

DIAGNOSIS

Bronchodilator response as a hallmark of uncontrolled asthma: a randomised clinical trial

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Abstract

Introduction: The goal of this study is to determine whether bronchodilator (BD) response can be used as a reliable measure of asthma control by analyzing the effects of a short course of oral corticosteroids (OC) or placebo (P) on spirometry, sputum cytology and BD response in controlled asthma patients scoring less than 1.5 on the ACQ5. **Methods:** Seventy patients with moderate to severe asthma who were undergoing combination therapy and were considered to be controlled based on ACQ5 scores, but who exhibited persistent positive BD response, were randomly assigned to two groups, one receiving OC and the other P. Patients were evaluated before and after 2 weeks of treatment. Intervention response (comparison of FEV₁ before and after OC or P treatment) was used as a measure of intervention efficacy, with values equal to or greater than 200 mL considered positive. **Results:** Patients who received OC showed significant improvement in FEV₁, and no longer exhibited a positive BD response. Those in the P group showed no change. In addition, sputum eosinophil counts significantly decreased in the OC group. **Conclusions:** BD response can be used as a reliable measure of asthma control. This study suggests that ACQ5 scores alone are not sufficient to fully assess asthma control, and that BD response should be included as an essential measurement in any algorithm of asthma control evaluation.

Keywords

Control/management, management/control, morbidity and mortality, prevention, therapy

History

Received 1 July 2013

Revised 17 December 2013

Accepted 19 December 2013

Published online 24 January 2014

Introduction

The ultimate goal of asthma therapy is to achieve complete (or near to complete) disease control [1]. International guidelines for asthma care all share a common message: control asthma with the lowest effective dose of medication (generally referring to the amount of anti-inflammatory maintenance therapy). Furthermore, guidelines recommend reducing the amount of asthma therapy once disease control has been achieved. However, few studies have validated feasible tools to characterize clinical asthma control and help the clinicians tailor an adequate step down therapy.

Although regular use of the Asthma Control Questionnaire (ACQ5) offers an estimate of control, spirometric evaluation provides important information, which can guide the management of patients with asthma [2]. Among lung function test outcomes, bronchodilator (BD) response has been shown to be a reliable indicator of asthma at diagnosis [3]; it has not, however, been evaluated specifically as a measure of asthma control.

Airway inflammation is considered to be the cause of uncontrolled asthma and guidelines suggest that measurements of airway inflammation should be included in evaluation of control status [4–6], although dissociation between eosinophilic airway inflammation, asthma symptoms and disordered airway function has been described in some asthma patients [7,8]. Induced sputum and nasal lavage cytology are currently used as relatively non-invasive, reliable and responsive techniques to measure airway inflammation [9–12].

The goal of this study is to determine whether BD response can be used as a reliable measure of asthma control. Using a randomized controlled trial, we tested the effect of additional oral corticosteroids (OC) treatment on spirometric values and induced sputum cytology in regularly treated controlled asthma patients who presented positive BD response.

Methods

We carried out a double blind, placebo (P) controlled, parallel-group, randomized clinical trial (RCT) to determine the effect of additional OC treatment on spirometric values and lower airway cytology of controlled asthma patients who exhibited persistent BD response. Eligible patients were recruited from the Hospital São Paulo/Unifesp Asthma Clinic.

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The institutional review board approved the protocol, and the study was conducted in accordance with the Good Clinical Practice Guidelines. All patients provided written informed consent. This RCT was enrolled in <https://register.clinicaltrials.gov>, Protocol ID: APITA, NCT00597064, on 1 August 2008.

The inclusion criteria were: patients over 15 years old, non-smokers or ex-smokers (less than 5 packs/year), having undergone inhaled corticosteroid therapy (400 mcg Budesonide) plus LABA (12 mcg Formoterol) twice daily for at least 3 months (step 4 of GINA), exhibiting positive BD response at the screening visit (V₀), and controlled asthma by ACQ5 definition. Positive BD response was defined as greater than 12% increase in post-BD FEV₁ value compared to pre-BD FEV₁ value, and an increase in the absolute value of FEV₁ of greater than 200 mL. Patients were excluded if they had upper and/or lower respiratory tract infections within 4 weeks prior to enrollment or other known chronic pulmonary diseases or relevant diseases that might interfere with the study requirements.

Patients who met the inclusion criteria were randomly assigned in a 1:1 ratio by means of randomization table to receive either prednisone 40 mg daily or placebo for 2 weeks, prednisone and placebo capsules were identical in taste and appearance.

Sample size was calculated by estimating that 30% of patients under OC treatment would achieve a significant improvement in pulmonary function, while only 5% of P subjects would. Under these conditions, it would be necessary to study 33 subjects for each condition to obtain a power of 80% and a confidence of 95% based on two-tail type I error. A total of 71 subjects were randomized. A schematic of the trial is shown in Figure 1. At V₀, patients were clinically evaluated and were given a prick test to evaluate atopic status and the spirometry with BD response test. They were also instructed to complete a diary card of the previous 10 ± 5 d to evaluate current asthma control based on a GINA guideline composite measurement.

At the baseline visit (V₁), patients were asked to complete a revised diary card which included additional questions on the following information: day and night symptoms, the use of rescue BD medication and measurement of peak expiratory

flow (PEF) over the last 7 d. Patients also answered the ACQ5 in which asthma score remained <1.5 [13]. Patients then underwent the spirometry with BD response test, and induced sputum was collected. All V₁ appointments were scheduled in the morning so that spirometry was performed at roughly the same time of day for each patient, and patients were asked to refrain from taking their LABA medications for 24 h before the appointment. Although all enrolled patients exhibited positive BD response of at least 12% at V₀, only a subset of enrolled patients were found to retain this level of BD response at V₁.

Between V₁ and the final evaluation visit (V₂), subjects received either prednisone 40 mg daily or placebo for two weeks. At V₂ patients were evaluated as they had been at V₁.

The atopic status of the subjects was measured using an ASAC pharma[®] skin-prick test system with 10 common environmental aeroallergens. Atopy was defined as at least one positive reaction with a diameter of > 3 mm larger than negative control [14].

The spirometric values and BD response were determined according to American Thoracic Society criteria and the Brazilian reference values using a Koko-PFT System Windows version 4.1.X spirometer (PDS Instrumentation, Inc., Louisville, CO, USA) [15,16]. In order to analyze pulmonary lung function two important parameters were considered:

- BD response at V₁, defined as $((\text{post-BD FEV}_1 - \text{pre-BD FEV}_1) / \text{pre-BD FEV}_1) \times 100$.
- Intervention response (a measure of intervention efficacy) defined as pre-BD FEV₁ at V₂ minus pre-BD FEV₁ at V₁, in mL.

The intervention response was defined as positive if there was an increase of FEV₁ greater than or equal to 200 mL [17].

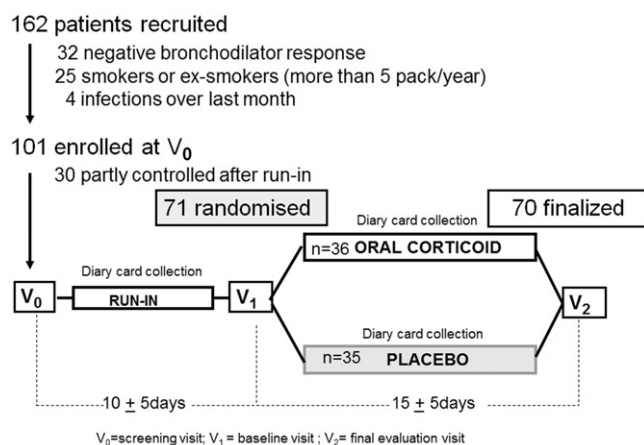
Sputum was induced by inhaling increasing concentrations of saline (3, 4 and 5%) for 7 min each and was processed according to a validated technique [10,12]. Sputum was then characterized by eosinophil or neutrophil sub types [18]. The sputum was considered eosinophilic when the relative eosinophil cell count exceeded 3%, and neutrophilic when the relative neutrophil count exceeded 65% [10,11,19–21]. Samples were examined in a blinded fashion by the same observer.

Efficacy analyses were performed in the intention-to-treat population, defined as all randomly assigned patients. Values were expressed as the mean and standard deviations (for parametric values) or the median and interquartile ranges (for non-parametric values). Independent *t*-tests were used to compare continuous variables with normal distribution, Mann–Whitney tests for non-parametric distributions and chi-square for categorical ones.

The following independent variables were included: BD response at baseline, age, the additional usage of OC and sputum eosinophil count.

A linear regression model was used to analyze the relationship between intervention response and BD response at baseline among patients, after adjusting for OC usage.

All analyses were conducted by using SPSS software 19 (IBM SPSS Statistics for Windows software, Version 19.0, Armonk, NY: IBM Corp). A *p* value less than 0.05 was taken as significant.



Results

Of the 162 patients invited to participate in the study, 61 were excluded at V0, as described in Figure 1, and 30 more were excluded at V1 because they no longer qualified as controlled at that time. Seventy-one patients were randomized but one patient dropped out due to an upper airway infection; therefore, 70 patients concluded the study (Figure 1).

Among the included patients, most were female (73%), the majority had atopy and the average age was approximately 50. They presented moderate airway obstruction ($FEV_1 = 71\%$). All patients were under combination therapy. Demographics and baseline characteristics were matched between groups (Table 1).

The subject characteristics according to intervention response are presented at Table 2. A positive intervention

response was observed in 62% of patients under OC treatment versus 12% of their P counterparts ($p < 0.001$). Interestingly, of the patients under OC, those who showed positive intervention response had significantly higher BD response at baseline than those who did not show an intervention response.

The patients who received additional OC showed significant improvement in FEV_1 at V2 (Figure 2A and B). Moreover, their BD response was reduced from positive at V1 to clinically insignificant at V2 (13.24 ± 10.08 versus 7.73 ± 6.28 , $p = 0.002$; Figure 2C). The P group had no significant change in FEV_1 or BD response at V2 (Figure 2).

Sputum values were eosinophilic in 54% and neutrophilic in 60% at V1 among overall included patients. The eosinophil count in induced sputum was reduced in the OC group at V2 (Figure 2D).

Figure 3 shows a significant positive linear relationship between BD response at baseline and intervention response among patients who received OC ($p = 0.002$), even among those who did not show a significant BD response at V1. An increase of one percentage of BD response at V1 was associated with an improvement in pre-BD FEV_1 of 11.23 mL at V2.

Discussion

This study demonstrates that asthma patients who are considered controlled based on ACQ5 scores but who exhibit persistent BD response can experience a gain in pulmonary function after a short course of OC treatment. OC treatment resulted in an increase in positive intervention response of 50% compared to placebo, as well as decreases in both BD response and sputum eosinophil count. These results suggest that BD response can identify controlled asthma patients who have the potential for further functional improvement, and, thus, that BD response is a good measure of asthma control. Furthermore, this study suggests that ACQ5 is not an adequate measure of asthma control.

Table 1. Demographics, pulmonary function, and induced sputum differential cell count at baseline (V1).

	Total	OC	Placebo
(n)	70	35	35
Female, n (%)	51 (73)	27 (77.1)	24 (68.6)
Age, years ^a	46.5 $\pm$ 13.9	43.9 $\pm$ 14.0	49.1 $\pm$ 13.6
Body mass index ^a	25.8 $\pm$ 6.41	24.7 $\pm$ 5.9	27.0 $\pm$ 6.8
ACQ ^a	0.56 $\pm$ 0.24	0.52 $\pm$ 0.25	0.60 $\pm$ 0.23
Atopy, n (%)	61 (87.1)	31 (91.2)	30 (88.2)
FEV_1 % pre-bronchodilator ^a	70.9 $\pm$ 16.9	73.4 $\pm$ 15.5	68.4 $\pm$ 16.4
FEV_1 % post-bronchodilator ^a	78.4 $\pm$ 15.1	81.7 $\pm$ 14.9	75.0 $\pm$ 14.7
Bronchodilator response, % ^a	12.1 $\pm$ 11.0	13.1 $\pm$ 10.0	11.2 $\pm$ 12.0
FEV_1/FVC pre-bronchodilator ^a	0.66 $\pm$ 0.08	0.67 $\pm$ 0.1	0.66 $\pm$ 0.1
FEV_1/FVC post-bronchodilator ^a	0.69 $\pm$ 0.09	0.71 $\pm$ 0.1	0.67 $\pm$ 0.1
Sputum neutrophil, % ^b	68 (48/83)	64 (50/80)	70 (44/84)
Sputum neutrophilia >65 , n (%)	40 (60)	19 (56)	21 (64)
Sputum eosinophil, % ^b	3 (1/6)	3 (1/8)	2 (1/6)
Sputum eosinophilia ≥ 3 , n (%)	36 (54)	20 (59)	16 (49)

OC, oral corticosteroid; ACQ, asthma control questionnaire; FEV_1 , forced expiratory volume at first second.

^aMean $\pm$ SD.

^bMedian (IQR).

Table 2. Demographics, pulmonary function, and induced sputum differential cell count according to the intervention response.

Intervention response	Positive ^a	None ^a	p Value
Oral corticosteroid arm ^x	62%	38%	<0.001*
Age in years mean (SD) ^b	43.9 (14.6)	36.2 (39)	0.42
Pre-BD FEV_1 % of predict, visit 1 mean (SD) ^b	71.5 (13.9)	76.4 (17.0)	0.38
Post-BD FEV_1 % of predict, visit 1 mean (SD) ^b	82.9 (13.3)	81.3 (17.5)	0.76
Pre-BD FEV_1/FVC mean (SD) ^b	0.65 (0.06)	0.70 (0.08)	0.06
Bronchodilator response % mean (SD) ^b	17.1 (9.9)	6.6 (5.9)	0.002*
Sputum eosinophil % median 25–75% interquartile ranges ^c	3.5 (1.1–15.2)	3.0 (0.7–8.5)	0.84
Sputum neutrophil % median 25–75% interquartile ranges ^c	65.0 (36.3–86.8)	53.0 (49.3–72.5)	0.32
Placebo arm ^x	12%	88%	<0.001*
Age in years mean (SD) ^b	41 (14.6)	50 (17.2)	0.14
Pre-BD FEV_1 visit 1 mean (SD) ^b	61 (7.4)	69 (14.9)	0.37
Post-BD FEV_1 visit 1 mean (SD) ^b	67 (14.1)	76 (14.9)	0.27
Pre-BD FEV_1/FVC mean (SD) ^b	0.63 (0.07)	0.65 (0.09)	0.55
Bronchodilator response % mean (SD) ^b	9 (9.8)	12 (12.4)	0.66
Sputum eosinophil % median 25–75% interquartile ranges ^c	2.0 (0.5–2.0)	2.5 (0.9–5.4)	0.88
Sputum neutrophil % median 25–75% interquartile ranges ^c	93.3 (73.0–93.0)	69.0 (41.8–82.3)	0.06

Lung function and cytology values were measured at V1.

FEV_1 values (in % of predicted values) expressed as the mean.

^aPositive = intervention response in FEV_1 greater than or equal to 200 mL; none = intervention response in FEV_1 less than 200 mL.

BD, bronchodilator.

^bIndependent Student's t test.

^cMann–Whitney test.

^xchi-square test.

*Statistically significant.

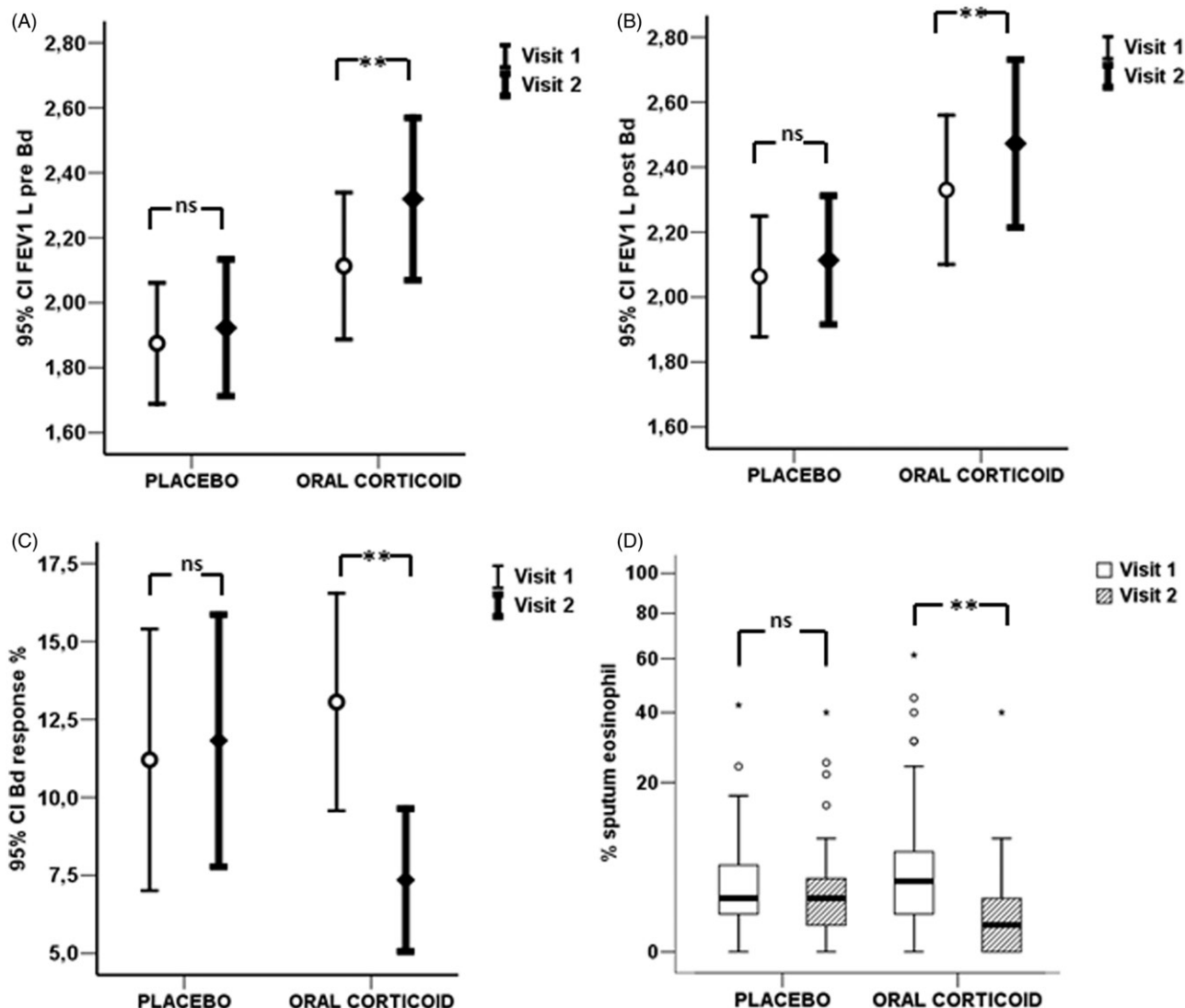


Figure 2. Pulmonary function and sputum cytology before and after treatment with OC or placebo. Pulmonary function parameters at Visit 1 (open circles/bars) and Visit 2 (closed rhombus/bars) are shown as mean and standard deviation (A, B, C). FEV1 levels are given in liters (L) (A, B) and BD response in percent (C). Induced sputum cytology is shown as median and 25–75% interquartile ranges (D). ** $p < 0.01$.

The BD response, as an independent predictor for good response to inhaled corticosteroid intervention, has been used to demonstrate the presence of airway inflammation without other clinical symptoms of asthma [17]. In the current study, linear regression showed that BD response value is a useful tool to predict the amount of FEV₁ gain after intervention.

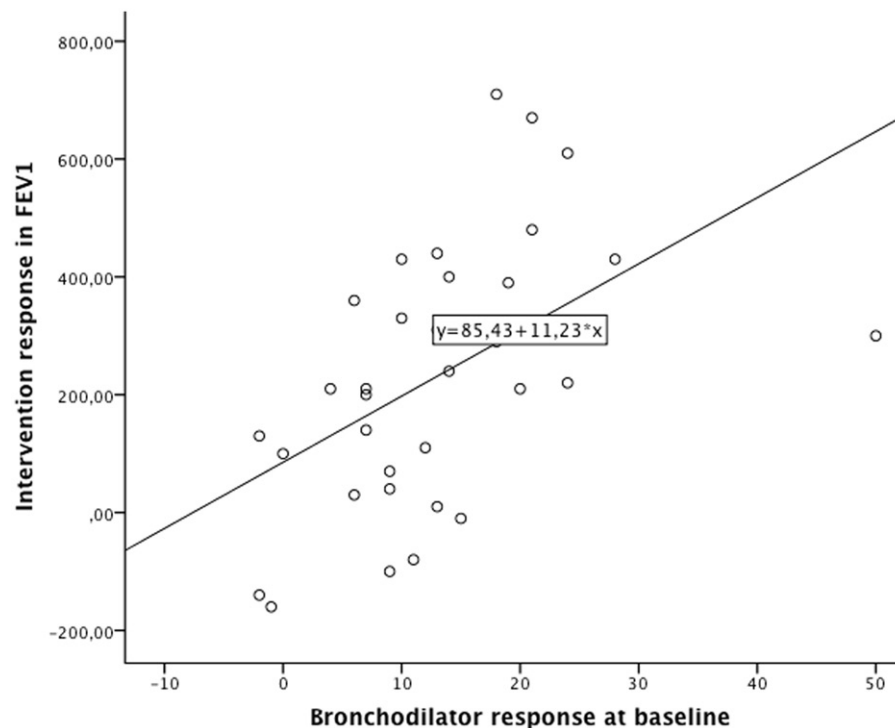
We chose to use FEV₁ to evaluate treatment response because there are extensive data in the literature pointing to gain in FEV₁ as one of the fundamental objective measures of asthma control [1]. Also, FEV₁ is a strong independent predictor of future risk of exacerbation [1].

We also found that eosinophil count was a good indicator of intervention response. Eosinophilic inflammation is a paramount feature of asthma and several studies have shown an increased number of eosinophils in the airways of symptomatic asthmatics [22–26]. Although sputum eosinophils decline with asthma treatment and correlate with asthma control, in this study 54% of the participants continued to show sputum eosinophilia at baseline, despite having been

treated with inhaled combination therapy according to GINA recommendations. The study participants randomized to receive OC experienced a significant decline in sputum eosinophils associated with functional improvement.

In this study, a significant number of patients who had been defined as controlled based on ACQ5 score showed positive intervention response after additional OC. A sub-optimal adherence to prescribed medication before trial should also be hypothesized as an explanation for this unexpected response, because subjects with symptomatic control tend to be less compliant with the medication regimen. It is possible that a self-reduction of maintenance medication or the use of Formoterol led to such a marked reduction in asthma symptoms in these patients that the amount of inhaled corticosteroid necessary to reach good inflammatory inhibition was underestimated [27]. It is also important to emphasize that symptomatic control does not equate with disease control. The persistence of positive BD response and the prevalence of eosinophilic sputum in these patients with good symptom control support this hypothesis.

Figure 3. Linear regression between intervention response and BD response at baseline visit (V1). Intervention response in FEV1 is given in mL and BD response is given in percent.



BD response has been used as a predictor of accelerated decrease in pulmonary function. Ulrick and Backer identified the relationship between the degree of BD response and excessive decline in lung function in a long-term study [28]. In this study, the use of an additional anti-inflammatory therapy in controlled patients with positive BD response modified their lung function, thereby confirming the activity of disease and altering the long-term risk of decline in pulmonary function and possible development of nonreversible airflow obstruction [28]. Similarly, airway eosinophilia has been used as a predictor of future exacerbation [29]. The short duration of OC treatment in the current trial limited the observation of the future risk of exacerbation or accelerated decline in pulmonary function.

While OC was chosen as the treatment option in this trial, in routine clinical practice controlled asthma patients with persistent BD response would be managed using more conservative approaches, including monitoring maintenance medication usage and adjusting inhaled corticosteroid dosage.

This study suggests that the ability of physicians to predict the presence and type of inflammation, based only on clinical assessment, is poor. In addition, the adherence of asymptomatic patients to maintenance medication is hard to assess. Consequently, the decisions employed to tailor anti-inflammatory treatment could be inappropriate. Based on our data, the ACQ was clearly inadequate as a tool to assess control on an individual basis.

Conclusions

A short course of OC improved clinical measures of asthma in patients who were considered controlled based on ACQ5 scores, but who exhibited persistent positive BD response. These results suggest that BD response can identify patients who have the potential for further functional improvement,

and, thus, BD response is a good measure of asthma control. The achievement of symptomatic control does not equate with disease control. Additionally, this study suggests that ACQ5 scores alone are not sufficient to evaluate asthma control, and that BD response should be included as an essential measurement in any algorithm of asthma control evaluation. Therefore, to define asthma control it is necessary to include a measurement of spirometry before and after BD.

Acknowledgements

We thank the patients and the study team at our medical. The authors acknowledged Mary Chaiken for copy editing of the article.

Declaration of interest

This study was supported by research grant # 2005/04714-1 from Fundação do Amparo a Pesquisa do Estado de São Paulo (Fapesp).

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