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,[g] Susan J. Boehmer, MA,[g] Vernon M. Chinchilli, PhD,[g] Fernando D. Martinez, MD,[a] Robert C. Strunk, MD,[f] Stanley J. Szefler, MD,[c] Robert S. Zeiger, MD, PhD,[d,e] Leonard B. Bacharier, MD,[f] Gordon R. Bloomberg, MD,[f] Ronina A. Covar, MD,[c] Theresa W. Guilbert, MD,[a] Gregory Heldt, MD,[d] Gary Larsen, MD,[c] Michael H. Mellon, MD,[e] Wayne J. Morgan, MD,[a] Mark H. Moss, MD,[b] Joseph D. Spahn, MD,[c] and Lynn M. Taussig, MD,[c] 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 $FEV_1 \geq 80\%$ predicted and methacholine FEV_1 $PC_{20} \leq 12.5$ 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. Outcomes included asthma control days (primary outcome), exacerbations, humanistic measurements, and pulmonary function measurements.

Results: Fluticasone monotherapy and PACT combination were comparable in many patient-measured outcomes, including percent of asthma control days, but fluticasone monotherapy was superior for clinic-measured FEV_1/forced vital capacity ($P = .015$), maximum bronchodilator response ($P = .009$), exhaled nitric oxide ($P < .001$), and PC_{20} ($P < .001$). 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).

From [a]the Arizona Respiratory Center, University of Arizona, Tucson; [b]the Clinical Science Center, University of Wisconsin, Madison; [c]the Department of Pediatrics, National Jewish and Research Center and University of Colorado Health Sciences Center, Denver; [d]the Department of Pediatrics, University of California–San Diego; [e]the Department of Allergy, Kaiser Permanente, San Diego; [f]the Department of Pediatrics, Washington University, St Louis; and [g]the Department of Health Evaluation Sciences, Pennsylvania State University, Hershey.

Supported by grants HL064307, HL64288, HL064295, HL64287, and HL064305 from the National Heart, Lung and Blood Institute. This study was performed in part by the General Clinical Research Centers at Washington University School of Medicine (M01 RR00036), National Jewish Medical and Research Center (M01 RR00051), and the University of Wisconsin (M01 RR03186).

Disclosure of potential conflict of interest: C. A. Sorkness has consultant arrangements with GlaxoSmithKline and AstraZeneca, has received grant support from GlaxoSmithKline and Pharmaxis, and is on the speakers' bureau for GlaxoSmithKline and Genentech. R. F. Lemanske has consultant arrangements with GlaxoSmithKline, Merck, AstraZeneca, Aventis, and Novartis, has received grant support from the National Heart, Lung, and Blood Institute (NHLBI), and is on the speakers' bureau for Merck, AstraZeneca, GlaxoSmithKline, and Aventis. D. T. Mauger, S. J. Boehmer, and V. M. Chinchilli have received grant support from the National Institutes of Health (NIH). F. D. Martinez has had consultant arrangements with Genentech and Pfizer, has served on the advisory board for Merck, and has received an honorarium for a lecture at a meeting sponsored by Merck. S. J. Szefler has consultant arrangements with AstraZeneca, GlaxoSmithKline, Aventis, Genentech, and Merck, and has received grant support from the NIH, NHLBI, National Institute of Allergy and Infectious Diseases, and Ross Pharmaceuticals. R. S. Zeiger has consultant arrangements with Aerocrine, AstraZeneca, Genentech, GlaxoSmithKline, Merck, Novartis, and Sanofi-Aventis, and 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. Guilbert 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. Larsen 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.

Received for publication June 9, 2006; revised August 30, 2006; accepted for publication September 5, 2006.

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/$32.00

© 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 $FEV_1 \geq 80\%$ predicted, confirming current guideline recommendations. (J Allergy Clin Immunol 2007;119: 64-72.)

Key words: *Childhood asthma, fluticasone propionate, salmeterol, montelukast, asthma control days, FEV_1, forced vital capacity, maximum bronchodilator response, exhaled nitric oxide, methacholine PC_{20}, 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 asthma[2] and decreasing bronchial responsiveness[2] 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 FEV_1 (measured more than 4 hours since the most recent use of a bronchodilator) $\geq$80% predicted normal at screening and $\geq$70% predicted normal at randomization, and a methacholine FEV_1 PC_{20} $\leq$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; $\geq$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 $\geq$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 FEV_1 $\geq$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

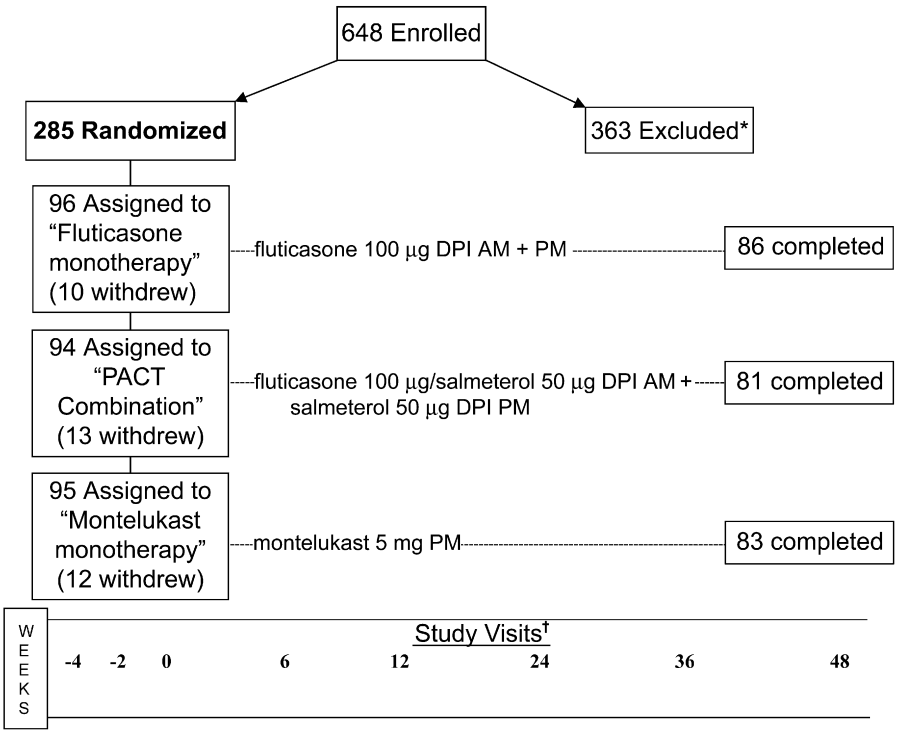

FIG 1. Cascade of enrollment. *Reasons for exclusion during the run-in period were mild intermittent asthma classification (n = 84), severe persistent asthma classification (n = 36), nonadherent/exclusionary medication use (n = 47), inability to swallow study capsule (n = 39), FEV_1 < 80% predicted at screen (n = 42), upper respiratory infection/prednisone burst (n = 36), PC_{20} > 12.5 mg/mL (n = 38), withdrew consent (n = 21), inability to perform spirometry (n = 13), and other reasons (n = 7). †Study visit activities included spirometry, impulse oscillometry, eNO, adherence review, asthma control and health care utilization questionnaire, adverse event evaluation, and height measurement via calibrated stadiometer.

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 FEV_1), race (white or nonwhite), and methacholine FEV_1 PC_{20} (<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[18] 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.[19] During the 12 months of treatment, participants were evaluated at visits at intervals of 6 to 12 weeks, as described in Fig 1. Methacholine FEV_1 PC_{20} 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),[2] 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).[20] Pulmonary function and growth were additional secondary outcomes.

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*

Characteristic	Fluticasone†	Combination‡	Montelukast§
Participants (n)	96	94	95
Age (y)	9.8 ± 2.2	10.3 ± 2.1	9.6 ± 2.2
Male sex, n (%)	57 (59.4)	61 (64.9%)	57 (60.0)
Minority, n (%)	45 (46.9)	42 (44.7)	41 (43.2)
Height (cm)	138.6 ± 13.5	141.9 ± 14.4	138.2 ± 13.8
Weight (kg)	40.6 ± 17.6	42.4 ± 16.3	38.3 ± 14.7
Age at doctor's asthma diagnosis (y)	4.2 ± 3.1	4.3 ± 2.7	3.8 ± 3.0
Age at onset asthma symptoms (y)	3.5 ± 2.9	3.2 ± 2.6	2.9 ± 2.6
Atopic, n (%)	75 (78.1)	74 (78.7)	73 (76.8%)
Serum IgE (kU/L)	321 ± 419	344 ± 552	311 ± 406
Blood eosinophils (%)	6.0 ± 3.8	5.9 ± 4.6	6.0 ± 4.0
Serum eosinophil cationic protein (μg/L)	25 ± 26	22 ± 20	26 ± 38
Urinary leukotriene E_4 (pg/mg creatinine)	106 ± 51	114 ± 81	112 ± 65
Medication use in previous year			
Inhaled/nebulized ICS, n (%)	58 (60.4%)	48 (51.1%)	55 (57.9%)
Leukotriene modifier, n (%)	28 (29.2%)	29 (30.9%)	38 (40.0%)
LABA, n (%)	10 (10.4%)	14 (14.9%)	14 (14.7%)
Theophylline, n (%)	0	0	0
Cromolyn/nedocromil, n (%)	0	1 (1.1%)	1 (1.1%)
≥1 Prednisone courses, n (%)	25 (26.0%)	33 (35.1%)	22 (23.2%)
Prebronchodilator FEV_1 (% predicted)	97.8 ± 12.2	96. 8 ± 11.2	97.7 ± 13.6
Prebronchodilator FEV_1/FVC (%)	80.2 ± 7.4	79.5 ± 7.4	80.1 ± 8.3
Maximum bronchodilator response (%)	10.9 ± 7.1	10.1 ± 8.5	10.9 ± 7.4
Average AM peak flow during run-in period (L/min)	249.3 ± 68.4	253.0 ± 71.2	241.2 ± 66.8
Average PM peak flow during run-in period (L/min)	256.6 ± 69.8	259.7 ± 72.7	246.2 ± 65.4
Peak flow variability during run-in period (%)	9.9 ± 5.7	10.0 ± 5.0	9.9 ± 5.2
Asthma control days during run-in period (%)	30 ± 24	24 ± 23	27 ± 23
Asthma control questionnaire‖	1.1 ± 0.6	1.1 ± 0.6	1.2 ± 0.6
ENO, ppb, median (Quartile 1, Quartile 3)	24.5 (11.9, 52.1)	24.8 (11.3, 51.7)	27.1 (12.4, 55.2)
Methacholine PC_{20} during run-in period, mg/mL, median (Quartile 1, Quartile 3)	0.93 (0.30, 2.72)	0.78 (0.33, 2.77)	0.93 (0.28, 2.51)

*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 FEV_1, FEV_1/forced vital capacity (FVC), methacholine FEV_1 PC_{20}, 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[1] 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

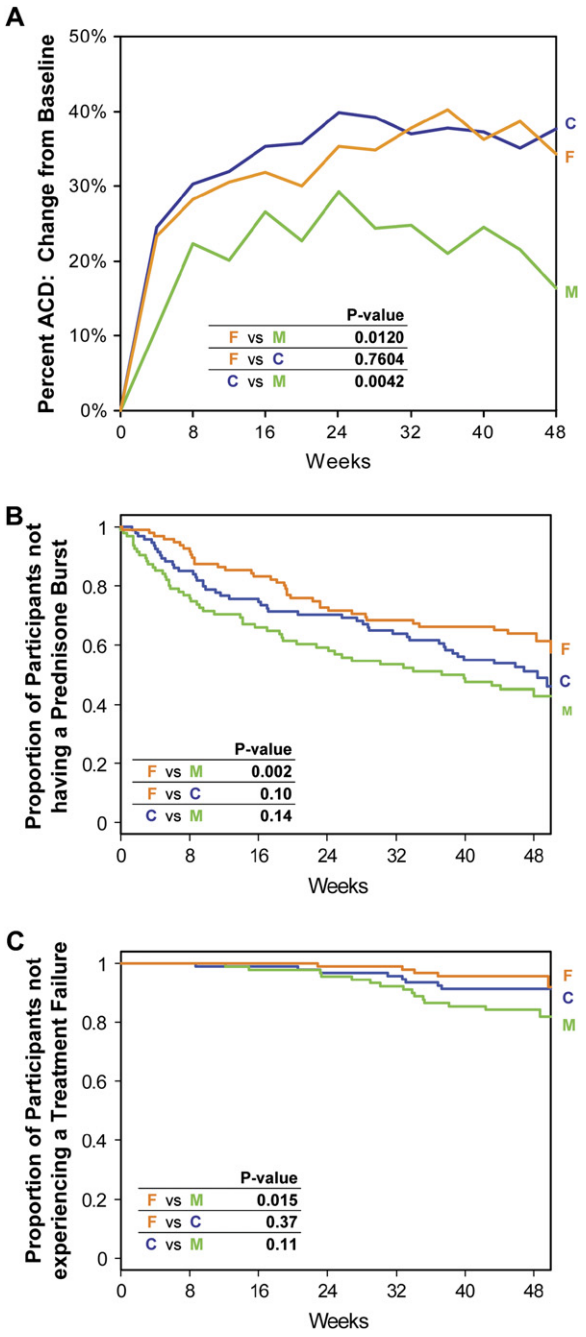

FIG 2. A, Biweekly average of the percentage of asthma control days change from baseline during the 48-week treatment period for the 3 treatment groups: PACT combination therapy *(C)*, fluticasone monotherapy *(F)*, and montelukast monotherapy *(M)*. The 3 treatment groups were compared longitudinally across the entire study period by repeated-measures ANOVA. *P* values given are those associated with the main-effect comparison of the 2 study groups indicated for that *P* value. **B and C,** Kaplan-Meier estimates for times to first course of prednisone and times to treatment failure for the 3 treatments: PACT combination therapy, fluticasone monotherapy, and montelukast monotherapy. *P* values given are those associated with the log-rank test comparison of the 2 study groups indicated for that *P* value. *ACD,* Asthma control days.

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

TABLE II. PACT primary and secondary outcome measures

Outcome	Fluticasone* (F) N = 96 Mean (95% CI)	Combination† (C) N = 94 Mean (95% CI)	Montelukast‡ (M) N = 95 Mean (95% CI)	F vs M Difference (95% CI) *P* value	F vs C Difference (95% CI) *P* value	C vs M Difference (95% CI) *P* value
Primary: asthma control days, % of treatment days	64.2 (58.5, 70.0)	59.6 (53.8, 65.5)	52.5 (46.8, 58.2)	11.8 (3.7, 19.8) .004	4.6 (−3.5, 12.7) .27	7.2 (−1.0, 15.3) .08
Values below reflect changes from baseline (measured daily from week –4 to week 0) to the end of the treatment period (measured daily from week 0 to week 48)						
Asthma control days, %	32.2 (26.3, 38.1)	33.3 (27.6, 38.9)	22.3 (16.1, 28.5)	9.9 (1.4, 18.4) .023	−1.1 (−9.2, 7.1) .80	10.9 (2.6, 19.3) .011
Episode-free days, %	26.4 (20.8, 31.9)	26.8 (21.2, 32.5)	17.8 (11.7, 23.9)	8.5 (0.4, 16.7) .040	−0.5 (−8.4, 7.4) .91	9.0 (0.8, 17.3) .032
Pre-BD AM PEF, % predicted	5.18 (2.99, 7.40)	5.33 (3.22, 7.44)	0.65 (−1.23, 2.52)	4.54 (1.67, 7.41) .002	−0.15 (−3.17, 2.88) .92	4.68 (1.88, 7.48) .001
Pre-BD PM PEF, % predicted	2.95 (0.66, 5.24)	4.31 (2.37, 6.25)	−0.57 (−2.38, 1.25)	3.52 (0.61, 6.43) .017	−1.36 (−4.34, 1.63) .37	4.88 (2.23, 7.52) <.001
Values below reflect changes from baseline (measured at week 0) to the end of the treatment period (measured at week 48); N = 86 (F), N = 81 (C), and N = 83 (M) participants completed the week 48 study visit						
ACQ§	−0.69 (−0.84, −0.54)	−0.55 (−0.75, −0.35)	−0.45 (−0.58, −0.33)	−0.24 (−0.44, −0.04) .018	−0.14 (−0.39, 0.10) .25	−0.10 (−0.33, 0.13) .42
Pre-BD FEV_1, % predicted	6.32 (4.47, 8.17)	3.62 (1.50, 5.74)	−0.58 (−2.96, 1.80)	6.90 (3.92, 9.88) <.001	2.70 (−0.08, 5.47) .06	4.20 (1.02, 7.39) .010
Pre-BD FEV_1/FVC (%)	3.95 (2.71, 5.19)	1.76 (0.50, 3.03)	0.07 (−1.41, 1.55)	3.88 (1.97, 5.79) <.001	2.19 (0.43, 3.95) .015	1.69 (−0.26, 3.63) .09
ENO, %‖	59.1 (50.1, 66.5)	22.9 (7.4, 35.8)	18.9 (5.1, 30.7)	40.2 (26.3, 54.1) <.001	36.2 (21.3, 51.1) <.001	4.0 (−13.5, 21.5) .68
Methacholine PC_{20}, doubling dose	2.65 (2.15, 3.16)	1.03 (0.57, 1.49)	0.62 (0.13, 1.10)	2.04 (1.34, 2.74) <.001	1.62 (0.94, 2.31) <.001	0.41 (−0.25, 1.07) .22
Maximum BD response, %¶	−3.61 (−5.43, −1.78)	0.30 (−2.07, 2.67)	1.69 (−0.61, 4.00)	−5.30 (−8.20, −2.40) <.001	−3.91 (−6.84, −0.98) .009	−1.39 (−4.67, 1.89) .41
Growth, cm	5.32 (4.95, 5.70)	5.26 (4.93, 5.58)	5.72 (5.31, 6.14)	−0.40 (−0.93, 0.13) .13	0.06 (−0.47, 0.59) .80	−0.46 (−0.99, 0.07) .08

*Fluticasone monotherapy: 100 μg BID.
†PACT combination: fluticasone 100 μg AM and salmeterol 50 μg BID.
‡Montelukast monotherapy: 5 mg PM.
§Measured on a 7-point scale; 0 = total control, 6 = extremely poor control.
‖Percent decrease.
¶Measured at week –4 and week 36.

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

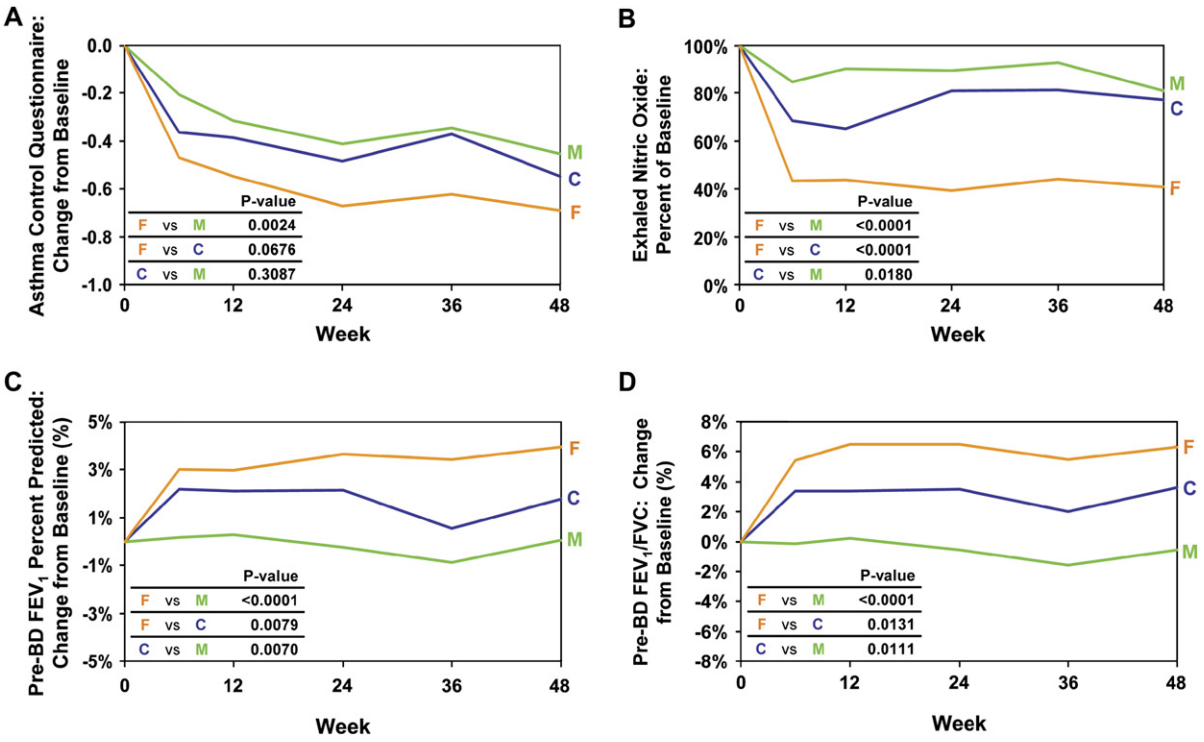

FIG 3. ACQ **(A)**, eNO **(B)**, percent predicted FEV_1 **(C)**, and FEV_1/FVC ratio **(D)**. Average change from baseline at each study visit for the 3 treatment groups: PACT combination therapy *(C)*, fluticasone monotherapy *(F)*, and montelukast monotherapy *(M)*. The 3 treatment groups were compared longitudinally across the entire study period by repeated-measures ANOVA. *P* values given are those associated with the main-effect comparison of the 2 study groups indicated for that *P* value. eNO data were analyzed on the log-scale, and the changes across time are presented graphically as the relative change from baseline expressed as a percentage. *BD*, Bronchodilator.

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 beclomethasone 200 μg (a dose equipotent to PACT fluticasone

monotherapy arm), beclomethasone 400 μg, or beclomethasone 200 μg plus salmeterol 50 μg. Verberne et al[12] concluded that patient-centered outcomes were very similar in these 3 groups.[12] These findings and ours differ, however, from those reported in adults,[23-25] 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[23-25] have used a positive response to bronchodilators and/or diminished baseline airway 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,[12] bronchial responsiveness to methacholine was an entry criterion, potentially favoring ICSs.[7,26] Moreover, we intentionally enrolled children in the PACT on the basis of the criteria of sufficient symptom frequency but with FEV_1 values $\geq$80%; these children were perhaps not as likely to respond to LABAs as those with lower FEV_1 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,[12] 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[12] 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 than 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.[16] Other trials have demonstrated the effectiveness of low-dose fluticasone even administered once daily.[27-31] 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.[2] 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,[32,33] 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 $FEV_1 \geq 80\%$ 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 or LTRAs to determine which options are capable of achieving optimal control to the greatest extent possible.

REFERENCES

1. National Asthma Education and Prevention Program. Expert panel report: guidelines for the diagnosis and management of asthma update on selected topics—2002. J Allergy Clin Immunol 2002;110(suppl): S141-219 [Erratum, J Allergy Clin Immunol 2003;111:466].
2. The Childhood Asthma Management Program Research Group. Long-term effects of budesonide or nedocromil in children with asthma. N Engl J Med 2000;343:1054-63.
3. Beck-Ripp J, Griese M, Arenz S, Koring C, Pasqualoni B, Bufler P. Changes of exhaled nitric oxide during steroid treatment of childhood asthma. Eur Respir J 2002;19:1015-9.
4. Agertoft L, Pedersen S. Effect of long-term treatment with inhaled budesonide on adult height in children with asthma. N Engl J Med 2000;343: 1064-9.
5. Knorr B, Matz J, Bernstein JA, Nguyen H, Seidenberg BC, Reiss TF, et al. Montelukast for chronic asthma in 6- to 14-year old children: a randomized, double-blind trial. JAMA 1998;279:1181-6.
6. Zeiger RS, Szefler SJ, Phillips BR, Schatz M, Martinez FD, Chinchilli VM, et al. Response profiles to fluticasone and montelukast in mild to moderate persistent childhood asthma. J Allergy Clin Immunol 2006;117:45-52.
7. Szefler SJ, Phillips BR, Martinez FD, Chinchilli VM, Lemanske RF, Strunk RC, et al. Characterization of within-subject responses to fluticasone and montelukast in childhood asthma. J Allergy Clin Immunol 2005;115:233-42.
8. Garcia MLZ, Wahn U, Gilles L, Swern A, Tozzi CA, Polos P. Montelukast, compared with fluticasone, for control of asthma among 6- to 14-year-old patients with mild asthma: the Mosaic Study. Pediatrics 2005; 116:360-9.

9. Lemanske RF Jr, Sorkness CA, Mauger EA, Lazarus SC, Boushey HA, Fahy JV, et al. Inhaled corticosteroid reduction and elimination in patients with persistent asthma receiving salmeterol. JAMA 2001;285:2594-603.
10. Russell G, Williams DA, Weller P, Price JF. Salmeterol xinafoate in children on high dose inhaled steroids. Ann Allergy Asthma Immunol 1995; 75:423-8.
11. Tal A, Simon G, Vermeulen JH, Petru V, Cobos N, Everard ML, et al. Budesonide/formoterol in a single inhaler versus inhaled corticosteroids alone in the treatment of asthma. Pediatr Pulmonol 2002;34:342-50.
12. Verberne AA, Frost C, Duiverman EJ, Grol MH, Kerrebijn KF. Addition of salmeterol versus doubling the dose of beclomethasone in children with asthma. The Dutch Asthma Study Group. Am J Respir Crit Care Med 1998;158:213-9.
13. Verberne AAPH, Frost C, Roorda RJ, van der Laag H, Kerrebijn KF. One year treatment with salmeterol compared to beclomethasone in children with asthma. Am J Respir Crit Care Med 1997;156:688-95.
14. Lee DK, Currie GP, Hall IP, Lima JJ, Lipworth BJ. The arginine-16 beta 2-adrenoceptor polymorphism predisposes to bronchoprotective subsensitivity in patients treated with formoterol and salmeterol. Br J Clin Pharmacol 2004;57:68-75.
15. Masoli M, Weatherall M, Holt S, Beasley R. Budesonide once versus twice-daily administration: meta-analysis. Respirology 2004;9:528-34.
16. Masoli M, Weatherall M, Beasley R. Fluticasone given once versus twice a day: meta-analysis. Respirology 2005;10:183-8.
17. Standardization of spirometry, 1994 update. American Thoracic Society. Am J Respir Crit Care Med 1995;152:1107-36.
18. Chapter 711. Dissolution. In: The United States Pharmacopeia/The National Formulary (USP 28/NF 23). Rockville (MD): United States Pharmacopeial Convention, Inc.; 2005. p. 2412-5.
19. Strunk RC, Szefler SJ, Phillips BR, Zeiger RS, Chinchilli VM, Larsen G. Relationship of exhaled nitric oxide to clinical and inflammatory markers of persistent asthma in children. J Allergy Clin Immunol 2003;112: 883-92.
20. Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. Eur Respir J 1999;14:902-7.
21. Zeiger RS, Bird SR, Kaplan MS, Schatz M, Pearlman DS, Orave J, et al. Short-term and long-term asthma control in patients with mild persistent asthma receiving montelukast or fluticasone: a randomized controlled trial. Am J Med 2005;118:649-57.
22. Ostrom NK, Decotis BA, Lincourt WR, Edwards LD, Hanson KM, Carranza R Jr, et al. Comparative efficacy and safety of low-dose fluticasone propionate and montelukast in children with persistent asthma. J Pediatr 2005;147:213-20.
23. Greening AP, Ind PW, Northfield M, Shaw G. Added salmeterol versus higher-dose corticosteroid in asthma patients with symptoms on existing inhaled corticosteroid. Allen & Hanburys Limited UK Study Group. Lancet 1994;344:219-24.
24. Woolcock A, Lundback B, Ringdal N, Jacques LA. Comparison of addition of salmeterol to inhaled steroids with doubling of the dose of inhaled steroids. Am J Respir Crit Care Med 1996;153:1481-8.
25. Pauwels RA, Löfdahl CG, Postma DA, Tattersfield AE, O'Byrne P, Barnes PJ, et al. Effect of inhaled formoterol and budesonide on exacerbations of asthma. N Engl J Med 1997;337:1405-11.
26. Sont JK, Willems LN, Bel EH, Van Krieken JH, Vandenbroucke JP, Sterk PJ. Clinical control and histopathologic outcome of asthma using airway hyperreponsiveness as an additional guide to long term treatment. Am J Respir Crit Care Med 1999;159:1043-51.
27. Wolfe J, Rooklin A, Grady J, Munk ZM, Stevens A, Prillaman B, et al. Comparison of once- and twice-daily dosing of fluticasone propionate 200 micrograms per day administered by Diskus device in patients treated with or without inhaled corticosteroids. J Allergy Clin Immunol 2000;105:1153-61.
28. Shigyo M, Inoue H, Honda Y, Takata S, Iwanaga T, Koto H, et al. Once-daily administration of fluticasone propionate does not worsen controlled airway responsiveness in patients with asthma. Respiration 2005;72: 480-5.
29. Holt S, Suder A, Weatherall M, Cheng S, Shirtcliffe P, Beasley R. Dose-response relation of inhaled fluticasone propionate in adolescents and adults with asthma: meta-analysis. BMJ 2001;323:1-8.
30. LaForce CF, Pearlman DS, Ruff ME, Silvers WS, Weinstein SW, Clements DS, et al. Efficacy and safety of dry powder fluticasone propionate in children with persistent asthma. Ann Allergy Asthma Immunol 2000;85: 407-15.
31. Li AM, Tsang TW, Chan K, Chan DF, Sung RY, Fok TF. Once-daily fluticasone propionate in stable asthma: study on airway inflammation. J Asthma 2006;43:107-11.
32. Nelson HS, Weiss ST, Bleecker ER, Yancey SW, Dorinsky PM. The Salmeterol Multicenter Asthma Research Trial: A comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. Chest 2006;129:15-26.
33. Salpeter SR, Buckley NS, Ormiston TM, Salpeter EE. Meta-analysis: effect of long-acting β-agonists on severe asthma exacerbations and asthma-related deaths. Ann Intern Med 2006;144:904-12.