Variability of symptoms in mild persistent asthma: baseline data from the MIAMI study

Robert S. Zeigera,*, James W. Bakerb, Michael S. Kaplanc, David S. Pearlmand, Michael Schatza, Steven Birde, Carolyn Hustade, Jonathan Edelmane, for the MIAMI Study Research Group1

aDepartment of Allergy-Immunology, Kaiser Permanente Medical Center, 7060 Clairemont Mesa Boulevard, San Diego, CA 92111, USA
bAllergy, Asthma, and Dermatology Research Center, 3795 Mercantile Drive, Suite 165, Lake Oswego, OR 97035, USA
cSouthern California Permanente Center for Medical Education, 1515 North Vermont Avenue, Los Angeles, CA 90027, USA
dColorado Allergy and Asthma Centers, PC, 125 Rampart Way, Suite 100, Denver, CO 80230, USA
eMerck & Co., Inc., P.O. Box 4, HM-220, West Point, PA 19486, USA

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Summary Objective: To describe the variability of the asthma phenotype in patients with mild persistent asthma enrolled in the Mild Asthma Montelukast versus Inhaled Corticosteroid (MIAMI) study.

Methods: The variability of asthma rescue-free days, asthma symptoms, albuterol use, medical resource use, and exercise limitations among patients with documented mild persistent asthma was compared between the month before study enrollment and the last 2 weeks of the run-in period.

Results: Patients eligible for randomization (n = 400), aged 15–85 years, exhibited symptoms (mean ± SD) 3.6 ± 1.3 days/week, β-agonist use 3.5 ± 1.3 days/week, and normal FEV1 (94.0 ± 9.9% predicted) during the last 2 weeks of the run-in period. In the year before enrollment, medical intervention for asthma flares was common: 38.5% made office visits, 15.8% had oral corticosteroids, and 8.3% required emergency room or hospitalized care. In the month before enrollment, 11.8% experienced daily symptoms, and 28.3% had limitations of normal activity. Patients with daily symptoms in the month before study enrollment, compared with those having less-than-daily symptoms, experienced fewer rescue-free days (P = 0.024) and had more days per week with symptoms (P = 0.008) and requiring albuterol (P = 0.048) during the run-in; FEV1 was similar for both groups (93.1% vs. 94.2% predicted, respectively).

Conclusion: Patients with mild persistent asthma reported a substantial disease burden in the year before enrollment. The asthma burden experienced by these patients both before and during the run-in period was of sufficient severity to
Introduction

Asthma afflicts approximately 7% of the total US population (~17 million individuals), including 7–8% of US children (~5 million children). It is estimated that approximately 20–30% of these patients have mild persistent asthma, defined as either 3–6 days of symptoms per week or increased peak expiratory flow variability in the presence of normal predicted FEV1. Patients with mild persistent asthma have significant airway inflammation that potentially may lead to lung remodeling, as recently documented by computerized lung tomography. Although asthma may appear mild, acute exacerbations may be life threatening: up to 33% of asthma-related deaths in a pediatric population occurred in individuals thought to have only trivial or mild asthma.

The 2002 updates from the Global Initiative on Asthma (GINA) and the National Asthma Education and Prevention Program (NAEPP) recommend low-dose inhaled corticosteroid therapy as the preferred first-line treatment for mild persistent asthma in both children and adults. However, this recommendation is based on trials that included patients with both mild and moderate persistent asthma. Until recently there have been few studies of patients with exclusively mild persistent asthma. These expert panels recognized the scarcity of head-to-head comparisons between asthma controllers in mild persistent asthma and recommended long-term trials to compare their effectiveness in this subgroup. To address this need, a randomized, parallel-group study, the Mild Asthma Montelukast versus Inhaled Corticosteroid (MIAMI) study, was designed to compare the effects of the leukotriene receptor antagonist, montelukast, and the inhaled corticosteroid, fluticasone, in patients with mild persistent asthma during a 12-week double-blind treatment period followed by a 36-week open-label period. This study affords the opportunity to assess the asthma burden of a cohort of adolescents and adults with mild persistent asthma during the year before the study and during a 3-week run-in period. This report documents that patients with mild persistent asthma eligible for participation in the MIAMI study experienced a substantial asthma burden and possessed a variable asthma phenotype.

Methods

Overview of MIAMI

MIAMI is a randomized two-arm, parallel-group, multicenter study of adults and adolescents with mild persistent asthma designed to determine whether oral montelukast (10 mg once daily) will provide a comparable percentage of asthma rescue-free days (RFD) as inhaled fluticasone (88 μg twice daily) during 12 weeks of double-blind therapy (primary outcome) and a subsequent 36-week open-label treatment period. A RFD is defined as a treatment day during which there is no asthma rescue medication use (i.e., inhaled albuterol or oral corticosteroids) and no rescue clinical care (i.e., unscheduled asthma care in the office, urgent care center, emergency department, or hospital).

Recruitment and eligibility

Institutional review boards at each study site approved the study protocol, and written informed consent was obtained from all patients and from the parents or guardians of patients under 18 years of age before enrollment. Male and female outpatients between the ages of 15 and 85 years with a history of intermittent or persistent asthma symptoms for at least 4 months before enrollment and naive to systemic corticosteroids for at least 4 weeks, inhaled corticosteroids, cromolyn, nedocromil, or leukotriene modifiers for at least 2 weeks, and theophylline, long-acting beta-agonists, or inhaled anticholinergic agents for at least 1 week before enrollment were screened to identify a cohort with mild persistent asthma. Patients meeting the NAEPP and GINA definitions of mild persistent asthma based on symptoms, albuterol use, and lung function during screening and run-in were eligible for the study.

Eligible patients had an average FEV1 during the run-in period ≥ 80% of predicted, with none of the qualifying values below 70%, and daytime symptoms and short-acting β-agonist use on an average of ≥ 2 days but ≤ 6 days per week during the last 2 weeks of run-in period before randomization. Patients were also required to demonstrate airway reversibility or reactivity by showing at least a 12% absolute increase in FEV1 or PEF after albuterol, a
methacholine $PC_{20} FEV_1 \leq 12.5 \text{mg/ml}$, or a decrease in FEV$_1$ of at least 15% during an exercise challenge.$^{11,28}$

Atopy was determined by serum assay using the qualitative CAP Phadiatop test (Pharmacia Diagnostics, Kalamazoo, Michigan), which determines the presence of allergen-specific IgE antibodies to any component of a mixture of common inhalant allergens (house dust mite; cat; dog; horse; cockroach; various grass, weed, and tree pollens; and mold spores). The Phadiatop assay gives a “Yes” or “No” result for the presence of atopy. The sensitivity and specificity of the Phadiatop assay are 96% and 94%, respectively.

Patients were excluded from the study if they had (1) an acute or chronic pulmonary disease in addition to asthma; (2) a hospitalization for asthma within the previous 3 months; (3) an emergency department/urgent care facility or office setting treatment for acute asthma within the month before Visit 1; or (4) used intravenous gamma globulin or immunosuppressants within 1 month or fexofenadine, loratadine, or cetirizine within 2 days of enrollment.

Study visits

A run-in period of 3 weeks was used to assess asthma severity and ensure a mild persistent asthma cohort. To minimize placebo effect during the randomized interventional period, all potential patients received single-blind placebo montelukast and fluticasone during the last 2 weeks of the 3-week run-in period (Period 1 of study). Also during this period, FEV$_1$, PEF, daytime symptoms, and $\beta$-agonist use were assessed to determine eligibility for randomization and to establish baseline values.

Before all scheduled clinic visits, inhaled $\beta$-agonists were withheld for at least 6 h, and antihistamines were withheld for at least 48 h. Spirometry was performed at least twice during the run-in period, in accordance with and using spirometers conforming to the American Thoracic Society (ATS) guidelines.$^{25}$

Study questionnaires

Patients completed an asthma and allergy history questionnaire and an Exercise Questionnaire at enrollment and the Exercise Questionnaire and the Asthma-Specific Quality-of-Life Questionnaire prior to randomization. To determine asthma severity according to both GINA$^{11}$ and NAEP$^1$ guidelines, patients were queried on the frequency of asthma symptoms and night awakenings during the previous month. The following two questions (5 possible responses each) were asked: (a) In the past month, on average, how often did you have symptoms of asthma: never, $\leq 2$ times per week, $>2$ times per week but not every day, every day, or continuously and (b) In the past month, on average, how often did you awaken during the night or early morning because of asthma symptoms: never, $\leq 2$ times per week, $>2$ times per week but not every day, every day, or continuously. In addition, patients answered other questions concerning asthma symptoms, assessment of therapy, work and productivity loss, and asthma activity via a telephone interview just prior to randomization.

Data analysis

Analyses were performed using baseline data obtained during screening and during the run-in period for all randomized patients. Descriptive analyses (percentages, means, and associated 95% confidence intervals (CI)) were used to characterize the demographics and asthma phenotype of the cohort.

To understand the variability in asthma severity in a cohort with documented mild persistent asthma, the cohort was stratified by the degree of asthma symptoms experienced in the month before enrollment. Two groups were defined: a group who reported at least daily symptoms (more consistent with moderate persistent asthma), and a group with less frequent symptoms in the month before enrollment. Those who reported daily symptoms in the month before randomization did not have daily symptoms during the last 2 weeks of the run-in period and so were not excluded from the study. These groups were compared with respect to asthma resource use in the prior year and asthma control during the last 2 weeks of the 3-week placebo run-in period. An exploratory analytical comparison across these subgroups was performed. For continuous data, the group means were compared using the $t$-distribution and associated 95% CIs on the group difference. For discrete data, the group percentages were compared using exact 95% CIs on the difference of two binomial proportions.

Results

Cohort baseline characteristics

Nine hundred patients attended a screening visit for participation in MIAMI, 735 patients entered the
placebo run-in period, and 400 were randomized into the study. Of those patients who were not randomized, most (401 patients) were excluded for not meeting eligibility criteria; the most common reasons were FEV₁ too low, spirometry technique unacceptable, and β-agonist reversibility <12%.

The 400 randomized patients in the MIAMI study had been first treated for asthma at a mean age of 20.6 ± 16.1 years and were predominately female, white, and atopic (Table 1). The cohort met the NAEPP and GINA guidelines for mild persistent asthma during the last 2-weeks of the run-in period: daytime asthma symptoms per week (mean 3.6 ± 1.3 days), albuterol use per week (mean 3.5 ± 1.3 days), FEV₁ (mean 94.0 ± 9.9%), and number of nighttime awakenings (>2 per month but not >1 time per week: 34.8%; <2 per month: 65.3%; Table 1). Patients had evidence of airway reversibility or reactivity based either on a ≥12% increase in FEV₁ or PEF (55.5% and 77.3% of patients, respectively), methacholine PC₂₀ FEV₁ ≤12.5 mg/ml (1.3% of patients), or ≥15% decrease in FEV₁ after exercise (1.3% of patients).

Asthma burden in mild persistent asthma

Mild persistent asthma was associated with a substantial asthma burden both in the month and in the year before the study. In the previous year, 38.5% had at least one physician office visit for asthma worsening, 15.8% required a course of oral corticosteroid for an asthma flare-up, and 8.3% of patients reported an emergency department visit or hospitalization (Fig. 1). In addition, in the month before enrollment, 11.8% experienced daily symptoms (Fig. 2), and 28.3% reported moderate-to-severe limitations to normal activity (Fig. 3).

Based on the history of asthma symptoms from the month before the study, the cohort was stratified into those with at least daily symptoms and those with less-than-daily symptoms (n = 47 and n = 353, respectively). These two groups were similar with respect to demographic characteristics, atopic status, and FEV₁ (Table 2). During the run-in period, as previously described, all patients reported β-agonist use as less than daily on a questionnaire and had an FEV₁ greater than 80% predicted. However, during the last 2 weeks of the

**Table 1** Patient baseline characteristics.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Randomized patients</th>
<th>N = 400</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years (sd)</td>
<td>35.0 (14.2)</td>
<td></td>
</tr>
<tr>
<td>Males/females (%)</td>
<td>30.5/69.5</td>
<td></td>
</tr>
<tr>
<td>Ethnicity (% Caucasian)</td>
<td>81.0</td>
<td></td>
</tr>
<tr>
<td>Atopy, % positive Phadiatop</td>
<td>79.8 (n = 377)</td>
<td></td>
</tr>
<tr>
<td>Mean age first treated for asthma, years (sd)</td>
<td>20.6 (16.1)</td>
<td></td>
</tr>
<tr>
<td>FEV₁</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean liters (sd)</td>
<td>3.26 (0.7)</td>
<td></td>
</tr>
<tr>
<td>Mean % predicted (sd)</td>
<td>94.0 (9.9)</td>
<td></td>
</tr>
<tr>
<td>Nighttime awakenings (≤2 per month, &gt;2 per month) during the run-in period (%)</td>
<td>65.3/34.8</td>
<td></td>
</tr>
<tr>
<td>Mean β-agonist use, days/week (sd) during last 2-weeks of the run-in period</td>
<td>3.5 (1.3)</td>
<td></td>
</tr>
<tr>
<td>Mean daytime asthma symptoms, days/week (sd) during last 2-weeks of the run-in period</td>
<td>3.6 (1.3)</td>
<td></td>
</tr>
<tr>
<td>Mean RFDs as % of days in run-in period (sd) during last 2-weeks of the run-in period</td>
<td>57.6 (31.3) (n = 344)*</td>
<td></td>
</tr>
</tbody>
</table>

RFD: rescue-free day (no short-acting β-agonist or oral corticosteroids).

*Faulty electronic devices in 56 patients.
of asthma severity during the 2-week placebo run-in period, even among patients with mild persistent asthma. Despite mean FEV\textsubscript{1} levels of 94\% predicted, this cohort had a history in the past year of substantial medical resource utilization due to asthma, requirement for oral course of corticosteroids, and limitation of normal activity (Tables 1 and 2). In addition, 11.8\% of the cohort experienced asthma symptoms daily in the month before enrollment. This subgroup with recent daily symptoms experienced significantly fewer RFDs, more days with asthma symptoms, and greater use of rescue bronchodilator during the run-in period than those with less frequent symptoms. Moreover, the medical resource use for asthma of those with daily symptoms was greater in the year before enrollment, although this difference did not reach statistical significance (Table 2).

The presence of significant variability in disease expression in mild asthma is not surprising. Pauwels and colleagues noted a substantial disease burden, including life-threatening asthma exacerbations and need for systemic corticosteroid courses, in a large cohort of children and adults with recent-onset mild persistent asthma.\textsuperscript{24} Zhang and colleagues\textsuperscript{33} highlighted the short-term disease variability in FEV\textsubscript{1} and symptom measurements in a population of mild-to-moderate asthmatics and cautioned that awareness of this variability is necessary in assessing the impact of therapy. While the presence of such variability in disease expression may confound both the classification of asthma severity and the measured response to therapy, it nonetheless highlights the importance of daily treatment to reduce morbidity.

Few studies have been conducted exclusively in patients with mild persistent asthma. Based on expert opinion, the GINA\textsuperscript{11} and NAEPP\textsuperscript{1} guidelines recommend continuous daily use of controller therapy for mild persistent asthma, including ICS (preferred choice), cromolyn, nedocromil, and leukotriene modifiers to minimize the consequences of asthma in these patients.\textsuperscript{34,35} The evidence of substantial disease burden in mild persistent asthmatics presented in this study further supports the GINA and NAEPP guidelines and should foster physician awareness of the variability and impact of asthma in this cohort. Hopefully, this awareness will encourage them to treat this asthma subgroup more aggressively and appropriately with chronic controller medication.

Specific therapy choices for patients with mild asthma must be individualized and, ideally, should

Discussion

The present analysis of baseline characteristics of the MIAMI cohort documented variability in degree
be influenced by comparative data from trials conducted exclusively in patients with mild disease. Particularly because these patients are frequently asymptomatic and may not perceive a benefit of therapy, it is important to determine the efficacy and safety under well-controlled experimental conditions, as well as the patient’s perception of benefits from the drug and long-term adherence with treatment in a naturalistic setting, as in the design of the MIAMI study.

Studies of patients with mild persistent asthma present unique challenges. Recruitment of a mild cohort is difficult because patients who do not feel ill are reluctant to participate in a trial of daily controller medication. In the present study, more than two patients were screened for each patient finally fulfilling the requirement for randomization. Assessment of efficacy cannot be limited to indices of airway caliber, which are typically used to assess more severe forms of asthma, because they are already normal or near normal at baseline in

### Table 2 Baseline profile in subgroups related to symptom frequency in the month before enrollment.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Daily symptoms pre-study, N = 47</th>
<th>Less-than-daily symptoms pre-study, N = 353</th>
<th>Difference (daily-less-than-daily) (95% C.I.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age, years (SD)</td>
<td>33.2 (13.2)</td>
<td>35.2 (14.3)</td>
<td>-2.0 (–6.3, 2.4)</td>
</tr>
<tr>
<td>Females (%)</td>
<td>74.5</td>
<td>68.8</td>
<td>5.6 (–9.6, 21.2)</td>
</tr>
<tr>
<td>Caucasian (%)</td>
<td>83.0</td>
<td>80.7</td>
<td>2.2 (–12.4, 17.8)</td>
</tr>
<tr>
<td>Atopic dermatitis (%)</td>
<td>31.9 (n = 47)</td>
<td>21.9 (n = 352)</td>
<td>10.0 (–3.8, 27.4)</td>
</tr>
<tr>
<td>Atopy, % positive Phadiatop</td>
<td>80.0 (n = 45)</td>
<td>79.8 (n = 332)</td>
<td>0.2 (–15.2, 16.2)</td>
</tr>
<tr>
<td>History in past year</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emergency or hospital care (%)</td>
<td>14.9</td>
<td>7.4</td>
<td>7.5 (–2.7, 23.7)</td>
</tr>
<tr>
<td>Office visits (%)</td>
<td>42.6</td>
<td>38.0</td>
<td>4.6 (–10.5, 22.0)</td>
</tr>
<tr>
<td>Oral corticosteroid courses (%)</td>
<td>17.0</td>
<td>15.6</td>
<td>1.4 (–9.9, 18.2)</td>
</tr>
<tr>
<td>Run-in period</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;, Litters, mean (SD)</td>
<td>3.24 (0.6)</td>
<td>3.26 (0.8)</td>
<td>-0.02 (–0.25, 0.21)</td>
</tr>
<tr>
<td>% predicted, mean (SD)</td>
<td>93.1 (9.2)</td>
<td>94.2 (10.0)</td>
<td>-1.1 (–4.1, 2.0)</td>
</tr>
<tr>
<td>Daytime symptoms, days/week, mean (SD)</td>
<td>4.1 (1.5)</td>
<td>3.5 (1.3)</td>
<td>0.5 (0.1, 0.9)</td>
</tr>
<tr>
<td>RFDs as % of days, mean (SD)</td>
<td>46.8 (30.7) (n = 38)</td>
<td>58.9 (31.2) (n = 306)</td>
<td>-12.1 (–22.6, –1.6)</td>
</tr>
<tr>
<td>Nighttime awakenings (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;2 per month</td>
<td>46.8</td>
<td>33.1</td>
<td>13.7 (–1.6, 31.0)</td>
</tr>
<tr>
<td>≤2 per month</td>
<td>23.4</td>
<td>26.3</td>
<td>-2.9 (–18.5, 12.2)</td>
</tr>
<tr>
<td>Never</td>
<td>29.8</td>
<td>40.5</td>
<td>-10.7 (–26.2, 4.6)</td>
</tr>
<tr>
<td>β-agonist use, days/week, mean (SD)</td>
<td>3.9 (1.5)</td>
<td>3.5 (1.3)</td>
<td>0.4 (0.0, 0.8)</td>
</tr>
<tr>
<td>Limitation of normal activity (%)</td>
<td>80.9</td>
<td>72.0</td>
<td>8.9 (–6.1, 24.4)</td>
</tr>
<tr>
<td>Moderate-to-severe limitation of exercise (%)</td>
<td>53.2</td>
<td>41.4</td>
<td>11.8 (–3.6, 29.1)</td>
</tr>
</tbody>
</table>

RFD: rescue-free day.

### Figure 4 Baseline characteristics in subgroups related to recent symptom frequency. Bars represent the mean number of days per week (± standard error bars) during the last 2 weeks of the run-in period for daytime asthma symptoms (left), β-agonist rescue medication use (middle), or rescue-free days (right) based on daily symptoms (n = 47) versus less-than-daily symptoms (n = 353) during the month before enrollment. Black bars = daily symptoms 1 month before run-in; striped bars = less-than-daily symptoms 1 month before enrollment.
patients with mild disease. The rescue-free day was chosen as the primary endpoint in the MIAMI study because of its established responsiveness to treatment in a mild cohort and its reflection of the goals of treatment.

The burden of asthma experienced by patients with mild persistent asthma in the present analysis supports the recommendation of GINA and NAEPP to manage mild persistent asthma with daily controller therapy to decrease the risk of potentially life-threatening exacerbations and the need for rescue medication. Because of the scarcity of comparative studies in patients with mild persistent asthma, physicians are forced to choose between the various controllers recommended by the guidelines based on trials conducted in patients with more severe forms of asthma. To better assess this selection process, the MIAMI study has been designed to provide comparative data for a leukotriene receptor antagonist and an inhaled corticosteroid as monotherapy in patients meeting the strict definition for mild persistent asthma.

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