Long-term comparison of 3 controller regimens for mild-moderate persistent childhood asthma: The Pediatric Asthma Controller Trial

Christine A. Sorkness, PharmD,b Robert F. Lemanske, Jr., MD,b David T. Mauger, PhD,b Susan J. Boehmer, MA,a Vernon M. Chinchilli, PhD,9 Fernando D. Martinez, MD,a Robert C. Strunk, MD,1 Stanley J. Szefler, MD,1 Robert S. Zeiger, MD, PhD,de Leonard B. Bacharier, MD,1 Gordon R. Bloomberg, MD,1 Ronina A. Covar, MD,2 Theresa W. Guiltier, MD,a Gregory Heldt, MD,4 Gary Larsen, MD,e Michael H. Mellon, MD,6 Wayne J. Morgan, MD,a Mark H. Moss, MD,b Joseph D. Spahn, MD,c and Lynn M. Taussig, MD,f for the Childhood Asthma Research and Education Network of the National Heart, Lung, and Blood Institute

Tucson, Ariz, Madison, Wis, Denver, Colo, San Diego, Calif, St Louis, Mo, and Hershey, Pa

Background: More evidence is needed on which to base recommendations for treatment of mild-moderate persistent asthma in school-aged children.

Objective: The Pediatric Asthma Controller Trial (PACT) compared the effectiveness of 3 regimens in achieving asthma control.

Methods: A total of 285 children (ages 6-14 years) with mild-moderate persistent asthma on the basis of symptoms, and with FEV1 ≥ 80% predicted and methacholine FEV1 PC20 ≤ 12.5 mg/mL, were randomized to 1 of 3 double-blind 48-week treatments: fluticasone 100 μg twice daily (fluticasone monotherapy), fluticasone 100 μg/salmeterol 50 μg in the morning and salmeterol 50 μg in the evening (PACT combination), and montelukast 5 mg in the evening.

Results: Fluticasone monotherapy and PACT combination were comparable in many patient-measured outcomes, including percent of asthma control days, but fluticasone monotherapy was superior to montelukast for asthma control days (64.2% vs 52.5%; P = .004) and for all other control outcomes. Growth over 48 weeks was not statistically different (fluticasone, 5.3 cm; PACT combination, 5.3 cm; montelukast, 5.7 cm).

Disclosure of potential conflict of interest: C. A. Sorkness has consultant arrangements with GlaxoSmithKline and AstraZeneca, has received grant support from AstraZeneca, GlaxoSmithKline, Merck, Sanofi-Aventis, and TEVA Pharmaceuticals. L. B. Bacharier has received grant support from the NIH and NHLBI, and is on the speakers’ bureau for Merck, GlaxoSmithKline, AstraZeneca, and Genentech. R. A. Covar has received grant support from AstraZeneca. T. W. Guiltier has participated on an advisory board sponsored by GlaxoSmithKline and as a consultant in the design of Continuing Medical Education (CME) courses and for asthma for the Innovia Medical Educational Institute, and has received consultant fees from GlaxoSmithKline and stocks or revenue from speakers’ bureaus, research, or grant activities from GlaxoSmithKline, AstraZeneca, Merck, and Pfizer, and is on the speakers’ bureau for GlaxoSmithKline, AstraZeneca, SOMA Medical Education (CME), Innovia Medical Education Institute (CME), Antidote (formerly Medical World Conferences, CME), and Health Matters. G. Lansen has consultant arrangements with GlaxoSmithKline and Schering Plough, and has received grant support from the NIH. M. H. Mellon is on the speakers’ bureau for AstraZeneca, Schering Plough, and Altana. W. J. Morgan has consultant arrangements with Genentech and has patent licensing arrangements with the Wisconsin Alumni Research Foundation. J. D. Spahn has consultant arrangements with GlaxoSmithKline and AstraZeneca, has received grant support from Merck, AstraZeneca, and GlaxoSmithKline, and is on the speakers’ bureau for GlaxoSmithKline. L. M. Taussig has consultant arrangements with GlaxoSmithKline. The rest of the authors have declared that they have no conflict of interest.

Disclosure of potential conflict of interest: C. A. Sorkness has consultant arrangements with GlaxoSmithKline and AstraZeneca, has received grant support from AstraZeneca, GlaxoSmithKline, Merck, Sanofi-Aventis, and TEVA Pharmaceuticals. L. B. Bacharier has received grant support from the NIH and NHLBI, and is on the speakers’ bureau for Merck, GlaxoSmithKline, AstraZeneca, and Genentech. R. A. Covar has received grant support from AstraZeneca. T. W. Guiltier has participated on an advisory board sponsored by GlaxoSmithKline and as a consultant in the design of Continuing Medical Education (CME) courses and for asthma for the Innovia Medical Educational Institute, and has received consultant fees from GlaxoSmithKline and stocks or revenue from speakers’ bureaus, research, or grant activities from GlaxoSmithKline, AstraZeneca, Merck, and Pfizer, and is on the speakers’ bureau for GlaxoSmithKline, AstraZeneca, SOMA Medical Education (CME), Innovia Medical Education Institute (CME), Antidote (formerly Medical World Conferences, CME), and Health Matters. G. Lansen has consultant arrangements with GlaxoSmithKline and Schering Plough, and has received grant support from the NIH. M. H. Mellon is on the speakers’ bureau for AstraZeneca, Schering Plough, and Altana. W. J. Morgan has consultant arrangements with Genentech and has patent licensing arrangements with the Wisconsin Alumni Research Foundation. J. D. Spahn has consultant arrangements with GlaxoSmithKline and AstraZeneca, has received grant support from Merck, AstraZeneca, and GlaxoSmithKline, and is on the speakers’ bureau for GlaxoSmithKline. L. M. Taussig has consultant arrangements with GlaxoSmithKline. The rest of the authors have declared that they have no conflict of interest.

Available online December 12, 2006.

Reprint requests: Christine A. Sorkness, PharmD, K4/950 University of Wisconsin Clinical Science Center, 600 Highland Avenue, Madison, WI 53792-3244. E-mail: Sorkness@facstaff.wisc.edu.

0091-6749/532.00 © 2007 American Academy of Allergy, Asthma & Immunology doi:10.1016/j.jaci.2006.09.042
Conclusion: Both fluticasone monotherapy and PACT combination achieved greater improvements in asthma control days than montelukast. However, fluticasone monotherapy was superior to PACT combination in achieving other dimensions of asthma control. Growth was similar in all groups.

Clinical implications: Therefore, of the regimens tested, the PACT study findings favor fluticasone monotherapy in treating children with mild-moderate persistent asthma with FEV1 ≥ 80% predicted, confirming current guideline recommendations. (J Allergy Clin Immunol 2007;119:64-72.)

Key words: Childhood asthma, fluticasone propionate, salmeterol, montelukast, asthma control days, FEV1, forced vital capacity, maximum bronchodilator response, exhaled nitric oxide, methacholine PC20, Asthma Control Questionnaire

Although children with mild to moderate persistent asthma benefit from daily maintenance medication to prevent symptoms and exacerbations,1 the regimen with the best benefit/risk ratio is not defined. Inhaled corticosteroids (ICSs) are effective in controlling childhood asthma2 and decreasing bronchial responsiveness2 and indirect markers of airway inflammation.3 However, in currently recommended doses, ICSs are associated with mild reduction in growth velocity.2 These growth effects are a concern for parents and clinicians alike, in spite of the fact that continuous ICS treatment does not seem to affect the attainment of final adult height.4 Therefore, achievement of asthma control with the lowest possible dose of ICS remains central to the treatment of childhood asthma.

Oral leukotriene receptor antagonists (LTRAs) are an alternative to ICSs. Although these medications are safe and have been shown to improve symptoms in children,5 available evidence suggests that ICSs provide better asthma control,6 lung function,7 and capacity to prevent exacerbations than LTRAs.8 Another alternative is to add long-acting β-agonists (LABAs) to ICSs to allow reduction in ICS dose.9 However, the potential role of LABAs in childhood asthma is not as well defined as in adults,10-13 and it could perhaps worsen some outcomes.14 Parents, as well as some clinicians, are concerned about the use of high doses of ICSs. Whereas some studies have suggested that once-daily ICSs are less effective than twice-daily administered doses,15,16 we believed that it was essential to evaluate the ability of LABAs to allow once-daily ICSs in children with mild-moderate asthma to test the feasibility of using a lower daily dose in children.

The Pediatric Asthma Controller Trial (PACT) was designed to determine whether, in children with mild to moderate persistent asthma, similar or greater efficacy with less potential for growth effects could be achieved if a LABA was added to half the dose of ICSs known to be efficacious in controlling asthma symptoms, to reduce total ICS exposure. In addition, the PACT was designed to define the relative efficacy and safety of an LTRA compared with the other 2 treatments.

Abbreviations used

ACQ: Asthma Control Questionnaire
eNO: Exhaled nitric oxide
FVC: Forced vital capacity
ICS: Inhaled corticosteroid
LABA: Long-acting β-agonist
LTRA: Leukotriene receptor antagonist
PACT: Pediatric Asthma Controller Trial
PEF: Peak expiratory flow

METHODS

Study participants

Participants were recruited at Childhood Asthma Research and Education Network centers between October 2002 and January 2004 (see this article’s Online Repository at www.jacionline.org). Each center’s Institutional Review Board approved the study, and parents/guardians provided informed consent, with verbal assent given by children younger than 7 years, and written assent from older children. Inclusion criteria were physician-diagnosed asthma, age 6 to less than 14 years, ability to perform reproducible spirometry,17 an FEV1 (measured more than 4 hours since the most recent use of a bronchodilator) ≥80% predicted normal at screening and ≥70% predicted normal at randomization, and a methacholine FEV1 PC20 ≤12.5 mg/mL. All children had mild-moderate persistent asthma, as defined by diary-reported symptoms or β-agonist use (not including pre-exercise) or peak flows < 80% calculated from the mean of morning and evening peak flows obtained during the final week of the run-in period, on average at least 3 times per week. Exclusion criteria included other lung diseases; respiratory tract infection, asthma exacerbation, or systemic corticosteroid use within 4 weeks; 2 or more asthma hospitalizations in the past year; history of a life-threatening asthma exacerbation; ≥4 courses of systemic corticosteroids in the past year; cigarette smoking within the past year; pregnancy or lactation; failure to practice abstinence or use a medically acceptable birth control method; and history of adverse reactions to the PACT medications. Enrolled children were not on controller medications for at least 2 weeks before randomization. Participants were excluded if they were unable to use the study drug delivery systems or to adhere with ≥75% of doses during the run-in.

Protocol

All children were enrolled in a run-in period of 2 to 4 weeks, during which they received a morning and evening placebo Diskus (GlaxoSmithKline, Research Triangle Park, NC), an evening placebo capsule, and open-label albuterol metered dose inhaler (MDI) as rescue. The purpose of the run-in period was to document that the subjects had mild-moderate asthma by symptom criteria, had FEV1 ≥80% predicted, and otherwise qualified for study inclusion. It also allowed us to characterize the asthma phenotype. This run-in period also allowed for evaluation of adherence to the study regimen and procedures. After the run-in, participants were assigned to 1 of 3 treatments: fluticasone propionate 100 μg morning and 100 μg evening (Flovent Diskus; GlaxoSmithKline) plus placebo oral drug in the evening (hereafter referred to as fluticasone monotherapy); fluticasone propionate 100 μg/salmeterol 50 μg (Advair Diskus; GlaxoSmithKline) in the morning and salmeterol 50 μg (Serevent Diskus; GlaxoSmithKline) in the evening plus placebo oral drug in the evening (hereafter referred to as PACT combination); or placebo Diskus in the morning and placebo Diskus in the evening plus montelukast 5 mg (Singulair; Merck, Whitehouse Station, NJ) in the evening (hereafter referred to as montelukast; Fig 1). All

VOLUME 119, NUMBER 1
J ALLERGY CLIN IMMUNOL
Sorkness et al 65

Asthma diagnosis and treatment
Diskus devices looked identical. Treatment assignment followed a double-blind, randomized parallel group design, stratified by center. Within each center, a stratified randomization scheme was applied on the basis of bronchodilator response (<12% or ≥12% change in FEV₁), race (white or nonwhite), and methacholine FEV₁ PC₂₀ (<2 or ≥2 mg/mL).

Flovent, Advair, Serevent, and matching placebo Diskus were donated by GlaxoSmithKline (see this article’s Online Repository at www.jacionline.org). Singulair 5-mg chewable tablets were purchased. Proclinical Pharmaceutical Services overencapsulated the tablets in accordance with United States Pharmacopeia standards to make identical active drug and placebo opaque capsules.

Electronic peak expiratory flow (PEF) measurements (AM1; Jaeger-Toenies GmbH, Hoechburg, Germany), asthma symptom scores, and albuterol use were recorded manually in diaries twice daily. Adherence to inhaled medication was estimated from the Diskus dose indicator, and oral medication adherence was assessed on the basis of capsule count and an Electronic Drug Exposure Monitor (AARDEX Ltd, Zug, Switzerland; see this article’s Online Repository at www.jacionline.org).

Participants received albuterol MDI (Ventolin; GlaxoSmithKline), prednisone, and an action plan to guide use. A standardized prednisone course was initiated for an asthma exacerbation if predetermined criteria were met.

Asthma was characterized before treatment by Childhood Asthma Research and Education Network procedures previously described. During the 12 months of treatment, participants were evaluated at visits at intervals of 6 to 12 weeks, as described in Fig 1. Methacholine FEV₁ PC₂₀ was performed at week 48 and maximal postbronchodilator spirometry at week 36. Short-acting bronchodilators were withheld at least 4 hours before these procedures, and study medications were withheld ≥12 hours before these measurements.

**Outcome variables**

The primary outcome was the percent of asthma control days during the 48-week treatment period. An asthma control day was defined as a day without albuterol rescue use (pre-exercise treatment permitted); use of oral corticosteroids for asthma; use of nonstudy asthma medications; daytime symptoms; nighttime awakenings; unscheduled health care visits, emergency department visits, or hospitalizations for asthma; and school absenteeism for asthma. Other measures of asthma control used in secondary analyses included percent of episode-free days (an asthma control day plus daily peak flows ≥80% of personal best), number of exacerbations requiring prednisone and time to the first exacerbation requiring prednisone, time to treatment failure, and the 7-item Asthma Control Questionnaire (ACQ).

Subjects who failed to respond to treatment who continued study visits were defined as those with hospitalization, hypoxic seizure, or intubation; requirement for a third prednisone burst for an exacerbation; or a significant adverse event related to study medication. Study dropouts were defined as those with withdrawal of consent or assent, pregnancy, or physician assessment.

**Sample size and statistical analysis**

The sample size of 275 participants provided 90% statistical power for detecting a difference of 20% asthma control days.
TABLE I. Baseline characteristics of the participants, according to treatment group*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Fluticasone</th>
<th>Combination</th>
<th>Montelukast$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants (n)</td>
<td>96</td>
<td>94</td>
<td>95</td>
</tr>
<tr>
<td>Age (y)</td>
<td>9.8 ± 2.2</td>
<td>10.3 ± 2.1</td>
<td>9.6 ± 2.2</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>57 (59.4)</td>
<td>61 (64.9%)</td>
<td>57 (60.0)</td>
</tr>
<tr>
<td>Minority, n (%)</td>
<td>45 (46.9)</td>
<td>42 (44.7)</td>
<td>41 (43.2)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>138.6 ± 13.5</td>
<td>141.9 ± 14.4</td>
<td>138.2 ± 13.8</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>40.6 ± 17.6</td>
<td>42.4 ± 16.3</td>
<td>38.3 ± 14.7</td>
</tr>
<tr>
<td>Age at doctor’s asthma diagnosis (y)</td>
<td>4.2 ± 3.1</td>
<td>4.3 ± 2.7</td>
<td>3.8 ± 3.0</td>
</tr>
<tr>
<td>Age at onset asthma symptoms (y)</td>
<td>3.5 ± 2.9</td>
<td>3.2 ± 2.6</td>
<td>2.9 ± 2.6</td>
</tr>
<tr>
<td>Asthma control days during run-in period (%)</td>
<td>30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum IgE (kU/L)</td>
<td>321</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum eosinophil cationic protein (µg/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medication use in previous year</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inhaled/nebulized ICS, n (%)</td>
<td>58 (60.4%)</td>
<td>48 (51.1%)</td>
<td>55 (57.9%)</td>
</tr>
<tr>
<td>Leukotriene modifier, n (%)</td>
<td>28 (29.2%)</td>
<td>29 (30.9%)</td>
<td>38 (40.0%)</td>
</tr>
<tr>
<td>LABA, n (%)</td>
<td>10 (10.4%)</td>
<td>14 (14.9%)</td>
<td>14 (14.7%)</td>
</tr>
<tr>
<td>Theophylline, n (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cromolyn/nedocromil, n (%)</td>
<td>0</td>
<td>1 (1.1%)</td>
<td>1 (1.1%)</td>
</tr>
<tr>
<td>≥1 Prednisone courses, n (%)</td>
<td>25 (26.0%)</td>
<td>33 (35.1%)</td>
<td>22 (23.2%)</td>
</tr>
<tr>
<td>Bronchodilator FEV1 (% predicted)</td>
<td>97.8 ± 12.2</td>
<td>96.8 ± 11.2</td>
<td>97.7 ± 13.6</td>
</tr>
<tr>
<td>Bronchodilator FEV1/FVC (%)</td>
<td>80.2 ± 7.4</td>
<td>79.5 ± 7.4</td>
<td>80.1 ± 8.3</td>
</tr>
<tr>
<td>Average AM peak flow during run-in period (L/min)</td>
<td>249.3 ± 68.4</td>
<td>253.0 ± 71.2</td>
<td>241.2 ± 66.8</td>
</tr>
<tr>
<td>Peak flow variability during run-in period (%)</td>
<td>9.9 ± 5.7</td>
<td>10.0 ± 5.0</td>
<td>9.9 ± 5.2</td>
</tr>
<tr>
<td>Asthma control days during run-in period (%)</td>
<td>30 ± 24</td>
<td>24 ± 23</td>
<td>27 ± 23</td>
</tr>
<tr>
<td>Methacholine PC20 during run-in period, mg/mL, median (Quartile 1, Quartile 3)</td>
<td>0.93 (0.30, 2.72)</td>
<td>0.78 (0.33, 2.77)</td>
<td>0.93 (0.28, 2.51)</td>
</tr>
</tbody>
</table>

*Differences not significant for any characteristic across treatment groups.
†Fluticasone: 100 µg DPI twice a day (BID).
‡Combination: fluticasone 100 µg DPI AM and salmeterol 50 µg BID.
§Montelukast: 5 mg at bedtime (PM).
||Seven-point scale; 0 = total control, 6 = extremely poor control.

(approximately 6 extra days per month) between any 2 treatment groups. This increase in 20% asthma control days could translate into 1 fewer day of symptoms per 5-day school week, a magnitude that we considered clinically meaningful. This analysis was performed at the .0167 significance level based on the Bonferroni correction, 2-tailed. Secondary analyses were performed at the .05 significance level, 2-tailed. All analyses were performed under the intent-to-treat paradigm.

Characteristics at baseline were summarized using descriptive statistics and compared across treatments using ANOVA for continuous measures and Fisher exact test for categorical measures.

The primary analysis of asthma control days consisted of the 3 pairwise comparisons by ANOVA with post hoc pairwise comparisons of group means. The reported P values are unadjusted and should be evaluated at the .0167 significance level. Other outcomes including percent predicted FEV1, FEV1/forced vital capacity (FVC), methacholine FEV1 PC20, maximum bronchodilator response, exhaled nitric oxide (eNO), ACQ, monthly asthma control days, monthly episode-free days, and growth were examined as change from baseline. Secondary analyses with these outcomes used ANOVA with post hoc pairwise comparisons to compare treatments, but evaluated at the .05 significance level. Time until significant asthma exacerbation was displayed by the Kaplan-Meier method and the log-rank test used in a pairwise fashion to compare treatments. Growth was defined as the change in height from baseline to study end.

RESULTS

Study cohort

Of the 648 participants screened, 285 were randomized, with 252 (88.4%) completing the study. There were no statistically significant differences in withdrawals across groups (Fig 1). The 3 treatment groups were well balanced, with baseline characteristics consistent with guideline definitions of mild-moderate persistent disease (Table I). There were 97% completed visits and 78% completed phone contacts, and there was 95% adherence to diary entries. Adherence to study medications estimated from Diskus indicator was 90% (interquartile range, 86.0% to 97.7%) and from Electronic Drug Exposure Monitor records was 86% (interquartile range, 77.5% to 96.9%).

Asthma control outcomes

During the 48 weeks, the percent of asthma control days averaged 64.2% for fluticasone monotherapy, 59.6% for PACT combination, and 52.5% for montelukast monotherapy. The fluticasone monotherapy group gained an
average of 42 asthma control days per year compared with the montelukast monotherapy group ($P = .004$). The change in asthma control days from baseline to end of treatment was significantly greater for fluticasone monotherapy versus montelukast and PACT combination versus montelukast but not for fluticasone monotherapy versus PACT combination (Fig 2, A; Table II). The percentages of children who achieved 20% more asthma control days during the treatment period compared with the run-in period were 65% for fluticasone monotherapy, 66% for PACT combination, and 50% for montelukast. The number needed to treat for both fluticasone monotherapy and PACT combination compared with montelukast was approximately 6.5, meaning that 7 children would need to be treated with fluticasone monotherapy or PACT combination instead of montelukast to achieve 1 additional treatment response defined as a 20% increase in asthma control days. Compared with montelukast monotherapy, both fluticasone monotherapy and PACT combination led to a greater percentage of episode-free days (Table II).

Kaplan-Meier survival curves showed significant superiority of fluticasone compared with montelukast monotherapies (in favor of the former) for time to first prednisone burst ($P = .002$; Fig 2, B) and time to treatment failure ($P = .015$; Fig 2, C), but no differences for PACT combination versus montelukast. Twenty-eight treatment failures occurred, 5 with fluticasone, 8 with PACT combination, and 15 with montelukast, with the comparison for fluticasone versus montelukast monotherapies significant ($P = .04$). Twenty-five of the 28 treatment failures (89%) were a result of the third prednisone burst for an exacerbation, and 3 were a result of an asthma hospitalization (0 with fluticasone monotherapy, 2 with PACT combination, 1 with montelukast). There were no treatment failures caused by serious adverse events from study medications.

There was no significant difference between fluticasone monotherapy versus PACT combination or PACT combination versus montelukast in regard to ACQ score improvement, although there was a significant difference favoring fluticasone compared with montelukast ($P = .018$; Fig 3, A, and Table II).

**Pulmonary function measures outcomes**

Prebronchodilator FEV$_1$ (% predicted) and FEV$_1$/FVC (%) increased more with fluticasone monotherapy than montelukast ($P < .001$ for both measures) and PACT combination ($P = .01$ for FEV$_1$; Fig 3, C and D; Table II). Treatment with montelukast did not improve these lung function measures. The mean change in FEV$_1$ % predicted from baseline was 6.32% with fluticasone monotherapy and 3.62% with PACT combination ($P = .06$ for difference; Table II). For FEV$_1$/FVC, the mean change from baseline was 3.95% for fluticasone monotherapy, compared with 1.76% for PACT combination ($P = .015$ for difference; Table II). Change in bronchodilator response at 36 weeks compared with baseline was a mean decrease of 3.6% with fluticasone monotherapy, compared with...
a 0.3% increase with PACT combination and a 1.69% increase with montelukast ($P < .001$, fluticasone vs montelukast; Table II).

For the participant-measured outcome of percent predicted prebronchodilator morning and evening PEFs, fluticasone monotherapy and PACT combination resulted in comparable increases in mean change from baseline (5.1% and 5.4%, respectively, for morning recordings, and 2.9% and 4.3%, respectively, for evening recordings; Table II). Montelukast treatment did not significantly improve peak flow measurements. Both fluticasone and PACT combination were significantly superior to montelukast for change from baseline in both PEF measurements (Table II).

Exhaled nitric oxide was significantly reduced by 59% by 6 weeks of fluticasone monotherapy and maintained throughout the study. This reduction was significantly
greater than achieved by either PACT combination ($P < .001$) or montelukast ($P < .001$; Fig 3, B; Table II).

Methacholine PC$_{20}$ improved by 2.65 doubling doses with fluticasone monotherapy, compared with a 1.03 doubling dose change with PACT combination ($P < .001$), and a 0.62 doubling dose change with montelukast ($P < .001$; Table II).

**Growth effects**

The unadjusted and intent-to-treat mean increase in height from baseline over 48 weeks was 5.3 ± 1.8 cm with fluticasone monotherapy, 5.3 ± 1.5 cm with PACT combination, and 5.7 ± 2.0 cm with montelukast monotherapy (Table II). Differences among the therapies in this outcome were about 0.4 to 0.46 cm less for fluticasone monotherapy and PACT combination compared with montelukast monotherapy, respectively, but these differences were not statistically significant, including when age-stratified (data not shown).

**DISCUSSION**

The PACT is the first trial in which the long-term efficacy and safety of 3 daily asthma controller regimens were compared in a single pediatric study. Once-daily fluticasone 100 μg together with 50 μg salmeterol twice daily (PACT combination) and twice the dose of ICS (100 μg twice daily) had very similar efficacy in both controlling symptoms and preventing exacerbations. However, PACT combination did not achieve other important dimensions of asthma control as well as fluticasone monotherapy including improvements in lung function, eNO, bronchial reactivity, and maximum bronchodilator response (Table II; Fig 3). Montelukast was not as effective as the other 2 treatments (Table II; Figs 2 and 3). Thus, in school-aged children with mild to moderate asthma, fluticasone monotherapy achieved the highest level of asthma control, without significant side effects. PACT confirms other studies$^{7,8,21,22}$ that have concluded montelukast is not as effective as ICSs with respect to most asthma control outcomes examined. However, it is possible that there are individuals with specific genotypic or phenotypic characteristics who are particularly responsive to LTRAs.

The efficacy of adding LABAs to ICSs was equivalent to using twice the dose of ICSs for patient-centered outcomes, similar to the findings of Verberne et al$^{12}$ in which asthma control outcomes were assessed in children treated for 54 weeks with twice-daily doses of beclometasone 200 μg (a dose equipotent to PACT fluticasone...
monotherapy arm), beclomethasone 400 μg, or beclomethasone 200 μg plus salmeterol 50 μg. Verberne et al. concluded that patient-centered outcomes were very similar in these 3 groups. These findings and ours differ, however, from those reported in adults, in whom the addition of salmeterol to a standard dose of ICSs produced better asthma control outcomes than doubling the dose of ICSs. Why results of pediatric studies differ from those performed in adults remains unknown. Most of the adult studies have used a positive response to bronchodilators and/or diminished baseline airflow function as criteria for entry, and this may have biased the results in favor of LABAs. Conversely, in our study and in the study by Verberne et al., bronchial responsiveness to methacholine was an entry criterion, potentially favoring ICSs. Moreover, we intentionally enrolled children in the PACT on the basis of the criteria of sufficient symptom frequency but with FEV1 values ≥80%; these children were perhaps not as likely to respond to LABAs as those with lower FEV1 values. These differences between studies may suggest that asthma phenotypic characteristics determine whether an individual will respond better to addition of LABA to ICSs or to increasing doses of ICSs. These considerations notwithstanding, and on the basis only of patient-centered outcomes, our results could suggest that PACT combination, even when the ICS is used once daily and in low doses, could allow for lower ICS exposure in children. However, comparison of the 2 treatments with respect to several other dimensions of asthma control does not support this conclusion. In fact, fluticasone monotherapy provided significantly more improvement in lung function and in bronchial hyperresponsiveness and greater reduction in eNO than PACT combination. In addition, and for several of these other outcomes, PACT combination was not superior to montelukast, which in turn was inferior to fluticasone monotherapy for all assessed asthma control outcomes. Again, these results differ from those of Verberne et al., who showed both lung function and bronchial hyperresponsiveness to be similar in the 3 study groups at the end of the trial. There are several possible explanations for this discrepancy. The dose of beclomethasone used by Verberne et al. in the combination arm was approximately twice the amount of equipotent ICSs used in the same arm in our study. It is thus possible that the ICS dose used in PACT combination was sufficient to control symptoms and exacerbations, but insufficient to control airway inflammation effectively. It is also possible that the once-daily ICS use, as in PACT combination, may be less effective in improving airway function and inflammation when ICS is used twice daily as monotherapy. A recent meta-analysis concluded that use of fluticasone once daily, although effective in controlling asthma symptoms, was less effective than using the same total daily dose but divided into 2 administrations. Other trials have demonstrated the effectiveness of low-dose fluticasone even administered once daily. However, the comparability of PACT combination to twice the ICS dose in achieving our primary study outcomes suggests that the argument is moot and that salmeterol has the potential to allow lower doses of ICS in children with mild-moderate asthma.

Of particular importance in our trial was the lack of evidence that the lower dose of fluticasone in PACT combination was superior to full-dose fluticasone with respect to growth effects (Table II). Throughout our trial, comparable growth velocities were observed in fluticasone monotherapy, PACT combination, and montelukast monotherapy. The lack of a significant effect of ICSs in both PACT arms may be a result of the influence of previous ICSs before enrollment, if growth effects of ICSs are limited to the early phases of treatment. Nevertheless, given the greater number and range of dimensions of asthma control achieved with fluticasone monotherapy compared with PACT combination, the recent concern about the use of LABAs and the lack of any differences in growth effects between these 2 controller regimens, the PACT results do not support the use of this particular combination regimen as an ICS-sparing strategy in children. Therefore, of the regimens tested, our study findings favor fluticasone monotherapy in treating children with mild to moderate persistent asthma (documented with bronchial responsiveness) with FEV1 ≥ 80% predicted. Of note, however, is that the maximum asthma control days (a high bar, indeed) achieved was still only 64.2% with fluticasone monotherapy. Thus, in children not well controlled on low-dose ICS monotherapy, this observation suggests the need for future studies designed to compare the relative efficacy and safety of higher doses of ICSs versus similar (low) doses in combination with adjunctive therapies such as LABAs and LTRAs to determine which options are capable of achieving optimal control to the greatest extent possible.

REFERENCES


