95.1 (20.3)
FEV1 postbronchodilator (cc)(N = 429)*	3070 (971)
FEV1 reversibility (%)(N = 429)*	9.6 (13.7)
*FEV1/FVC pre**(N = 434)*	72.9 (10.9)
*FEV1/FVC post**(N = 429)*	76.8 (10.5)

*Means (SD)+no proof of physical exam.

For the comparison of established groups with ACT or GINA control levels and levels of FeNO or functional variables the ANOVA test was used and post-hoc tests (2 to 2 comparison). Previously the homogeneity of variance between groups was determined (Levene Test), and for non-homogeneous variables the Welch test for the equality of the means was used. To analyse the differences between the groups (2 to 2) the Bonferroni Test or the Games-Howell Test were used, according to whether the variables were homogeneous of not, respectively. Linear correlations were assessed with the Pearson coefficient. Differences were considered significant as from $p < 0.05$.

Results

Description of General Data of the Population

We included 144 patients of 14-78 years of age, mean age 39 (17) and mostly female (>65%). Table 1 shows that although the majority were non-smokers, there was a percentage with a history of smoking, and more than 13% were active smokers. The largest percentage of patients had persistent moderate asthma (46%), with demonstrated allergic sensitisation (atopic) in more than 74% of cases. According to GINA degrees of control there was a greater percentage of patients with non-controlled asthma (38.3%) and a lower percentages of partially controlled and controlled asthma. The mean ACT score was 18 (4.8) and mean exhaled FeNO levels

Table 2
Symptoms, prior treatment of patients

History	
Symptoms in High Respiratory Airways	
Nasal Symptoms	317 (71.9%)
Ocular Symptoms	212 (48.1%)
Pharyngeal Symptoms	139 (31.5%)
Sinusitis	59 (13.4%)
Bronchial Symptoms	
Wheezing	291 (66%)
Dyspnoea	342 (77.6%)
Coughing	317 (71.9%)
Expectoration	222 (50.3%)
Chest Oppression	220 (50.3%)
Prior Treatment	
Continued treatment	347 (78.7%)
Only steroids	43 (9.6%)
Steroids+LABA	293 (66.4%)
Antileukotrienes	148 (33.6%)
Without continued treatment	94 (21.3%)

*% with respect to total number of patients. Antileukotrienes added to steroids or steroids+LABA.

were 36.8 (33.6). Basal FEV1 values expressed as a % of theoretical value had relatively high mean values, 95.1 (20.3) with values below 80% in only 20% of included patients. However, the mean of the percentage of reversibility was 9.6 (13.7) with wide variations according to each case, as can be seen from the standard deviation values. Table 2 shows predominant symptoms and treatments of patients at the moment of inclusion. Most patients (78.7%) had received prior treatment, and the greatest percentage had received steroids+LABA (66.4%).

Sensitivity/Specificity Study, ACT Cut-off Points

Table 3 shows sensitivity, specificity, predictive values, and areas under the curve for the different ACT cut-off points for controlled asthma (in relation to partial and non-controlled asthma, according to GINA). Values presented are from ≥ 15, since values for lower cut-off points are very low and have therefore not been included. As can be seen for controlled asthma the ACT cut-off point ≥ 21 shows the highest Youden Index (0.58) and the greatest area under the curve (0.791). The second point for both highest values is 20, although with minimum differences in favour of the indicated cut-off point. Table 4 shows data for non-controlled asthma (in relation to partially controlled and controlled asthma). In this case the cut-off points analysis is shown from ≤ 13. The highest Youden index (0.54) and area under the curve (0.774) correspond to the ACT cut-off point ≤ 18, and the second point with the highest values is 19. In this way we established the cut-off points: for controlled asthma at ≥ 21, non-controlled at ≤ 18 and, by elimination, partially controlled at 19 and 20.

Percentage of Patients According to ACT Cut-off points and GINA Control Levels

Figure 1 shows the percentage of patients in each control group, according to ACT cut-off points and GINA degrees of control. Most patients with controlled, partially controlled and non-controlled asthma according to GINA, are correctly classified by ACT level (59.4%, 54.1% or 63.6% respectively). Only 6.4% of patients with controlled asthma according to GINA had ACT ≤ 18, whereas on the contrary, a bit more than 8% of patients with non-controlled asthma had values ≥ 21.

Table 3
Asthma Control Test (ACT) score, validity of different cut-off points for the classification of controlled asthma*

ACT cut-off point	Sensitivity, %	Specificity, %	Positive predictive value, %	Negative predictive value, %	Youden Index	Area under the ROC curve
25	26.4	98.1	84.2	77.9	0.24	0.622
≥ 24	42.1	94.7	75	81.2	0.36	0.684
≥ 23	57.9	91.6	72.2	85.2	0.48	0.747
≥ 22	71.1	85	64.2	88.6	0.56	0.780
≥ *21*	*78.5*	*79.7*	*59.4*	*90.7*	*0.58*	*0.791*
≥ 20	86	71.9	53.6	93.1	0.57	0.789
≥ 19	88.4	64.4	48.4	93.6	0.52	0.764
≥ 18	92.6	58.1	45.5	95.4	0.50	0.753
≥ 17	92.6	48.1	40.3	94.5	0.40	0.703
≥ 16	93.4	40.3	37.2	94.2	0.33	0.668
≥ 15	94.2	32.2	34.4	93.6	0.26	0.632

*Controlled asthma/vs. non-controlled and partially controlled asthma.

Table 4
Asthma Control Test (ACT) score, validity of different cut-off points for the classification of non-controlled asthma*

ACT cut-off point	Sensitivity, %	Specificity, %	Positive predictive value, %	Negative predictive value, %	Youden Index	Area under the ROC curve
≤ 23	97.6	34.2	48	95.9	0.31	0.659
≤ 22	93.5	45.2	51.5	91.8	0.38	0.693
≤ 21	92.3	54	55.5	91.9	0.46	0.731
≤ 20	89.3	64.7	61.1	90.7	0.53	0.770
≤ 19	82.8	70.6	63.6	86.9	0.53	0.767
≤ *18*	78.1	*76.8*	*67.7*	*85*	*0.54*	*0.774*
≤ 17	69.2	83.1	71.8	81.3	0.52	0.761
≤ 16	60.4	87.1	74.5	78	0.47	0.735
≤ 15	49.7	90.4	76.4	74.3	0.39	0.700
≤ 14	43.2	93.4	80.2	72.6	0.36	0.682
≤ 13	35.5	94.1	78.9	70.1	0.29	0.648

*Non-controlled asthma/vs. controlled and partially controlled asthma.

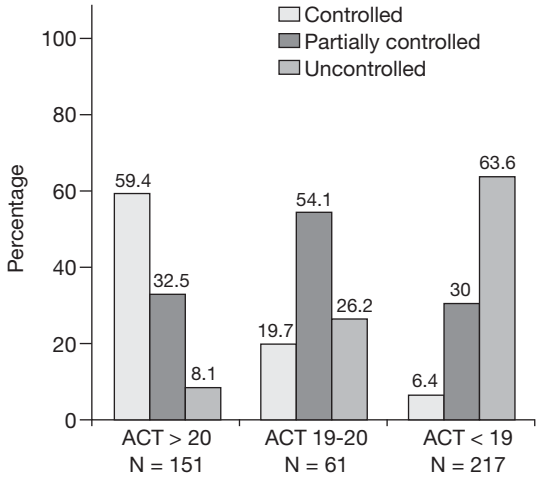

Figure 1. Percentage of patients according to ACT score and control level (GINA).

Table 5
Relationship of control levels established by ACT, according to FeNO, age and functional parameters

	Mean (SD)	F	p
FeNO &		4.749+	<0.01+
ACT ≤ 18 (N = 220)	41.1 (37.9)		
ACT 19-20 (N = 61)	36.9 (28.5)		
ACT≥ 21 (N = 160)	30.8 (27.9)		
Age		1.365	NS (0.256)*
ACT ≤ 18 (N = 220)	40.4 (16.9)		
ACT 19-20 (N = 61)	36.8 (17.5)		
ACT≥ 21 (N = 160)	38.4 (15.7)		
Absolute basal FEV1 (cc) &		7.848	0.0001*
ACT ≤ 18 (N = 218)	2686 (940)		
ACT 19-20 (N = 61)	2828 (925)		
ACT≥ 21 (N = 155)	3074 (924)		
Basal FEV1 % &		3.297	0.038*
ACT ≤ 18 (N = 218)	92.6 (20.7)		
ACT 19-20 (N = 61)	96.6 (20.3)		
ACT≥ 21 (N = 155)	97.9 (19.2)		
Postbronchodilator FEV1 (cc) &		6.425	0.002*
ACT ≤ 18 (N = 217)	2919 (979)		
ACT 19-20 (N = 61)	3142 (903)		
ACT≥ 21 (N = 151)	3281 (964)		
Reversibility FEV1% &		6.538+	0.002+
ACT ≤ 18 (N = 217)	11.06 (15.39)		
ACT 19-20 (N = 61)	11.01 (17.38)		
ACT≥ 21 (N = 151)	6.86 (8.18)		
Basal FEV_1/FVC		1.189	NS (0.306)*
ACT ≤ 18 (N = 218)	72.32 (11.03)		
ACT 19-20 (N = 61)	72.42 (11.36)		
ACT≥ 21 (N = 155)	74.04 (10.64)		
Postbronchodilator FEV1/FVC		0.852	NS (0.427)*
ACT ≤ 18 (N = 217)	76.31 (10.7)		
ACT 19-20 (N = 61)	76.29 (9.4)		
ACT≥ 21 (N = 151)	77.69 (10.49)		

Two by tow post-hoc analysis. Bonferroni Test or Games-Howell Test according to homogeneous variance or not, respectively: & Significant differences between ACT ≤ 18 and ACT≥ 21 (all variables p < 0.01, for basal FEV1 basal% p < 0.04). Not significant between ACT 19-20 and remaining levels.

*ANOVA Test, + Welch test for the equality of the means.

Table 6
Relationship of control levels established by GINA, according to FeNO, age and functional parameters

	Mean (SD)	F	p
FeNO		1.775	
Non-controlled (N = 169)	40.5 (36.1)		NS (0.171)*
Partially controlled (N = 151)	35.4 (31.5)		
Controlada (N = 121)	33.4 (27.9)		
Age		0.603	
Non-controlled (N = 169)	38.7 (16.7)		NS (0.548)*
Partially controlled (N = 151)	40.4 (17.3)		
Controlled (N = 121)	38.5 (15.6)		
ACT $		163.256+	0.000+
Non-controlled (N = 169)	14.4(4.1)		
Partially controlled (N = 151)	18.78 (3.6)		
Controlled (N = 121)	22.2 (3.2)		
Absolute basal FEV1 (cc) Ç		6.955	0.001*
Non-controlled (N = 167)	26.44 (937)		
Partially controlled (N = 149)	2.910 (960)		
Controlled (N = 118)	30.46 (896)		
Basal FEV1 % Ç		6.608	0.001*
Non-controlled (N = 167)	90.6 (22.5)		
Partially controlled (N = 149)	98 (18.5)		
Controlled (N = 118)	97.6 (19.5)		
Postbronchodilator FEV1 (cc) Ç		5.025	0.007*
Non-controlled (N = 166)	2940 (995)		
Partially controlled (N = 147)	3128 (993)		
Controlled (N = 116)	3264 (888)		
Reversibility FEV1% Ç		6.580+	0.002+
Non-controlled (N = 166)	12.99 (18.83)		
Partially controlled (N = 147)	7.14 (8.50)		
Controlled (N = 116)	7.78 (8.18)		
Basal FEV_1/FVC Ç		8.701+	0.0001+
Non-controlled (N = 167)	70.42 (11.80)		
Partially controlled (N = 149)	75.34 (9.09)		
Controlled (N = 118)	73.50 (11.16)		
Postbronchodilator FEV1/FVC Ç		6.321	0.002*
Non-controlled (N = 166)	74.67 (11.34)		
Partially controlled (N = 147)	78.79 (9.1)		
Controlled (N = 116)	77.29 (10.39)		

Two by two post-hoc analysis. Bonferroni Test or Games-Howell Test according to homogeneous variance or not, respectively: $: Significant differences between the three levels (p < 0.01). Ç: Significant differences between Non-controlled and Controlled (p < 0.01), except for basal FEV1/FVC (p < 0.07) and between Non-controlled and Partially controlled (p < 0.01), except for postbronchodilator FEV1 (p = 0.124). Not significant between Controlled and Partially controlled.

*ANOVA Test, + Welch test for the equality of the means.

Differences in FeNO, Functional Data Between Control Levels

Tables 5 and 6 show the differences in FeNO, functional parameters according to established ACT cut-off points and GINA control levels. ACT cut-off points present significant differences in mean FeNO and in most functional parameters (basal absolute FEV1, % of theoretical value, postbronchodilator, FEV1% of reversibility) although in the post hoc analysis these differences are between values of ACT ≤ 18 and ≥ 21, with no differences between intermediate values (19-20) and the previous ones. On the contrary, in the case of GINA degrees of control we found differences in the functional parameters assessed both for controlled and non-controlled asthma (except for basal FEV1/FVC), as also for controlled and partially controlled asthma (except for postbronchodilator FEV1). No differences were found between controlled and partially controlled asthma. Nor did we find significant differences in FeNO values between any of the GINA control levels. The correlation of basal FEV1 in absolute values or

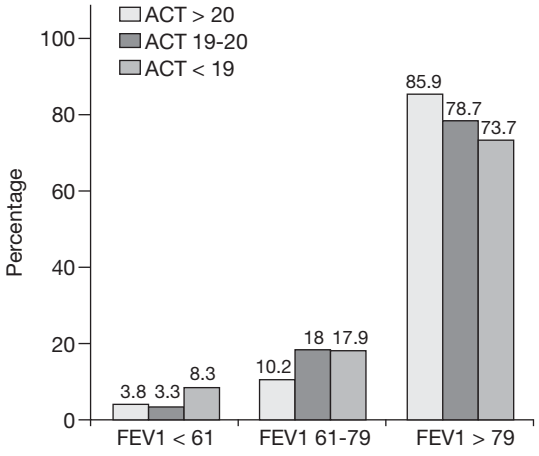

Figure 2. Percentage of patients according to FEV1 level (% with respect to theoretical value) and ACT score.

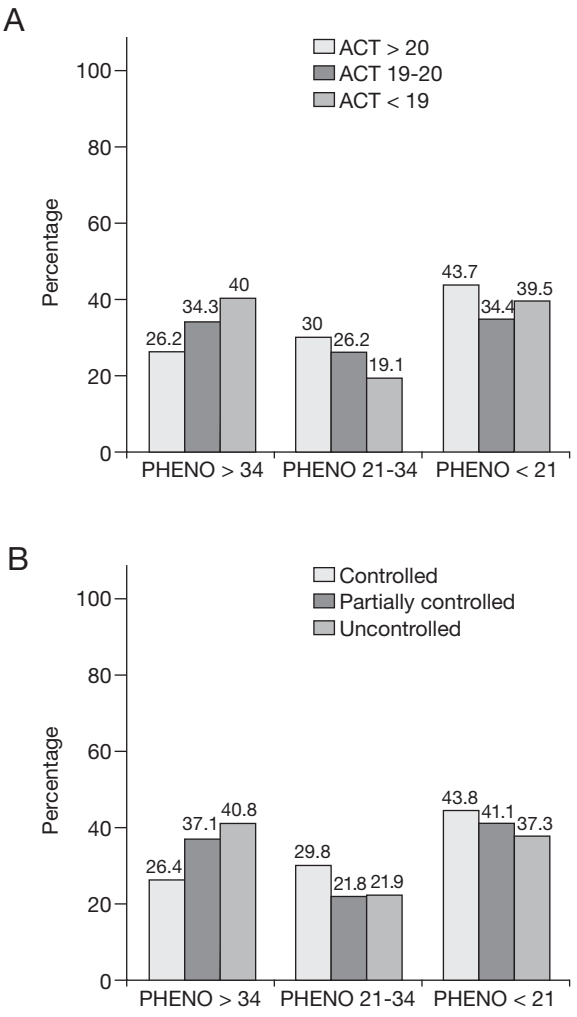

Figure 3. Percentage of patients according to FeNO (ppb) levels and degrees of control according to ACT (A) or GINA (B) score.

percentages to theoretical value and ACT was low but significant in both cases (r = 0.19 or r = 0.14, p < 0.01 respectively).

And lastly, figures 2 and 3 show the percentages of patients according to FEV1, FeNO and control levels. Most patients (fig. 2) had a FEV1 ≥ 80%, with a slightly higher percentage in patients with ACT≥ 21, although with very slight differences with the other levels of control. It must be highlighted that only 26.3% of the patients with ACT ≤ 18 (cut-off point for non-controlled asthma) had a FEV1 < 80%. As to FeNO (fig. 3), both for degrees of control, according to ACT or GINA, very slight differences were found in the percentage of patients according to the 3 levels of FeNO included (normal FeNO ≤ 20, medium 21-34, high ≥ 35). It must be noted that about 40% of patients with non-controlled asthma (or ACT ≤ 18) presented clearly elevated FeNO (≥ 35), whereas on the contrary, more than 26% of patients with controlled asthma (or ACT≥ 21) presented these high levels. The correlation between ACT and FeNO was significant but slight, r = –0.16, p < 0.01).

Discussion

In this study we established the following ACT cut-off points ≥ 21, 19-20 or ≤ 18, respectively for controlled, partially controlled and non-controlled asthma. This study was the first one in our environment that established cut-off points for the 3 control levels established by GINA.

The ACT control questionnaire has been previously assessed both during specialised consultations[2] and primary care[8] and has been validated in the Spanish language.[3,4] It has shown a good relationship with therapeutic decisions made by specialists, even higher than those of functional tests or FeNO.[10]

The cut-off points that we have described in our work differ from some of those seen in previous studies that established cut-off points for controlled and non-controlled asthma. The reason for these differences can be found in the different criteria used to classify non-controlled asthma and there may even be an ethnic differences factor that could cause differences in the perception of asthma control. Therefore, In the initial study carried out by Nathan et al.[2] that developed the questionnaire for the first time, the criteria for the definition of non-controlled asthma was determined as the assessment made by the specialists (with a 5 point score from totally non-controlled to completely controlled), and therefore different to GINA degrees. It is not to be wondered at that the cut-off point (ACT ≤ 19) is slightly higher than the one we describe, since it included not only non-controlled asthma, but also in great measure, partially controlled asthma. This same method was used in a subsequent study carried out by Shatz et al.[8] at a primary care level and which describes the same cut-off point, or the Spanish questionnaire validation study carried out by Vega et al.[3] that includes "poorly controlled" asthma and non-controlled asthma. This same cut-off point (ACT ≤ 19) is used in the multicentric study recently published by Thomas et al.[9] which, in contrast to those mentioned previously, follows GINA control criteria. In relation to our study, the difference in methods used, lies in that for analysis they use the GINA categories of partial and non-controlled asthma (in comparison with controlled), whereas we analyse the cut-off point for non-controlled asthma (in comparison with partial and controlled). Therefore, as in previous cases, the established cut-off point also includes patients with partially controlled asthma. None of these studies suggests, therefore, ACT levels for partially controlled asthma. Lastly there are 2 recent studies carried out in China using methods similar to the ones we used and slightly different cut-off points. The study carried out by Fanny et al.[10] in specialists consultations, established a cut-off point for non-controlled asthma of ≤ 20, whereas that of Zhou et al.,[5] in

primary care, had a cut-off point of ≤ 17 for non-controlled asthma, 18 and 19 for partially controlled and ≥ 20 for controlled asthma. The differences between these studies and ours lie in the greater severity of disease in the population studied (28% had severe asthma, in comparison with 8.9% of our cases) and therefore had a greater functional involvement, with a higher percentage (> 50%) of non-controlled asthma. These circumstances together with possible ethnic and cultural differences in the perception of asthma control, could explain the disparities.

In any case, we consider that both control measures (those established by physicians and those self-perceived by patients) are complementary and can provide 2 necessary views for a correct assessment of the clinical evolution of this disease. Therefore, in spite of the method used in our study, we wish to highlight that about 8% of the patients that had an ACT≥ 21 during their assessment, were classified as non-controlled asthma by the physician, which could mean that this group of patients has hypoperception of their symptoms.

On the other hand, we found a significant but slight correlation between levels of FEV1, FeNO and Act. Similar results have been described for the relationship between FEV1[2,10] and FeNO,[10] whereas in other studies the correlation between both parameters is slightly higher.[16-18] In our study we found significant differences between lung function parameters only when ACT cut-off points for non-controlled and controlled asthma were compared. The same was true for FeNO. We wish to highlight the percentage of patients with non-controlled asthma and normal levels of FeNO (near to 40% in both classifications), and, on the contrary, the percentage of patient with controlled asthma and levels above 35ppb (more than 26%). These same results have been described in studies carried out in both adults[15] and children.[17] The study carried out by Khailii et al.[15] shows how up to 38% of patients with appropriately controlled asthma have FeNO> 35ppb. These cases could have persistent subclinical inflammation that could subsequently cause problems. Therefore, in some studies it has been shown that high levels of FeNO predict exacerbation of asthma with a 80-90% positive predictive value.[21] An accelerated decrease in lung function has also been described in patients with high levels of FeNO, in comparison with those patients with normal values.[22] On this point it is important to highlight that FeNO levels can be significantly affected according to the area and ethnic group studied (higher levels in oriental countries[10,16]), by previous treatment with steroids, diet, comorbidities, active smoking, and all this can modify the relationship between this measurement and ACT and functional exam.

In conclusion, these results underline the already known fact that asthma has different phenotype expressions, and that furthermore, each phenotype expression can show a specific combination of different control parameters. As a result, we consider that for a complete and correct assessment of the degree of control of asthma in each patient it is necessary to combine these measurements (functional, bronchial hyperreactivity, FeNO, clinical questionnaires).

The limitation of the results we have presented lies in the need to validate the cut-off points suggested with patient follow-up for at least one year, to establish a correlation with disease evolution parameters. Since the "Gold Standard" for calculating these cut-off points has been degrees according to GINA (which we must remember have not been ratified), we consider that another clinical validation is necessary. We will assess results after patient follow-up during the course of the year. Another possible limitation of our results, especially in relation to FeNO values, is the inclusion in the study of active smokers. It is well known that this circumstance decreases values, which may cause a bias in the results of this test in particular. However, we did not exclude this group of patients precisely to maintain conditions of usual clinical practice and to obtain results that could be extrapolated to the global population of asthmatics and not only to non-smokers.

In conclusion, we have established ACT cut-off points of ≥ 21 for controlled asthma, 19-20 for partially controlled asthma and ≤ 18 for non-controlled asthma. The degrees of control have a significant but slight correlation with functional situation and degree of inflammation estimated by FeNO levels, therefore it would be necessary to include these parameters to obtain a more complete assessment of asthma control.

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Conflict of Interest

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