

VARIABILITY IN ASTHMA SEVERITY IN PEDIATRIC SUBJECTS WITH ASTHMA PREVIOUSLY RECEIVING SHORT-ACTING β_2 -AGONISTS

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Objective An analysis of 5 double-blinded, randomized, 12-week asthma trials was undertaken to evaluate pediatric subjects (4 to 11 years; n = 276) who were previously receiving short-acting β_2 -agonists alone and subsequently received treatment with placebo. At baseline, all subjects met National Asthma Education and Prevention Program criteria for moderate/severe asthma.

Study design Asthma severity was categorized individually for symptoms, albuterol use, and morning peak expiratory flow and then overall taking into account all three parameters.

Results Subjects spent the majority of weeks (55%) in the moderate/severe category. Subjects spent approximately 48%, 31%, and 22% of weeks in intermittent, mild, and moderate/severe categories and 57%, 27%, and 15% of weeks, respectively, based on asthma symptoms and albuterol use. Subjects spent approximately 62%, 31%, and 8% of weeks in intermittent/mild, moderate, and severe categories, based on peak expiratory flow; however, >35% of subjects exhibited ≥ 15 changes in asthma severity classification, based on peak expiratory flow.

Conclusions Asthma is a disease with varying symptomatology, and pediatric subjects frequently move between severity categories, especially in children with inadequate asthma control. These data also emphasize that asthma severity cannot be determined in many pediatric subjects by discrete, point-in-time assessments of lung function, albuterol use, or asthma symptoms. Failure to recognize this problem may contribute to underestimation of disease severity in pediatric subjects. (*J Pediatr* 2006;148:517-21)

In 1999, more than 3.1 million children under the age of 15 years in the United States had an episode of asthma or an asthma attack in the preceding 12 months.^{1,2} During this same period, asthma was responsible for 190,000 hospitalizations and 658,000 emergency department visits.² In one study, only 7.3% of individuals with asthma were classified as having mild intermittent disease and 77.3% had moderate to severe persistent disease when overall asthma burden was considered.³ This observation is in contrast to previous reports of a higher incidence of subjects with mild disease.⁴⁻⁷ However, these previous studies must be interpreted in the context that both subjects and healthcare professionals tend to underestimate asthma severity.⁷

According to national and international guidelines, subjects with persistent asthma can be classified into one of three categories (mild, moderate, or severe), based on lung function, asthma symptoms, and nighttime awakenings before therapy.⁸ One possible limitation of this severity classification system is that subjects may not remain consistently in a given severity category over time. As such, disease severity may be underestimated, thus contributing to inadequate therapy and ultimately asthma morbidity, and, perhaps, mortality.

The current evaluation was undertaken, therefore, to assess the variability in asthma severity classification of pediatric subjects who had not yet been prescribed an asthma maintenance therapy.

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FEV ₁	Volume in liters of air expired during first second of forced expiration	NAEPP	National Asthma Education and Prevention Program
FP	Fluticasone propionate	PEF	Peak expiratory flow
FVC	Forced vital capacity		

Table I. Studies included in the analyses

Study	Baseline FEV ₁ or PEF entry requirements	Treatment arms in addition to placebo for 12 wk	Primary/secondary efficacy outcomes
FLTA2006	FEV ₁ 50–85% predicted (6–11 y) PEF ≤85% (4–5 y)	FP 50 μg bid via Diskus or FP 50 μg or FP 100 μg bid via Diskhaler	Change from baseline in FEV ₁ (6–11 y) or PEF* (4–11 y)
FLTA2007	FEV ₁ 50–85% predicted (6–11 y) PEF ≤85% (4–5 y)	FP 50 μg bid or FP 100 μg QD via Diskus	Subject-recorded AM PEF Probability of remaining in study asthma symptoms rescue albuterol use nighttime awakenings requiring albuterol use
FLTA2008	FEV ₁ 50–85% predicted (6–11 y) PEF ≤85% (4–5 y)	FP 100 μg bid or FP 200 μg qd via Diskus	
SLGA3014	FEV ₁ or PEF 45–75% predicted	SAL 25 μg or SAL 50 μg bid via Diskus or ALB 200 μg QID via Rotahlaer	Serial measurements of FEV ₁ (6–11 y) or PEF* (4–11 y) on day 1 and week 12
SLD390	FEV ₁ or PEF 50–75% predicted	SAL 50 μg bid via Rotadisk	2-h postdose PEF and FEV ₁ † subject-recorded AM PEF rescue albuterol use asthma symptoms, nighttime awakenings requiring albuterol use asthma exacerbations

ALB, albuterol; FP, fluticasone propionate; SAL, salmeterol.

*PEF measurements collected twice daily (AM and PM) in all studies, except SLGA3014, which collected AM PEF measurements only.

†At treatment week 6 for SLGA3014 and at treatment weeks 4 and 8 for SLD390.

METHODS

Data from 5 randomized, double-blinded, placebo-controlled, parallel-group, clinical trials (FLTA2006,⁹ FLTA2007,¹⁰ FLTA2008,¹¹ SLGA3014,¹⁰ and SLD390¹²) were combined for these post hoc analyses. Only data from subjects who had been treated with short-acting β_2 -agonists alone and were then randomly assigned to placebo from these previously conducted trials were used in these analyses.

Population and Study Design

Boys and premenarchal girls were eligible for the 5 studies if they were 4 to 11 years old. Subjects had a medical history of asthma (as defined by the American Thoracic Society¹³) of at least 3 or 6 months' duration that required pharmacotherapy over at least 3 or 6 months' preceding the study. Subjects in all 5 studies had lung function predicted calculated from Polgar standards,¹⁴ with race adjustment for blacks^{13,15} and had to demonstrate the presence of reversible airways disease, as defined by an increase in FEV₁ (volume in liters of air expired during first second of forced expiration) of ≥15% over baseline values within 30 minutes after 2 puffs (180 μg) of albuterol inhalation aerosol. Additional information about each study is provided in Table I.

Asthma Severity Classification

Asthma severity was categorized individually for symptoms, albuterol use, and morning peak expiratory flow (PEF), based on National Asthma Education and Prevention Program (NAEPP) guidelines.⁸ For asthma severity based on symptoms, "intermittent" was defined as ≤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, as there is no clear differentiation between moderate and severe within the guidelines for this parameter. Asthma severity based on albuterol use was defined in the same manner as for asthma symptoms. For asthma severity based on morning PEF percent predicted, "intermittent/mild" was defined as ≥80% predicted, as there is no distinction between "intermittent" or "mild" asthma with regard to PEF in the guidelines; "moderate" was defined as >60% but <80% predicted; and "severe" was defined as ≤60% predicted.

Overall asthma severity was also categorized on the basis of NAEPP guidelines. "Intermittent" was defined as symptoms and albuterol use on ≤2 days per week and morning PEF ≥80% predicted. "Mild" persistent was defined as symptoms and/or albuterol use on 3 to 6 days per week and morning PEF ≥80% predicted. "Moderate" persistent was defined as symptoms and/or albuterol use daily and/or morning PEF >60% but <80% predicted. "Severe" persistent was defined as symptoms and/or albuterol use daily and/or morning PEF ≤60% predicted.

The highest (best effort) was recorded and used for both PEF and FEV₁ at baseline and throughout the study, according to the American Thoracic Society (ATS) standards. Measurements were done in duplicate or triplicate, depending on the individual study protocol. Mean weekly PEF values were used for determination of asthma severity.

Statistical Analyses

The population analyzed was the intention-to-treat population of subjects previously treated with β_2 -agonists alone and randomly assigned to placebo. All data collected on

Table II. Baseline characteristics and demographics

Baseline characteristic	Overall population (n = 276)
Male/female (%)	61/39
Age (y) mean (SD)	8.1 (2.3)
Ethnic origin, n (%)	
White	207 (75)
Black	30 (11)
Other	39 (14)
FEV ₁ % predicted, mean (SD)	67.9 (13.1)
FEV ₁ % reversibility, mean (SD)	30.1 (15.6)
Morning PEF % predicted, mean (SD)	79.7 (17.6)
Days per week with symptoms, mean (SD)	4.2 (2.7)
Days per week with albuterol use, mean (SD)	3.7 (2.8)

these subjects, including those who discontinued, were included in the analyses.

Classification of asthma severity based on asthma symptoms only were tabulated by study week. Baseline week (week 0) was defined as the 7 days before random assignment to study drug, and each set of 7 days during the treatment period was defined as 1 week (weeks 1 through 12). All subjects met one of the three classifications so that percentages summed to 100% for each study week. Asthma severity based on albuterol use alone, PEF alone, and overall asthma severity was summarized in the same manner. Asthma severity based on 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, symptoms, and albuterol use criteria were calculated for each patient. Means were then calculated, summarizing the mean percent of treatment weeks by asthma severity. Mean percent of treatment days by PEF severity was calculated in a similar manner.

RESULTS

Subjects (n = 276) were randomly assigned to placebo treatment in the 5 studies. Baseline characteristics and demographics are presented in Table II. At enrollment, all subjects met NAEPP criteria for moderate or severe persistent asthma at baseline, with a mean FEV₁ of 68% predicted, a mean of 3.7 days with albuterol use per week, and a mean of 4.2 days per week with asthma symptoms.

Overall Asthma Severity

Subjects spent, on average, 56% of weeks meeting all criteria for moderate or severe persistent asthma in the 12 weeks of the study. The mean percentage of weeks that subjects met all criteria for intermittent, mild, moderate, or severe asthma was 27%, 18%, 48%, and 8%, respectively (Table III).

Table III. Mean percentage of weeks that subjects spent in each severity category

Parameter evaluated	Asthma severity classification			
	Intermittent	Mild	Moderate	Severe
Overall	27%	18%	48%	8%
PEF % predicted	Intermittent/mild*		31%	8%
	62%			
Symptoms	48%	31%	Moderate/severe†	
			22%	
Albuterol use	57%	27%	15%	

*PEF categories: intermittent/mild; moderate; severe.

†Symptoms and albuterol categories: intermittent, mild, moderate/severe.

Asthma Severity Based on Individual Measures

PEF AND FEV₁. The mean percentage of days during the 12-week study that subjects met criteria for intermittent/mild, moderate, or severe persistent asthma based on NAEPP criteria for PEF percent predicted was 62%, 31%, and 8%, respectively (Table III). The number of times individual subjects had a change in severity classification based on PEF during the 12-week trials is shown in the Figure. More than 35% of children had ≥ 15 changes in their asthma severity classification, and more than 18% of children changed > 24 times, based on PEF during the 12-week studies, denoting an extreme degree of variability in this population.

Severity analyses were also conducted by using $\geq 90\%$ predicted PEF for intermittent/mild classification; moderate as $> 70\%$ to $< 90\%$, and severe as $\leq 70\%$, as well as by using $\geq 100\%$ predicted PEF for intermittent/mild classification, moderate as $> 80\%$ to $< 100\%$, and severe as $\leq 80\%$. By using these analyses, the mean percentage of days during the 12-week study that subjects met criteria for intermittent/mild, moderate, or severe persistent asthma based on these criteria for PEF percent predicted were 37%, 44%, and 18%, respectively, for PEF $\geq 90\%$ predicted and 18%, 44%, and 38%, respectively, for PEF $\geq 100\%$ predicted.

In addition, the mean percentage of days during the 12-week study that subjects met criteria for intermittent/mild, moderate, or severe persistent asthma based on NAEPP criteria for FEV₁ percent predicted was 48%, 41%, and 11%, respectively.

Albuterol Use

Asthma severity classification based on albuterol use varied little during the 12-week study. However, fewer than 20% of subjects (all of whom met 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. The percentage of weeks that subjects spent in intermittent/mild, moderate, or severe categories, based on days per week with supplemental albuterol use, was 57%, 27%, and 15%, respectively (Table III).

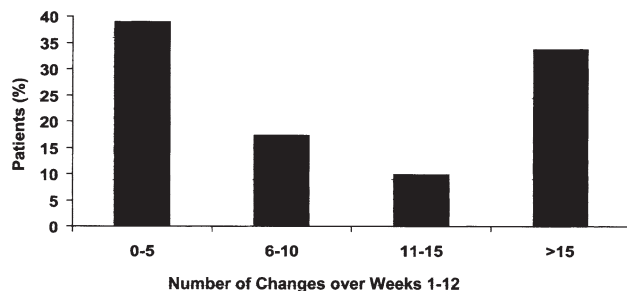


Figure. Number of changes in asthma severity, based on percent predicted morning PEF.

Asthma Symptoms

Results for asthma severity classification based on days per week with asthma symptoms were similar to those noted for albuterol (Table III). No single parameter (PEF, symptoms, or albuterol use) reliably predicted overall severity for individual subjects at any given point in time.

Study Withdrawals

Over the 12-week studies, 84 of the 276 placebo-treated subjects withdrew prematurely from the study. Of these, 57 subjects (68%) withdrew due to “lack of efficacy.” At the time of withdrawal, overall severity classifications for the week immediately before withdrawal were analyzed. A total of 13% of subjects were classified as intermittent, 21% as mild, 48% as moderate, and 18% as severe.

Discussion

The results of this retrospective analysis of pediatric subjects randomly assigned to placebo in previously conducted, prospective, randomized, placebo-controlled trials are consistent with the premise that asthma is a disease with varying symptomatology. Wide fluctuations can and do occur in morning PEF, asthma symptoms, and albuterol use, resulting in individual subjects moving frequently across severity categories over time. Despite the fact that all subjects met the criteria for moderate or severe persistent asthma at enrollment (based on FEV₁ measurements) and that more than 60% met overall criteria for moderate or severe persistent asthma at baseline, on average, subjects spent 45% of weeks over a 12-week period meeting all criteria for intermittent or mild persistent asthma. In addition, the majority of subjects met criteria for intermittent/mild asthma, based on PEF criteria, and nearly three fourths of the subjects met criteria for intermittent or mild asthma, based on symptoms or albuterol use criteria on any given week during the 12-week study, regardless of age. Even after analyzing subjects by baseline severity of intermittent/mild or moderate/severe, only 30% of subjects did not have a change in severity from baseline over the course of the study; the majority of subjects (~70%) did have changes from baseline in their severity classification.

Taken together, these data indicate that the use of individual parameters to assess asthma control may lead to underes-

timination of disease severity and potentially to increases in asthma morbidity. In addition, individual parameters may not be useful in predicting asthma control or response to therapy. This is especially relevant because more than 30% of subjects were classified as intermittent or mild when they withdrew from the study because of worsening asthma.

Interestingly, these results in children are in contrast to recent data reporting that a majority of subjects with asthma have asthma severity that is moderate and persistent in nature rather than intermittent or mild.³ In addition, the overall asthma severity and individual parameter results noted in this pediatric population are in contrast to those previously documented in adult subjects.¹⁶ Pediatric subjects spent almost equal amounts of time in the intermittent or mild category, whereas adults spent the majority of time in the moderate category.

One possible explanation for these discrepancies may be that lung function in adults correlates more closely with symptom criteria, compared with a pediatric population.¹⁷ In our analyses, when PEF was used to determine severity, the majority of subjects were classified as having intermittent or mild disease, and very few were classified as severe. PEF did not correlate with symptoms and/or albuterol use, as when those parameters were considered, more subjects were classified as having moderate/severe disease. Furthermore, when assessing overall asthma severity, almost one half of the pediatric population had PEF, symptoms, and albuterol use consistent with intermittent or mild asthma, compared with fewer than 25% of adults.

The current system of classifying asthma severity is based primarily on a cross-sectional evaluation of symptomatology (ie, symptoms and lung function at a specific point in time) but does not provide a way to assess true underlying disease severity and need for therapy to maintain asthma control. In addition, the criteria to define intermittent, mild, moderate, or severe asthma in pediatric subjects are the same as the criteria used in adults. When different parameters for PEF percent predicted were used (ie, $\geq 90\%$ or $\geq 100\%$ for intermittent/mild versus $\geq 80\%$), similar to an alternate scheme conducted by Fuhlbrigge, et al,¹⁸ a shift occurred with more pediatric subjects being classified as moderate or severe. These data demonstrate that symptoms and albuterol use may not correlate with lung function in pediatric subjects, and, although a useful tool, PEF may be less reliable in children with asthma.^{19,20} Furthermore, in this pediatric population, PEF and FEV₁ did not correlate with asthma severity. Based on baseline PEF percent predicted, all subjects were classified as having mild disease; however, when using FEV₁, all subjects were classified as having moderate disease, which correlated more closely with reported symptoms and albuterol use. This finding is supported by the Childhood Asthma Management Program, in which more than 50% of the cohort had moderate persistent asthma, based on symptoms, yet mean FEV₁ percent predicted values were between 90% and 105% predicted.²¹ In addition, the vast majority of subjects evaluated with regard to risk of asthma exacerbations by Fuhlbrigge et al¹⁸ had FEV₁ percent predicted values greater than 80%.

Perhaps measures that focus on asthma symptomatology are more appropriate in pediatric populations, as many children with asthma have normal lung function. Several studies have used the ratio of FEV₁ to forced vital capacity (FVC) [FEV₁/FVC ratio], which may be a more appropriate measure of lung function in pediatric subjects.^{22,23} In a recent analysis by Bacharier et al,²⁴ the FEV₁/FVC ratio was the most strongly correlated measure of lung function in determining asthma severity. However, the authors concluded that symptom frequency and medication usage most accurately classified asthma severity in a pediatric population.

Often, both subjects and physicians underestimate asthma severity, which may lead to undertreatment of the disease and contribute to asthma morbidity, and, perhaps, mortality. The data from the current study indicate that lung function (specifically PEF), asthma symptoms, or albuterol requirements, as individual measures, can lead to underestimation of asthma control caused by the large variability within the data.

It must be stressed that the children studied had been randomly assigned to receive placebo during the 12-week study, and these children with moderate persistent asthma probably were suboptimally controlled. We clearly demonstrate that children with asthma who are not adequately treated demonstrate extreme variability in PEF. Similar results were reported in adults with asthma before institution of inhaled corticosteroid therapy.²⁵ The results from our study emphasize the need to use effective controller therapy in children with persistent asthma. It also clearly demonstrates the limitations of our current guidelines with respect to classifying asthma severity.

In conclusion, the results from this analysis provide strong support for the fact that asthma symptomatology is highly variable and that pediatric subjects frequently move between severity classification categories, even more so than adults. As such, asthma severity cannot be determined in pediatric subjects on the basis of discrete, point-in-time assessments of lung function, frequency of short-acting β -agonist use, or asthma symptoms. And even more importantly, in pediatric subjects, PEF may be normal and may not correspond with FEV₁, symptom severity, or supplemental albuterol use. Failure to recognize this mismatch may directly contribute to underestimation of disease severity for individual subjects, resulting in unnecessary asthma morbidity, and, perhaps, mortality.

Finally, the results of this analysis support consideration of a reevaluation of the current NAEP asthma severity classification for children with childhood asthma.

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