

Asthma variability in patients previously treated with β_2 -agonists alone

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Background: According to national asthma guidelines, asthma severity can be classified as intermittent, mild, moderate, or severe on the basis of lung function, symptoms, nighttime awakenings, and exacerbations. Although it is widely believed that patients might not remain consistently in any given severity category over time, few studies have examined this directly. **Objective:** We sought to assess the variability in disease severity-control among patients with persistent asthma who have not yet received an asthma maintenance treatment.

Methods: We performed an analysis of asthma severity-control over time in placebo-treated patients (n = 85) from 2 randomized, double-blind, 12-week clinical trials in patients with asthma previously receiving β_2 -agonists alone. Asthma severity-control was assessed on the basis of morning percent predicted peak expiratory flow, albuterol use, and symptoms.

Results: At baseline, all patients met the criteria for moderate or severe persistent asthma (mean FEV₁ of 64% of predicted value or albuterol use and symptoms on 4.7 and 6.0 days per week, respectively). The mean percentage of treatment weeks that patients met all criteria for intermittent, mild, moderate, and severe asthma were 9%, 14%, 71%, and 6%, respectively. On the basis of morning peak expiratory flow, patients were classified as having intermittent-mild, moderate, or severe disease on 52%, 41%, and 7% of days, respectively. With regard to days per week with albuterol use or asthma symptoms, patients spent 59% and 45% of weeks, respectively, in the intermittent and mild categories.

Conclusion: Asthma control cannot be adequately assessed in many patients by using discrete point-in-time assessments of lung function, short-acting β -agonist use, or asthma symptoms. This might lead to underestimation of disease severity and contribute to inadequate therapy and, ultimately, asthma morbidity. (*J Allergy Clin Immunol* 2003;112:1088-94.)

Key words: Asthma, asthma variability, lung function test, asthma severity, symptoms, albuterol use, clinical trial

Asthma imposes a growing burden on today's society in terms of health care costs, quality of life, and morbidity.

Abbreviations used

FP: Fluticasone propionate
MDI: Metered-dose inhaler
NAEPP: National Asthma Education and Prevention Program
PEF: Peak expiratory flow

Asthma affects up to 26 million people in the United States, and as recently as 1999, asthma accounted for approximately 4600 deaths and more than 475,000 hospitalizations annually.¹ It is important to note that despite the significant morbidity and mortality associated with asthma, numerous studies report that many patients with persistent asthma have mild disease.²⁻⁵ However, this notion has been recently challenged. For example, Fuhlbrigge et al⁶ published a study based on a random telephone survey of 1788 patients with asthma, which noted that 77.3% of the patients had moderate-to-severe persistent disease when functional effect, in addition to short- and long-term symptom burden, was considered. Such observations, together with the fact that both patients and health care professionals tend to underestimate the severity of asthma,^{5,7} suggest that current paradigms for assessing asthma severity and control might be inadequate, thus contributing to inadequate therapy and, ultimately, asthma morbidity in individual asthma patients.

Relative to the assessment of asthma severity, national and international asthma treatment guidelines have attempted to account for the complexity of physiologic, genetic, and environmental factors that underlie the disease. According to these guidelines, patients with persistent asthma can be classified as having mild, moderate, or severe disease on the basis of lung function, asthma symptoms, nighttime awakenings, and exacerbations.⁸ However, it must be recognized that asthma is a complex and variable disease. As such, one possible limitation of current classification systems is that patients might not remain consistently in a given severity category over time. For example, Zhang et al⁹ showed large variabilities in outcomes over 12 weeks for single point-in-time measurements (FEV₁, morning peak expiratory flow [PEF], daily symptoms, and rescue albuterol use). The variability was reduced when measurements were taken at multiple time points and averaged, suggesting that changes in a single measurement at any one time point cannot be used to adequately describe the state of the disease. However, few studies have directly examined whether patients remain consistently in a given severity category over time. Therefore the current evaluation was

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Presented in part at the American College of Allergy, Asthma, and Immunology Annual Meeting in San Antonio, Tex, November 15-20, 2002, and at the CHEST 2002 Annual Meeting in San Diego, Calif, November 2-7, 2002.

Supported by GlaxoSmithKline, Inc, Research Triangle Park, NC.

Received for publication July 30, 2003; revised September 3, 2003; accepted for publication September 12, 2003.

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0091-6749/2003 \$30.00 + 0

doi:10.1016/j.jaci.2003.09.044

undertaken to evaluate the variability in disease severity-control among patients with asthma who had not yet been prescribed an asthma maintenance treatment.

METHODS

Data from the placebo arms of 2 randomized, double-blind, placebo-controlled, parallel-group clinical trials (SAS30003¹⁰ and SFCA3002¹¹) were combined for these post hoc analyses. Only data from patients receiving placebo who had previously been treated with β_2 -agonists alone were used in this analysis.

Patient population

Male and female patients were eligible for the 2 studies (SAS30003 and SFCA3002) if they were at least 12 years old and had a medical history of asthma (as defined by the American Thoracic Society¹²) of at least 6 months' duration that required pharmacotherapy over the 6 months preceding the study. Patients who had been treated with β_2 -agonists only (and whose data were included in the current analysis) had to have been using β_2 -agonists for at least 1 week before study entry. Patients were required to have an FEV₁ value of between 40% and 85% of the predicted values on the basis of European Community for Coal and Steel standards for ages 18 years and older (race adjusted for black subjects)^{13,14} or Polgar standards for patients aged 12 to 17 years.¹⁵ Patients also had to have a greater than or equal to 15% increase in FEV₁ within 30 minutes after 2 puffs (180 μ g) of albuterol inhalation aerosol. Exclusion criteria included a history of life-threatening asthma; hypersensitivity reactions to sympathomimetic drugs or corticosteroids; smoking within the previous year or a history of greater than 10 pack-years; use of oral, inhaled, or injectable corticosteroid therapy within the previous month (SFCA3002 only); use of intranasal corticosteroids except for Flonase (fluticasone propionate [FP]) Nasal Spray (GlaxoSmithKline, Research Triangle Park, NC); use of daily oral corticosteroid treatment within the previous 6 months; use of any other prescription or over-the-counter medication that might affect the course of asthma or interact with sympathomimetic amines; abnormal chest x-ray films; clinically significant abnormal 12-lead electrocardiograms; or a history of significant concurrent disease (eg, glaucoma, diabetes, and hypertension). All patients (or guardians) provided informed consent before entry into the study.

Study design

In the SAS30003 study, patients entering the double-blind phase were randomized to one of the following treatments twice daily for 12 weeks: 88 μ g of FP/42 μ g of salmeterol HFAa34a propellant combination, 42 μ g of salmeterol chlorofluorocarbon administered through a metered-dose inhaler (MDI), 88 μ g of FP administered through a chlorofluorocarbon MDI, or placebo HFAa34a propellant MDI. In the SFCA3002 study, patients entering the double-blind phase were randomly allocated to receive one of the following treatments through the Diskus device twice daily for 12 weeks: 100 μ g of FP/50 μ g of salmeterol combination, 50 μ g of salmeterol, 100 μ g of FP, or placebo.

Measurements and evaluations

At each clinic visit, pulmonary function tests were performed before the morning dose of study medication and after withholding albuterol for a minimum of 6 hours. The spirometry equipment used for these studies was calibrated at least weekly and met or exceeded the minimal performance recommendations as set forth by the American Thoracic Society.¹³ Throughout the study, patients also recorded the following each day on diary cards: morning and evening PEF (highest of triplicate measurements), symptoms (wheezing, shortness of breath, and cough) on a 6-point scale rang-

ing from 0 (no symptoms) to 5 (symptoms that severely interfered with daily activities), the number of nighttime awakenings because of asthma symptoms requiring albuterol, and the number of puffs of supplemental albuterol used.

At each clinic visit, diary card information was assessed, and pulmonary function tests were performed to determine whether patients met predetermined asthma stability criteria. Patients were withdrawn from the studies because of worsening asthma if they met any of the following criteria: a clinical exacerbation requiring emergency treatment, hospitalization, or asthma medication not allowed by the protocol; a 20% decrease from the randomization visit predose FEV₁; a 20% decrease from baseline in morning PEF on more than 3 of 7 days immediately preceding a visit; 12 or more albuterol puffs per day on 3 or more of 7 days immediately preceding a visit; or more than 2 nighttime awakenings because of asthma symptoms that required albuterol aerosol during the 7 days immediately preceding a clinic visit.

Asthma severity classification

Asthma severity was categorized individually for symptoms, albuterol use, and morning PEF on the basis of National Asthma Education and Prevention Program (NAEPP) guidelines.⁸ For asthma severity on the basis of symptoms, *intermittent* was defined as less than or equal to 2 days per week with symptoms, *mild persistent* was defined as 3 to 6 days per week with symptoms, and *moderate-severe* was defined as greater than 6 days per week with symptoms. Asthma severity on the basis of albuterol use was defined in the same manner as for asthma symptoms. For asthma severity on the basis of morning PEF percent predicted, *intermittent-mild* was defined as greater than or equal to 80% of predicted value, *moderate* was defined as greater than or equal to 60% but less than 80% of predicted value, and *severe* was defined as less than 60% of predicted value.

Overall asthma severity was also categorized on the basis of NAEPP guidelines.⁸ *Intermittent* was defined as symptoms and albuterol use on 2 or fewer days per week and morning PEF of greater than or equal to 80% of predicted value. *Mild persistent* was defined as symptoms, albuterol use, or both on 3 to 6 days per week and morning PEF of greater than or equal to 80% of predicted value. *Moderate persistent* was defined as symptoms and/or albuterol use daily and/or morning PEF of greater than or equal to 60% but less than 80% of predicted value. *Severe persistent* was defined as symptoms and/or albuterol use daily and/or morning PEF of less than 60% of predicted value.

Statistical analyses

The population analyzed was the intent-to-treat population of patients previously treated with β_2 -agonists alone and randomized to placebo. All data collected on these patients, including patients who discontinued the study, were included in the analyses.

Classification of asthma severity on the basis of asthma symptoms only (intermittent, mild, and moderate-severe) were tabulated by study week. The baseline week (week 0) was defined as the 7 days before randomization to the study drug, and each set of 7 days during the treatment period was defined as 1 week (weeks 1-12). All patients met one of the 3 classifications at each study week so that percentages summed to 100% at each study week. Asthma severity on the basis of albuterol use alone, PEF alone, and overall asthma severity were summarized in the same manner. Asthma severity on the basis of daily PEF measures was also summarized, and the number of changes between severity classifications during the 12-week study was summed for each patient. Percentages of treatment weeks meeting each of the severity classifications for the overall, PEF, symptom, and albuterol use criteria were calculated for each patient.

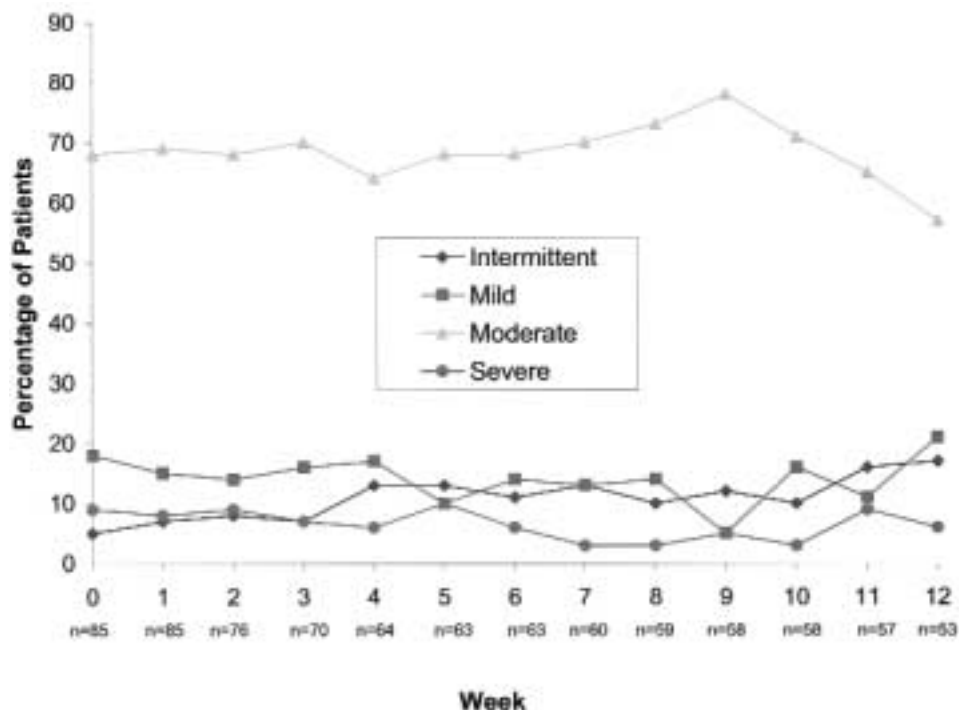


FIG 1. The percentage of patients by week who met overall asthma severity classification criteria (morning percent predicted PEF, albuterol use, and symptoms).

TABLE I. Baseline characteristics and demographics (n = 85)

Male/female	62%/38%
Age (y), mean (range)	29 (12-72)
Ethnic origin, n (%)	
White	68 (80%)
Black	8 (9%)
Other	9 (11%)
FEV ₁ % predicted, mean (SD)	64% (11%)
Morning PEF % predicted, mean (SD)	82% (15%)
Days per week with symptoms, mean (SD)	6.0 (1.8)
Days per week with albuterol use, mean (SD)	4.7 (2.6)

TABLE II. Mean percentage of weeks that patients spent in each severity category

Parameter evaluated	Asthma severity classification			
	Intermittent	Mild	Moderate	Severe
Overall	9%	14%	71%	6%
PEF % predicted	52%*		42%	6%
Symptoms	18%	27%	55%†	
Albuterol use	30%	29%	41%†	

*PEF categories: intermittent-mild, moderate, and severe.

†Symptoms and albuterol use categories: intermittent, mild, and moderate-severe (on the basis of NAEPP criteria for asthma classification).

Means were then calculated summarizing the mean percentage of treatment weeks by asthma severity. Mean percentage of treatment days by PEF severity was calculated in a similar manner. No inferential analyses were performed.

RESULTS

Eighty-five patients previously treated with only β_2 -agonists were randomly assigned to placebo treatment in the 2 studies. Baseline characteristics and demographics are presented in Table I. All patients met the criteria for moderate or severe persistent asthma at baseline, with a mean FEV₁ of 64% of predicted value, a mean of 4.7 days with albuterol use per week, and a mean of 6.0 days per week with asthma symptoms.

Overall asthma severity

Overall asthma severity results are presented in Fig 1. Of note, an overall asthma severity classification consistent with NAEPP criteria for intermittent or mild asthma was observed on at least 1 week in 12% and 38% of patients, respectively, over the 12 weeks of the study. In addition, patients spent, on average, 23% of weeks meeting all criteria for intermittent or mild persistent asthma in the 12 weeks of the study. The mean percentage of weeks that patients met all criteria for intermittent, mild, moderate, or severe asthma was 9%, 14%, 71%, and 6%, respectively (Table II and Fig 2).

Individual asthma severity categories

Fig 3 shows examples of individual patient data for morning percent predicted PEF, symptoms, and albuterol use over 12 weeks. These data show the large variability observed within each of the outcome measurements for individual patients from the study.

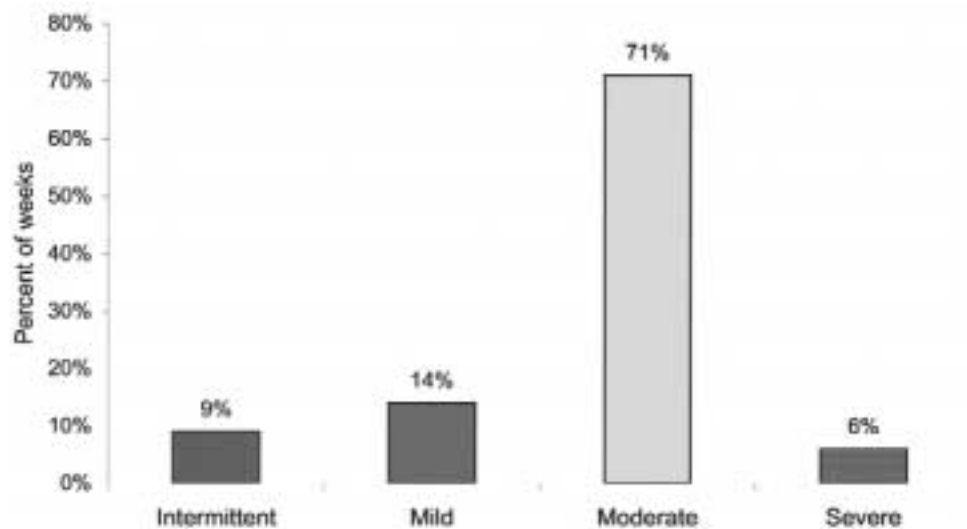


FIG 2. The percentage of weeks that patients met all asthma severity criteria (morning percent predicted PEF, albuterol use, and symptoms).

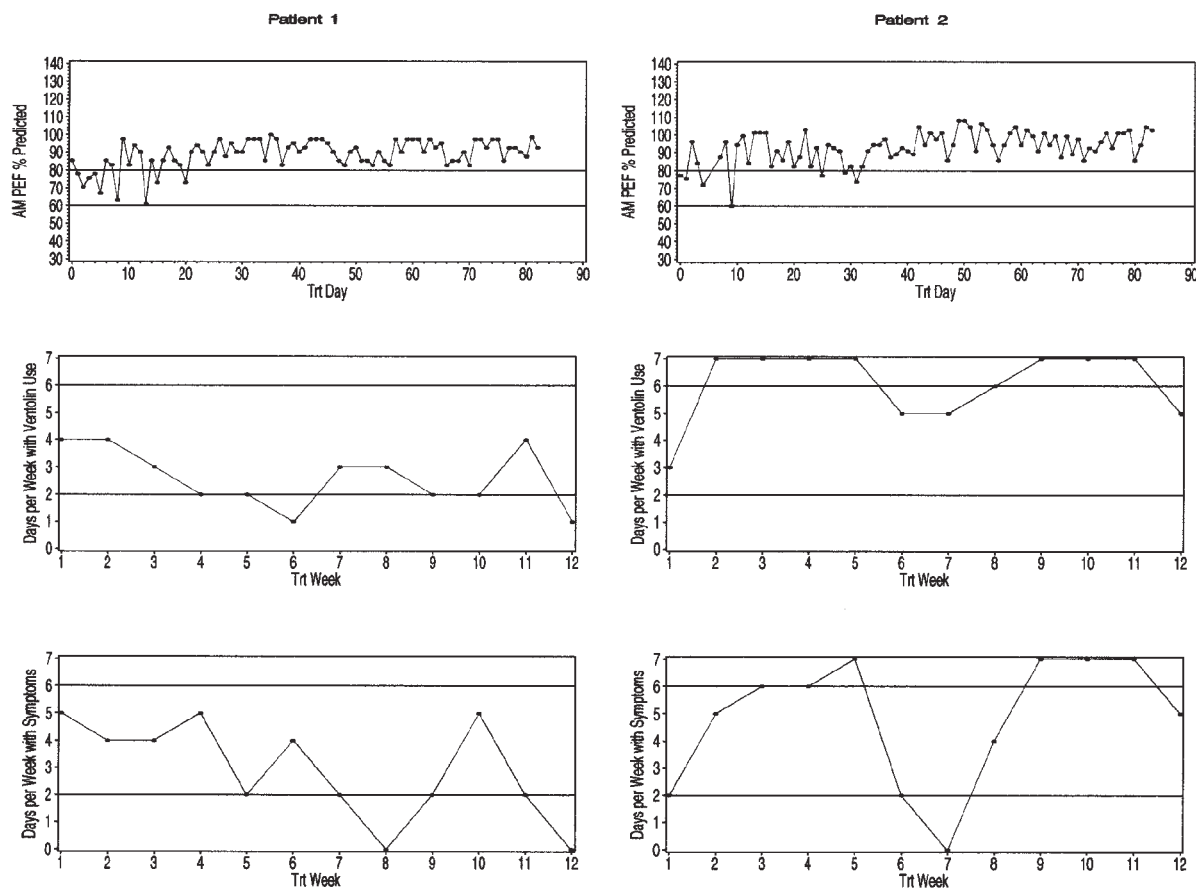


FIG 3. Variability in morning percent predicted PEF, albuterol use, and symptoms over 12 weeks in 2 individual patients.

The mean percentage of days during the 12-week study that patients met the criteria for intermittent-mild, moderate, or severe persistent asthma on the basis of NAEPP criteria for PEF percent predicted was 52%,

41%, and 7%, respectively. The number of times individual patients experienced a change in severity category on the basis of PEF, a measure of their disease variability, is shown in Fig 4. Approximately 70% of patients experi-

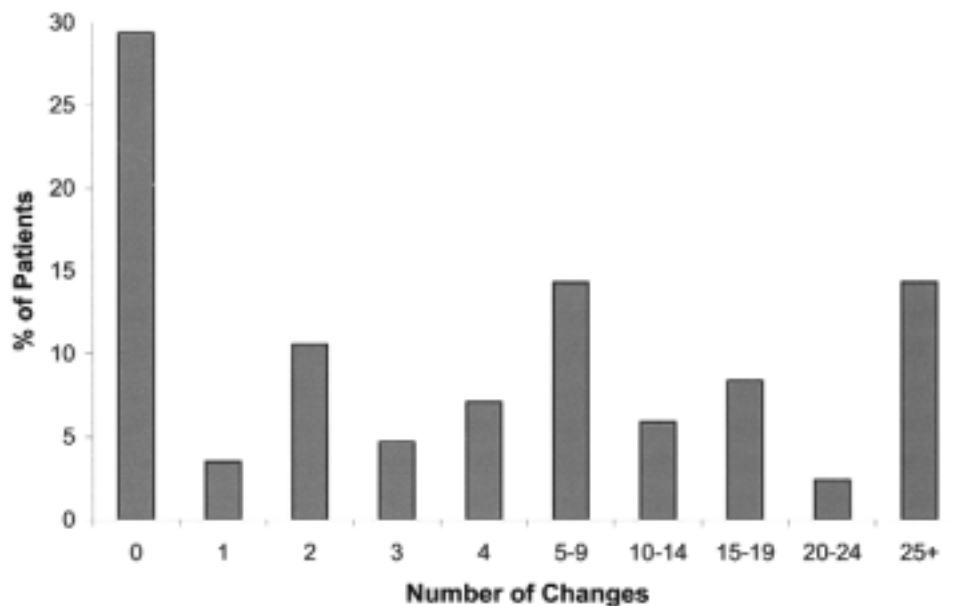
Asthma, rhinitis, other
respiratory diseases


FIG 4. Number of changes in asthma severity-control on the basis of percent predicted morning PEF during the 12-week study.

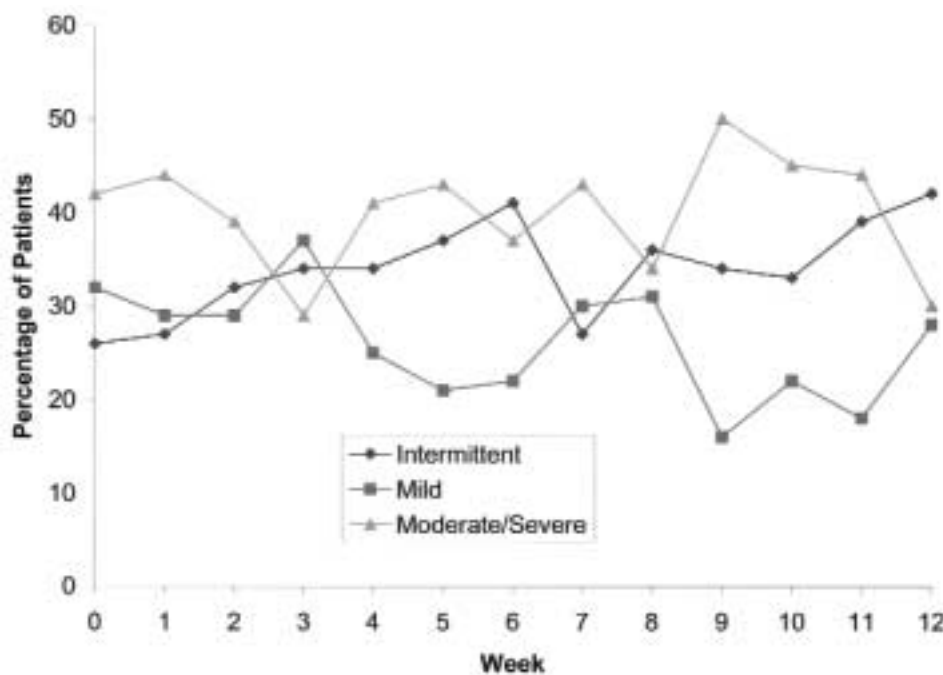


FIG 5. The percentage of patients by week who met albuterol severity criteria.

enced one or more change in asthma severity on the basis of PEF, with 45% experiencing 5 or more changes and 31% experiencing 10 or more changes in asthma severity during the 12-week study.

Asthma severity classification on the basis of albuterol use varied widely during the 12-week study and is presented in Fig 5. Of note, fewer than 50% of patients (all of whom met the criteria for moderate or severe persistent asthma at baseline) had albuterol requirements that

were consistent with moderate-severe disease on any given week during the 12-week study (Fig 5). The percentage of weeks that patients spent in the intermittent, mild, or moderate-severe categories on the basis of days per week with supplemental albuterol use was 30%, 29%, and 41%, respectively (Table II).

Results for asthma severity classification on the basis of days per week with asthma symptoms were similar to those noted above for albuterol. Specifically, the percent-

age of weeks that patients spent in the intermittent, mild, or moderate-severe categories on the basis of days per week with asthma symptoms was 18%, 27%, and 55%, respectively (Table II); patients spent, on average, 45% of weeks in the intermittent-mild categories.

DISCUSSION

The data from these two 12-week studies are consistent with the premise that asthma is a variable disease and that wide fluctuations can and do occur in morning PEF, asthma symptoms, and albuterol use, with the result that individual patients move frequently across severity categories over time. Despite the fact that all patients met the criteria for moderate or severe persistent asthma at baseline, patients spent, on average, 23% of weeks over a 12-week period meeting all the criteria for intermittent asthma or mild persistent asthma. In addition, the majority of patients met the criteria for intermittent-mild asthma on the basis of PEF criteria, and nearly half of the patients met the criteria for intermittent or mild asthma on the basis of symptoms or albuterol use criteria on any given week during the 12-week study. Taken together, these data indicate that the use of individual parameters to assess asthma control might lead to underestimation of disease severity and potentially to increases in asthma morbidity.

Large variations in asthma severity end points have also been described by Zhang et al⁹ in a post hoc analysis of 2 previously completed clinical trials comparing montelukast, beclomethasone dipropionate, and placebo in patients with mild-to-moderate persistent asthma. These investigators noted large variations in each of the 4 single time point measurements: FEV₁, morning PEF, daily symptoms, and rescue albuterol use. The observed variability was reduced when measurements at multiple time points were taken and averaged. Similar to the results from our analyses, these data suggest that single measurements or changes in single measurements at any point in time might not be useful in predicting asthma severity, asthma control, or the response to therapy.

These results also support recent data indicating that a majority of patients with asthma have asthma severity consistent with moderate persistent disease rather than intermittent or mild disease. Specifically, using data from a telephone survey conducted in 1788 asthmatic patients or parents of asthmatic patients in the United States in 1998, Fuhlbrigge et al⁶ reported on the association between overall asthma burden and sociodemographic variables, medication use, health-related quality of life, and hospitalizations—emergency department visits by using NAEPP Expert Panel II recommendations for assessing asthma severity.⁸ When based on short- and long-term symptom burden alone, a large percentage of patients (43.7% and 46.1%, respectively) had disease severity consistent with mild intermittent asthma. However, when functional effect was combined with short- and long-term symptom burden, the majority of patients were classified as having a global asthma burden consistent with moderate or severe persistent disease (77.3%),

whereas only 7.3% had a global asthma burden consistent with mild intermittent disease. Patients with moderate or severe persistent asthma had an almost 4-fold increase in hospitalization rates in the prior year and a greater than 2-fold increase in urgent care visits and were 4 times more likely to miss more than 5 days of school or work related to their asthma than were patients with mild intermittent asthma. These data, on the basis of NAEPP severity recommendations, are in contrast to previous studies that reported a higher incidence of patients with mild disease and emphasize the importance of considering the functional effect of asthma, in addition to the short- and long-term symptom burden, in assessing asthma disease severity and control.²⁻⁵

The current system of classifying asthma severity is based primarily on a cross-sectional evaluation of disease severity (ie, disease severity at a specific point in time) but does not provide a way to assess or evaluate long-term disease control for individual asthmatic patients.⁸ These limitations, as evidenced in the report by Fuhlbrigge et al,⁶ have very practical applications for asthma care. Namely, both patients and physicians underestimate asthma severity, which might lead to undertreatment of the disease and contribute to asthma morbidity and, perhaps, mortality.^{8,16} In this regard Robertson et al¹⁶ reported that more than one third of 51 pediatric deaths that occurred over the 3-year period from 1986 through 1989 in the Australian province of Victoria occurred in patients who were thought to have mild persistent asthma. Similarly, Burr et al¹⁷ reported that one third of the 52 asthma fatalities in Wales from 1994 through 1996 occurred in patients with mild or moderate asthma. Studies such as these provide compelling evidence to refute the broad-based misconception that mild asthma is not associated with morbidity or mortality. In addition, these data, together with the data from the current study, emphasize the fact that asthma control changes over time and is frequently underrecognized. Consequently, patients and physicians need to continually monitor and evaluate not only short- and long-term symptom burden and lung function but also the functional effect of the disease on individual patients.

An additional factor that might contribute to undertreatment and be manifested by variability in overall asthma control is reliance on one clinical marker to assess asthma severity or control. This was evident from the analyses in the current study and has been borne out in other clinical studies as well.^{17,18} The data from the current study indicate that lung function, asthma symptoms, or albuterol requirements, as individual measures, can lead to overestimation of asthma control (ie, a patient with high albuterol requirements or daily symptoms might have normal lung function and vice versa). This was also evident in a recent study by Kendrick et al.¹⁸ In an evaluation of 11 UK practices, Kendrick et al¹⁸ reported that asthma severity was underestimated in 60% of patients when evaluation was based on symptoms alone. Likewise, Green et al¹⁹ have suggested that eosinophilic airway inflammation is a more valid marker of disease

control than traditional clinical and lung function markers of asthma control. These investigators compared the effect of using 2 different asthma management strategies on the frequency of severe exacerbations: (1) British Thoracic Society asthma guidelines (including symptoms, lung function, and rescue albuterol use criteria) and (2) normalization of the induced sputum eosinophil count along with reduction of symptoms. The 2 strategies were equally effective with respect to overall disease control (eg, symptoms, lung function, and total inhaled corticosteroid dose). By contrast, patients in the sputum management group had markedly fewer severe asthma exacerbations and fewer hospital admissions than patients in the British Thoracic Society management group. This apparent dissociation between control of inflammation, exacerbations, and traditional markers of asthma control supports the idea that a composite of end points at multiple points over time might be the optimal way to assess and maintain asthma control and reduce the overall burden of the disease.

Additional studies are needed to define a sensitive, comprehensive, and user-friendly method for assessing asthma control for individual patients over time. Such a method does not currently exist. Although it is possible in the setting of a clinical study to collect clinical and lung function measures of asthma control over time, this is not practical in the clinical practice setting. However, even if it were practical, Green et al,¹⁹ Sont et al,²⁰ and Szefer et al²¹ have demonstrated that there is a dissociation between control of inflammation, exacerbations, and traditional markers of asthma control. In this regard the development of biomarkers that function as a hemoglobin A1c equivalent for asthma (eg, exhaled breath condensates or exhaled nitric oxide), by noninvasively reflecting control of airway inflammation, could possibly help guide treatment decisions, with the result being that the overall burden of the disease could be significantly reduced.

In conclusion, the results from this analysis provide strong support for the premise that asthma is a highly variable condition and that patients frequently move between severity categories. As such, asthma severity cannot be determined in many patients on the basis of discrete, point-in-time assessments of lung function, frequency of short-acting β -agonist use, or asthma symptoms. Failure to recognize this might directly contribute to underestimation of disease severity for individual patients, resulting in unnecessary asthma morbidity and, perhaps, mortality. Future studies are clearly needed to bridge the gaps that exist in our understanding of how best to assess asthma severity and monitor disease control over time in individual patients.

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