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Randomized Comparison of Strategies for Reducing Treatment in Mild Persistent Asthma

The American Lung Association Asthma Clinical Research Centers*

ABSTRACT

BACKGROUND

Treatment guidelines recommend the use of inhaled corticosteroids in patients with asthma who have persistent symptoms and the “stepping down” of therapy to the minimum needed to maintain control of asthma. Whether patients with asthma that is well controlled with the use of inhaled corticosteroids twice daily can receive a step-down treatment with once-daily montelukast (our primary hypothesis) or once-daily fluticasone propionate plus salmeterol (our secondary hypothesis) has not yet been determined.

METHODS

We randomly assigned 500 patients with asthma that was well controlled by inhaled fluticasone (100 μ g twice daily) to receive continued fluticasone (100 μ g twice daily) (169 patients), montelukast (5 or 10 mg each night) (166 patients), or fluticasone (100 μ g) plus salmeterol (50 μ g) each night (165 patients). Treatment was administered for 16 weeks in a double-blind manner. The primary outcome was the time to treatment failure.

RESULTS

Approximately 20% of patients assigned to receive continued fluticasone or switched to treatment with fluticasone plus salmeterol had treatment failure, as compared with 30.3% of subjects switched to montelukast. The hazard ratio for both comparisons was 1.6 (95% confidence interval, 1.1 to 2.6; $P=0.03$). The percentage of days on which patients were free of asthma symptoms (78.7 to 85.8%) was similar across the three groups.

CONCLUSIONS

Patients with asthma that is well controlled with the use of twice-daily inhaled fluticasone can be switched to once-daily fluticasone plus salmeterol without increased rates of treatment failure. A switch to montelukast results in an increased rate of treatment failure and decreased asthma control; however, patients taking montelukast remained free of symptoms on 78.7% of treatment days. (ClinicalTrials.gov number, NCT00156819.)

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TREATMENT GUIDELINES FOR ASTHMA recommend the use of inhaled corticosteroids as first-line therapy for persistent asthma of all severities.¹⁻³ When asthma control has been achieved, the guidelines further recommend the “stepping down” of therapy to minimize the adverse effects of medication. Most studies of step-down therapy involve patients with moderate or severe asthma.⁴⁻¹¹

It has not yet been systematically investigated whether, in patients with mild asthma that is well controlled with the use of low-dose inhaled corticosteroids twice daily, therapy can be stepped down to an alternative, less intensive treatment strategy without a loss of asthma control. Simpler treatment regimens are important because large numbers of patients have mild persistent asthma, and most patients with asthma refill their prescriptions for controller medication irregularly.¹² Providing patients with efficacious alternatives that are more convenient than corticosteroid therapy and associated with fewer adverse effects or fewer negative perceptions could increase the adherence of patients to treatment and minimize exposure to medication while maintaining asthma control.

We investigated the following step-down treatment strategies as substitutions for fluticasone propionate (100 μg twice daily): montelukast (5 mg or 10 mg) once daily (the primary alternative) or fluticasone (100 μg) plus salmeterol (50 μg) once daily (the secondary alternative). Montelukast given once daily was shown to be equivalent to low-dose fluticasone (100 μg twice daily) in patients with mild persistent asthma during 12 weeks of double-blind treatment and in those with mild asthma during 36 weeks of open-label treatment.¹³ Fluticasone (100 μg) plus salmeterol (50 μg) once daily, administered in a combination inhaler, has been shown to produce bronchodilation that persists for at least 24 hours.¹⁴ Therefore, the step-down treatment strategies we evaluated are favorable alternatives to twice-daily inhaled corticosteroids, because they are administered only once daily and they offer reduced exposure to corticosteroids. Monotherapy with salmeterol was not considered, since studies have shown that it is associated with increased rates of asthma exacerbation and treatment failure.¹⁵ In this study (the Leukotriene or Corticosteroid or Corticosteroid-Sal-

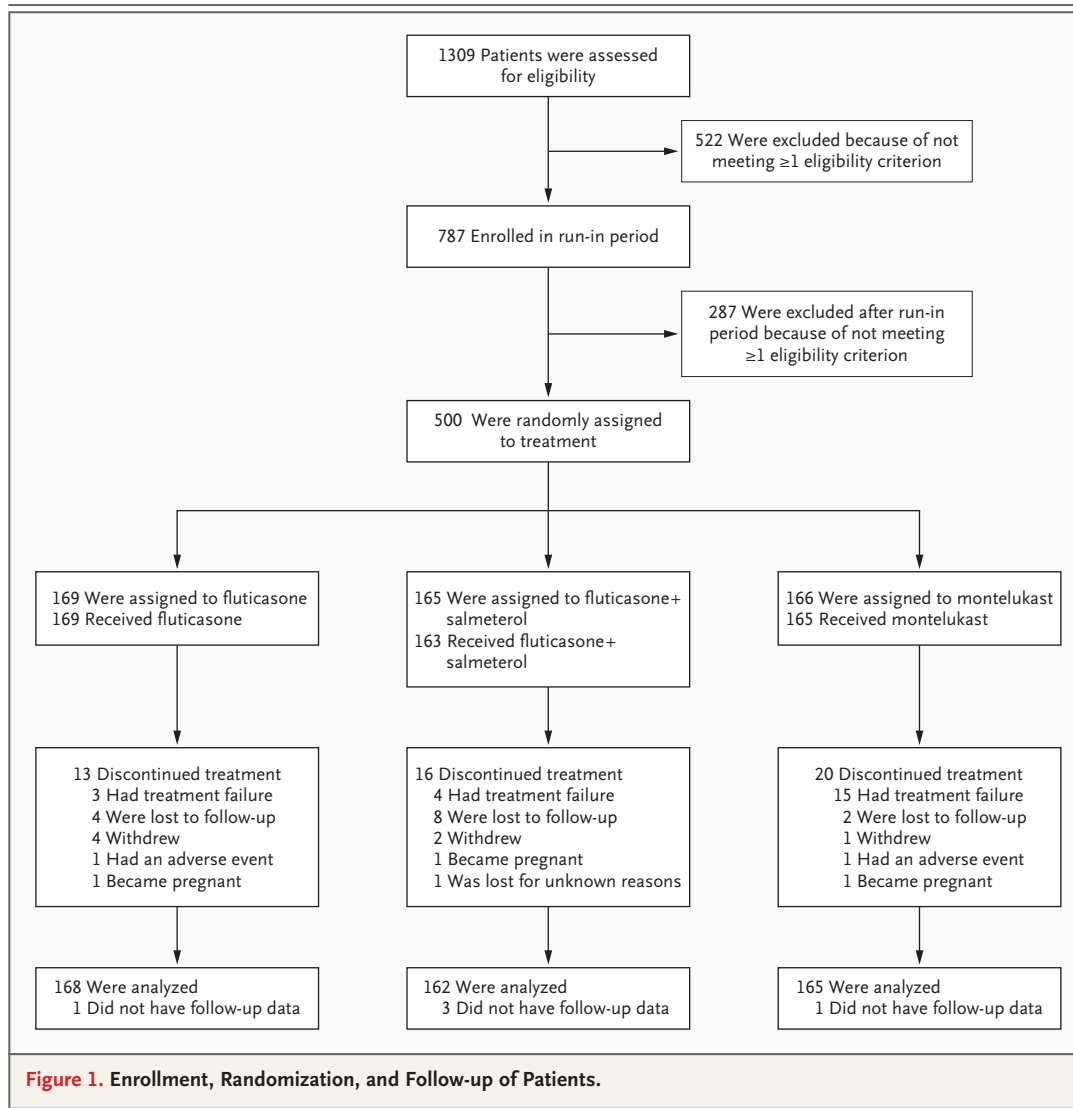
meterol [LOCSS, NCT00156819] trial by the American Lung Association Asthma Clinical Research Center), we compared the use of montelukast or a combination of fluticasone and salmeterol as step-down therapy.

METHODS

The protocol was written by the lead academic member of the writing committee, in collaboration with the Protocol Committee of the American Lung Association Asthma Clinical Research Centers. GlaxoSmithKline reviewed the protocol but played no role in the study design, in the collection, analysis, or interpretation of the data, or in the preparation of the manuscript. The data were collected and analyzed by the Data Coordinating Center of the American Lung Association Asthma Clinical Research Centers, which vouches for the data analysis. The manuscript was written by the lead academic committee member in collaboration with the writing committee. GlaxoSmithKline reviewed the final manuscript and offered comments for consideration by the writing committee; there were no confidentiality agreements with GlaxoSmithKline regarding the study results.

SUBJECTS

All study centers received approval from the institutional review board. All subjects provided written informed consent. From June 6, 2003, to April 13, 2005, a total of 1309 patients from 19 American Lung Association Asthma Clinical Research Centers clinics¹⁶ were assessed for eligibility (Fig. 1). Of these patients, 522 were excluded before enrollment, and 287 were excluded after enrollment, during the run-in period. Five hundred patients whose asthma was acceptably controlled after 4 to 6 weeks of open-label treatment with fluticasone propionate (Flovent Diskus, GlaxoSmithKline), 100 μg twice daily, were randomly assigned to receive double-blind treatment for 16 weeks with either continued inhaled fluticasone propionate (100 μg twice daily); montelukast (Singulair, GlaxoSmithKline), 5 mg once daily for children ages 6 to 14 years and 10 mg once daily for persons 15 years or older; or inhaled fluticasone (100 μg) and salmeterol (50 μg) (Advair Diskus, GlaxoSmithKline) once daily. The placebos (for Diskus and both doses of montelukast) and matching montelukast tablets



were prepared by GlaxoSmithKline, using a method involving a sugar overcoating. The study ended on July 31, 2005.

PROTOCOL

Detailed study methods are given in the Supplementary Appendix (available with the full text of this article at www.nejm.org). Key inclusion criteria for enrollment in the run-in period, during which open-label fluticasone was given for 4 to 6 weeks, included physician-diagnosed asthma; an age of 6 years or older and a forced expiratory volume in 1 second (FEV₁) of 60% or more of the predicted value before administration of a bronchodilator;

and a reversibility of airway obstruction by 12% or more with the use of a beta-agonist or a provocative concentration of methacholine producing a 20% decrease in FEV₁ of 8 mg per milliliter or less within the previous 2 years.

Inclusion criteria for randomization after the run-in period (Fig. 2) were as follows: adequate adherence (i.e., completion of at least 10 of the previous 14 days of daily diary cards and fluticasone treatment for at least 21 of the previous 28 days); a prebronchodilator FEV₁ of at least 80% of the predicted value; a score on the Asthma Control Questionnaire¹⁷ of less than 1.5 (range, 0 to 6, with lower values indicating less-severe asthma

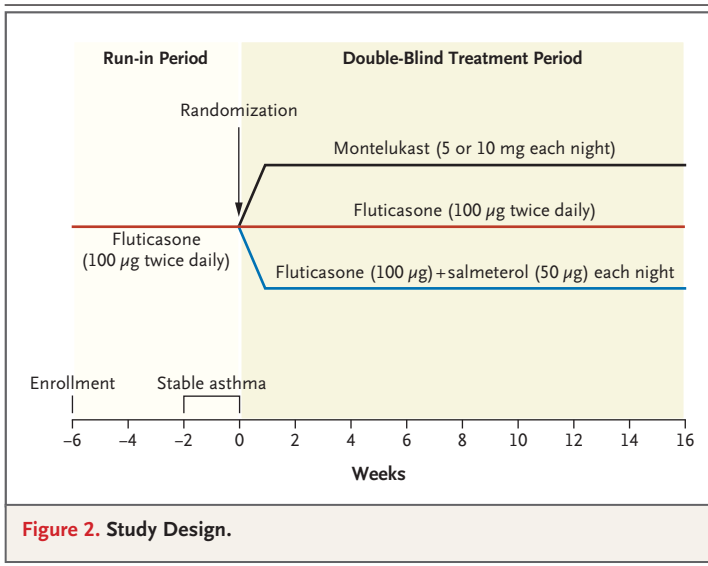


Figure 2. Study Design.

and 0.5 unit as the minimal clinically important difference¹⁸); fewer than 16 puffs of a rescue beta-agonist used per week during the final 2 weeks of the run-in period (except as medication before exercise); urgent medical care received for asthma, oral corticosteroid use, use of additional asthma medication, and absence of hospitalization during the run-in period; and an absence of febrile illness (temperature exceeding 38.0°C [100.4°F]) within the previous 24 hours.

Patients were randomly assigned to one of the three treatment groups (with an assignment ratio of 1:1:1) on the basis of a permuted-block design, stratified according to clinic and age (6 to 14 years vs. ≥15 years). Double-blind treatment lasted 16 weeks, with clinic visits after 2, 4, 8, 12, and 16 weeks of treatment.

OUTCOME VARIABLES

The primary outcome measure was the time to treatment failure, defined as the occurrence of any one of the following events: hospitalization or an urgent medical visit for asthma initiated by the patient or physician; use of systemic corticosteroids for asthma or need for open-label use of inhaled corticosteroids for asthma, as determined by the study physician or an asthma care provider; a decrease in prebronchodilator FEV₁ to more than 20% below the baseline value measured at randomization; a decrease in the morning peak expiratory flow rate to more than 35% below the baseline value (the mean over the final 2 weeks of the run-in period) on 2 consecutive days; use of 10 puffs

or more per day of rescue beta-agonist for 2 consecutive days (except as medication before exercise); refusal of the patient to continue because of lack of satisfaction with treatment; or judgment by a physician that the patient should stop treatment for reasons of safety. Follow-up continued according to protocol after the treatment failures were noted.

Secondary outcomes specified in the protocol included measures of pulmonary function (morning peak expiratory flow rate from the patients' daily diary cards and FEV₁),¹⁹ measures of asthma symptoms and medication use from the patients' daily diary cards, the number of days on which patients were free of asthma symptoms, and scores related to the quality of life of patients. Scores on the mini-Asthma-Specific Quality-of-Life Questionnaire ranged from 1 to 7, with higher values indicating better asthma control (less-severe asthma)^{20,21}; scores on the Asthma Control Questionnaire ranged from 0 to 6, with higher scores indicating more-severe asthma¹⁷; and scores on the Asthma Symptom Utility Index ranged from 0 to 1, with higher scores indicating fewer symptoms (less-severe asthma).²² A post-hoc analysis of the percentage of patients with well-controlled asthma, as defined by Bateman et al.,²³ for each of the 16 weeks of follow-up was also performed.

The numbers of patients were chosen for the study to have a statistical power of 90%, with a type 1 error rate of 2.5% and a 5% inflation factor, to detect an absolute difference of 8% or more in the percentage of patients with a treatment failure between the montelukast group or the fluticasone-salmeterol group and the fluticasone group.

STATISTICAL ANALYSIS

Analyses were performed on the basis of the intention-to-treat principle; all available data from all patients were included in all analyses. Kaplan-Meier and Cox proportional-hazards regression techniques were used to evaluate times to treatment failure.^{24,25} Linear and logistic-regression models were used to evaluate differences among treatment groups for continuous and dichotomous outcomes, respectively. Differences between values at enrollment and randomization were evaluated with the use of paired t-tests. The results of regression analyses presented were adjusted for clinic, age, baseline values, and follow-up time. Analysis of repeated measures (i.e., pulmonary function, asthma symptom scores, and asthma control) in-

volved generalized estimating equations to account for correlations among measurements for each patient.^{26,27} Continuous data skewed toward 0 were analyzed on the basis of the ranks of the data. The data were analyzed with SAS software (version 8)²⁸ and Stata software (version 9).²⁹

RESULTS

CHARACTERISTICS OF PATIENTS

Table 1 summarizes characteristics of all 500 patients at enrollment and randomization. The mean age of patients was 30.8 years, 60.2% were women, and 35.4% were self-reported blacks or Hispanics. Prebronchodilator pulmonary function and scores on the Asthma Control Questionnaire increased after completion of the run-in period. At randomization, patients' disease was mild, as verified with the use of pulmonary-function tests and scores on questionnaires reflecting asthma control and quality of life. However, in the previous year, approximately one third of patients (34.0%) had had one or more unscheduled health care visits for asthma and had received one or more courses of oral corticosteroids (29.4%). Most patients reported asthma symptoms that were worsened by allergies (81.0%), as well as rhinitis (63.2%), whereas a minority reported sinusitis (30.0%), food allergies (25.6%), gastroesophageal reflux disease (22.2%), and eczema (18.6%).

Data on a few characteristics differed across the three treatment groups. Before enrollment, a higher percentage of patients assigned to receive montelukast were taking an inhaled corticosteroid daily, as compared with those assigned to receive fluticasone or fluticasone plus salmeterol, and the fluticasone group had fewer former smokers and a higher mean score on the mini-Asthma-Specific Quality-of-Life Questionnaire for patients aged 6 to 14 years. As compared with the fluticasone group and the montelukast group, the fluticasone-salmeterol group had fewer patients with gastroesophageal reflux disease and more with allergies that trigger asthma. Most patients (86%) met the eligibility criterion for enrollment because of the reversibility of airway obstruction with the use of a bronchodilator during the previous 2 years, rather than bronchial hyperresponsiveness to methacholine during the same period. The recruitment of the children, aged 6 to 14 years, varied according to clinical center. At 11 centers, up to 37.0% of patients were children, and 8 centers did not enroll children.

ADHERENCE

Of 2500 scheduled clinic visits, 93% were completed. The missed visits (6.8%) were fairly evenly distributed across the three treatment groups: 7.6% of visits were missed in the fluticasone group and in the fluticasone-salmeterol group, and 4.1% of visits were missed in the montelukast group. Adherence to treatment was evaluated on the basis of diary cards, drug-dispensing forms, clinic visit forms, and pill counts and inhaler counters. Adherence ranged from 90.5 to 100.0%, with similar values among the three groups (Table A in the Supplementary Appendix).

PRIMARY OUTCOME

Figure 3 shows the cumulative percentages (estimated with the use of Kaplan-Meier curves) of patients with treatment failure in the three groups. The rates of treatment failure were 20.2% and 20.4% in the fluticasone group and the fluticasone-salmeterol group, respectively, and 30.3% in the montelukast group, which represented an approximately 60% higher rate in the montelukast group as compared with the other two groups (hazard ratio, 1.6; 95% confidence interval [CI], 1.1 to 2.6; $P=0.03$ for both comparisons). The most common reason for treatment failure was a decrease in FEV₁ of 20% or more below the baseline value, which represented 47.8% of events (Table 2). (Treatment failed for some patients according to more than one criterion.) Treatment failure owing to a need for the systemic use of corticosteroids, a need for the open-label use of inhaled corticosteroids, or an unscheduled urgent care visit for asthma occurred in 17 patients (10.7%) in the fluticasone group, 18 patients (11.1%) in the fluticasone-salmeterol group, and 22 patients (13.3%) in the montelukast group ($P=0.64$). Five of the six patients for whom one reason for treatment failure was that treatment was stopped owing to physician judgment also had another reason for failure. The remaining patient, assigned to receive fluticasone twice daily, had a possible allergic reaction 46 days after the start of treatment.

PRESPECIFIED SECONDARY OUTCOMES

Mean prebronchodilator FEV₁ values were higher in the fluticasone group (91.1% of the predicted value) and the fluticasone-salmeterol group (91.8% of the predicted value) than in the montelukast group (88.8% of the predicted value) ($P=0.002$ and $P<0.001$, respectively) (Table 3). Asthma control, as measured with the use of the Asthma Control

Table 1. Characteristics of Patients at Enrollment and Randomization, According to Treatment Group.*				
Characteristic	Fluticasone (N=169)	Fluticasone + Salmeterol (N=165)	Montelukast (N=166)	P Value†
Age at randomization				
Mean ±SD (yr)	29.3±14.6	30.8±14.9	32.4±15.4	0.15
6–14 yr (no.)	29	24	26	
≥15 yr (no.)	140	141	140	
Male sex (%)	39.1	37.6	42.8	0.61
Race or ethnic group (%)‡				
White	64.5	58.8	68.1	0.13
Black	30.2	27.3	25.3	
Hispanic	4.7	10.9	6.0	
Other	0.6	3.0	0.6	
Former smoker (%)	10.1	18.2	17.5	0.06
Exposed to second-hand smoke (%)	24.3	28.5	18.1	0.08
Asthma characteristics at enrollment				
Age at asthma onset (yr)	16.2±22.0	15.1±17.1	16.4±18.7	0.82
≥1 Urgent visit for asthma in previous year (%)	35.5	35.8	30.7	0.55
≥1 Course of oral corticosteroids in previous year (%)	28.4	31.5	28.3	0.77
Short-acting beta agonist >2 times/wk (%)	69.8	63.0	61.4	0.23
Daily inhaled corticosteroids (%)	39.6	43.0	53.0	0.03
Asthma scores§				
ASUI score at randomization	0.89±0.09	0.89±0.10	0.89±0.11	0.78
ACQ score¶				
At enrollment	1.63±0.74	1.79±0.83	1.64±0.86	0.13
At randomization	0.67±0.38	0.72±0.38	0.70±0.40	0.52
Mini-AQLQ score				
For patients ≥15 yr, at randomization	5.74±0.89	5.90±0.79	5.76±0.84	0.24
For patients 6–14 yr, at randomization	6.48±0.57	6.14±0.73	6.09±0.69	0.03
Pulmonary function 				
Prebronchodilator (% of predicted value)				
FEV₁				
At enrollment	85.8±13.3	85.8±15.7	85.5±13.1	0.97
At randomization	92.8±10.4	92.4±15.3	91.9±11.1	0.81
FVC				
At enrollment	96.5±13.5	95.9±16.0	95.2±13.1	0.69
At randomization	101.1±11.6	100.3±15.1	99.4±12.4	0.52
PEF				
At enrollment	90.5±18.3	89.9±18.8	92.6±18.3	0.39
At randomization	95.7±18.8	94.9±18.2	95.8±18.6	0.89

Table 1. (Continued.)

Characteristic	Fluticasone (N=169)	Fluticasone + Salmeterol (N=165)	Montelukast (N=166)	P Value†‡
Postbronchodilator (% of predicted value)				
FEV ₁				
At enrollment	99.3±12.4	95.7±12.4	97.2±13.1	0.08
At randomization	99.3±11.6	98.7±17.6	98.0±12.1	0.72
FVC				
At enrollment	102.8±13.1	100.4±13.5	101.6±13.0	0.35
At randomization	102.0±12.3	101.1±16.1	101.1±14.7	0.80
Other				
Postbronchodilator FEV ₁ (% change from prebronchodilator value)				
At enrollment	17.5±12.0	14.2±9.3	15.6±8.4	0.03
At randomization	7.1±7.0	6.7±6.1	6.7±7.2	0.83
Postbronchodilator FVC (% change from prebronchodilator value)				
At enrollment	7.8±10.1	7.1±8.8	7.0±8.9	0.87
At randomization	0.9±5.7	0.8±5.2	1.7±9.9	0.46
PC ₂₀				
At randomization (mg/ml)	3.0±2.6	1.8±2.7	2.6±2.1	0.33
Other conditions self-reported at enrollment (%)				
Chronic obstructive pulmonary disease	0.6	0.6	0.6	1.00
Gastroesophageal reflux disease	22.5	16.4	27.7	0.05
Eczema	16.0	22.4	17.5	0.29
Sinusitis	29.6	32.1	28.3	0.74
Rhinitis	63.9	63.0	62.7	0.97
Food allergies	26.0	24.8	22.9	0.86
Allergies that trigger asthma	77.5	87.3	78.3	0.04

* Plus–minus values are means ±SD. FEV₁ denotes forced expiratory volume in 1 second, FVC forced vital capacity, PEF peak expiratory flow rate, and PC₂₀ provocative concentration of methacholine required to produce a 20% decrease in FEV₁ of 8 mg per milliliter or less.

† P values were derived from a chi-square test for differences among percentages for categorical variables and from analysis of variance for continuous variables.

‡ Race or ethnic group was self-reported.

§ Higher values indicate less-severe asthma. Asthma Symptom Utility Index (ASUI) scores range from 0 to 1. Mini–Asthma-Specific Quality-of-Life Questionnaire (mini-AQLQ) scores range from 1 to 7.

¶ Asthma Control Questionnaire (ACQ) scores range from 0 to 6, with higher values indicating more-severe asthma.

|| Predicted values for pulmonary function were from Hankinson et al.¹⁹

Questionnaire, was better in the fluticasone group and in the fluticasone–salmeterol group than in the montelukast group (Table 3). The percentage of days on which patients used a rescue inhaler in the montelukast group tended to be higher than that in the fluticasone–salmeterol group (22.9% vs. 17.1%, P=0.06) and in the fluticasone group (22.9% vs. 18.2%, P=0.09). Fewer patients reported nocturnal awakenings due to asthma in the fluticasone group than in the montelukast group (16.7%

vs. 25.4%, P=0.04), with a similar trend in the fluticasone–salmeterol group (17.3%, vs. 25.4% in the montelukast group; P=0.06). The percentage of days on which patients were free of symptoms was similar across groups, ranging from 78.6% to 85.8%.

POST HOC DATA ANALYSIS

In a post hoc analysis, the percentage of patients whose asthma met the criteria for being well con-

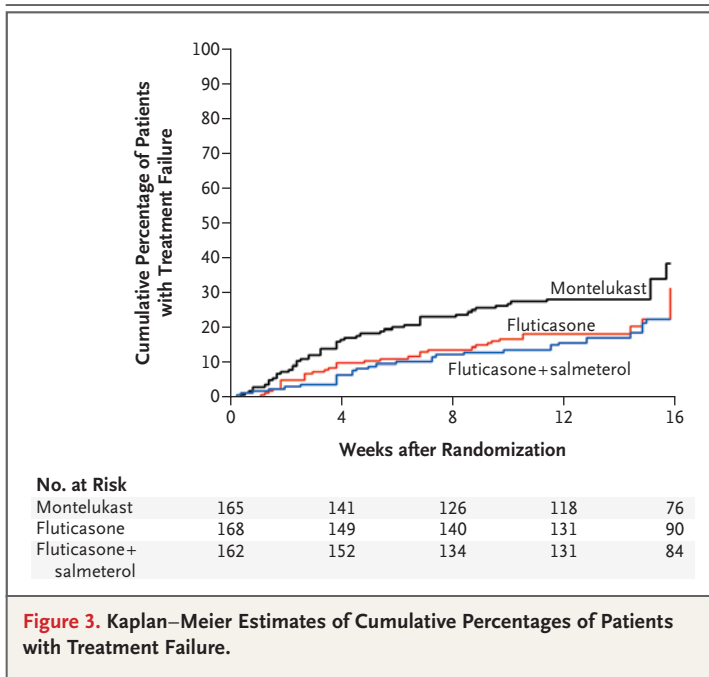


Figure 3. Kaplan–Meier Estimates of Cumulative Percentages of Patients with Treatment Failure.

trolled each week according to criteria of Bateman et al.²³ during the 16-week treatment period ranged from 58.8 to 71.3% for the montelukast group, 59 to 71% for the fluticasone group, and 64.7 to 73.5% for the fluticasone–salmeterol group (Fig. B in the Supplementary Appendix). Odds ratios for well-controlled asthma were 0.67 (95% CI, 0.47 to 0.96; $P=0.03$) for the montelukast group as compared with the fluticasone group; 0.57 (0.40 to 0.81, $P=0.002$) for the montelukast group as compared with the fluticasone–salmeterol group; and 1.17 (0.82 to 1.64, $P=0.37$) for the fluticasone–salmeterol group as compared with the fluticasone group. At the end of the study, more of the patients assigned to receive fluticasone twice daily (69.7%) or fluticasone plus salmeterol once daily (78.4%) wished to continue the treatment than did those assigned to receive montelukast (56.4%) ($P<0.001$).

ADVERSE EVENTS

We could only identify adverse events occurring during a 16-week period. The percentage of patients reporting minor side effects was similar among groups: those involving the ear, nose, and throat (91.5%), lower respiratory effects (18.2%), neurologic effects (mostly headache) (70.2%), gastrointestinal effects (47.4%), musculoskeletal effects (40.9%), and nonspecific effects (21.5%) (Table C in the Supplementary Appendix). However, fewer patients reported upper respiratory infections in

the montelukast group (26.7%) than in the fluticasone group (37.5%) or in the fluticasone–salmeterol group (38.5%) ($P=0.03$ and $P=0.02$, respectively). Similarly, fewer patients reported viral respiratory infections in the montelukast group (7.3%) than in the fluticasone group (15.5%) or in the fluticasone–salmeterol group (13.7%) ($P=0.04$ and $P=0.08$, respectively). More patients reported nausea and vomiting (33.3%) and fever (26.8%) in the fluticasone group than in the montelukast group (21.2% and 15.1%, respectively) ($P=0.01$ for both comparisons).

There were 20 serious adverse events during the study: 6 during the run-in period and 14 during the treatment period (see the Supplementary Appendix). Serious events after randomization occurred in six patients (3.6%) in the fluticasone group, four patients (2.4%) in the fluticasone–salmeterol group, and four patients (2.4%) in the montelukast group. Two of the 14 events occurring during the treatment period (1 asthma exacerbation and 1 decrease in peak expiratory flow rate) were judged to be possibly related to the study medication; 1 event (burning in the mouth and tightening of the throat) was judged to be definitely related; 11 events were judged to be unrelated; and for 1 event (depression), the role of study medication was unclear.

DISCUSSION

Current treatment guidelines for asthma recommend the continuous evaluation of asthma control by physicians and patients and the stepping down of therapy to the minimum required to maintain such control.^{1–3} Although the strategy for step-down therapy is obvious — decrease the dose of inhaled corticosteroids^{4–11} — for patients receiving high-dose inhaled corticosteroids, combination therapy, or both, strategies for the stepping down of therapy for patients whose asthma is successfully controlled with the use of conventional doses of an inhaled corticosteroid have not been well defined.

We describe the effect of stepping down therapy to either therapy with the leukotriene modifier montelukast or with once-daily fluticasone plus salmeterol in patients with mild asthma that was well controlled with the use of twice-daily fluticasone. These strategies were selected for evaluation because some patients may prefer an oral, nonsteroidal medication (montelukast) or a once-

Table 2. Reasons for Treatment Failure, According to Treatment Group.*

Variable or Comparison	Fluticasone (N = 168)	Fluticasone + Salmeterol (N = 162)	Montelukast (N = 165)	Hazard Ratio (95% CI)	P Value†
Treatment failure — no. of patients (%)	34 (20.2)	33 (20.4)	50 (30.3)		
Fluticasone + salmeterol vs. fluticasone				1.0 (0.6–1.6)	0.99
Montelukast vs. fluticasone				1.6 (1.1–2.6)	0.03
Montelukast vs. fluticasone + salmeterol				1.6 (1.1–2.6)	0.03
Reasons for treatment failure — no. of patients					
No. of reasons					
1	23	26	36		
2	4	4	8		
≥3	7	3	6		
Urgent care for asthma	8	7	6		
Systemic corticosteroid use	11	9	13		
Inhaled corticosteroid use	8	9	12		
≥20% Decrease in FEV ₁ from baseline value	14	16	26		
≥35% Decrease in PEF from baseline value	6	1	6		
≥10 Uses of rescue inhaler	4	1	5		
Refusal of treatment by patient	2	1	3		
Treatment stopped owing to physician judgment	1	1	4		

* Hazard ratios and 95% confidence intervals (CIs) were derived from a Cox proportional-hazards model stratified according to clinic and age. FEV₁ denotes forced expiratory volume in 1 second, and PEF peak expiratory flow rate.

daily inhaled medication (fluticasone plus salmeterol) to a twice-daily inhaled controller medication (fluticasone). We used a composite definition of treatment failure that included seven general measures of asthma control.^{15,30,31} Our results showed a difference in the rates of treatment failure for patients receiving montelukast (30%) and those receiving either twice-daily fluticasone or once-daily fluticasone plus salmeterol (20%). Although fluticasone plus salmeterol has been approved by the Food and Drug Administration for twice-daily administration, the bronchodilation it provides for 24 hours in patients with mild asthma is a rationale for its once-daily use in those patients.¹⁴

Other outcome measures — including prebronchodilator FEV₁, asthma control as measured according to the Asthma Control Questionnaire, and numbers of nocturnal awakening — also favored fluticasone and fluticasone plus salmeterol over montelukast, although these differences may not

be clinically important. These results are consistent with a recent study by Sorkness et al.³² comparing these three regimens in children, with the exception of effects on lung function. We found fluticasone and fluticasone plus salmeterol to have similar effects on lung function in children and adults, whereas Sorkness et al. found fluticasone to be superior to the combination drug in children, albeit over a longer period of follow-up.

Our findings with regard to the post hoc composite outcome of well-controlled asthma²³ are also consistent with those of other studies: approximately 10% more patients were classified as having well-controlled asthma each week during follow-up in the fluticasone group and the fluticasone plus salmeterol group than in the montelukast group (Fig. B in the Supplementary Appendix). Despite the increased rate of treatment failure associated with montelukast, the rates of clinically significant asthma exacerbation did not differ significantly among the three groups. This finding

Table 3. Additional Outcomes, According to Treatment Group.*

Outcome	Fluticasone (N=168)	Fluticasone + Salmeterol (N=161)	Montelukast (N=165)	P Value		
				Fluticasone + Salmeterol vs. Fluticasone	Montelukast vs. Fluticasone	Montelukast vs. Fluticasone + Salmeterol
Prebronchodilator pulmonary function — mean (95% CI)†						
Percentage of predicted FEV ₁ value	91.1 (89.6–92.6)	91.8 (90.4–93.2)	88.8 (87.4–90.1)	0.31	0.002	<0.001
Percentage of predicted FVC value	99.0 (97.7–100.3)	98.8 (97.6–99.9)	98.2 (97.0–99.4)	0.68	0.25	0.41
Percentage of predicted PEF value	96.2 (94.5–98.0)	99.0 (97.0–100.9)	94.7 (93.1–96.3)	0.007	0.09	<0.001
Assessment scores from questionnaires‡						
ACQ score§						
Mean (95% CI)	0.73 (0.67–0.78)	0.71 (0.65–0.76)	0.82 (0.76–0.89)	0.58	0.02	0.004
No. of patients	167	161	165			
ASUI score						
Mean (95% CI)	0.89 (0.88–0.90)	0.89 (0.88–0.90)	0.89 (0.88–0.90)	0.85	0.44	0.53
No. of patients	167	160	161			
Mini-AQLQ score						
For patients ≥15 yr						
Mean (95% CI)	5.8 (5.7–5.9)	5.8 (5.7–6.0)	5.8 (5.7–5.9)	0.66	0.82	0.80
No. of patients	128	127	132			
For patients 6–14 yr						
Mean (95% CI)	6.6 (6.4–6.8)	6.6 (6.4–6.8)	6.4 (6.2–6.5)	0.82	0.19	0.14
No. of patients	27	23	22			
≥1 Nocturnal awakening — no. of patients (%)	28 (16.7)	28 (17.3)	42 (25.4)	0.92	0.04	0.06
Symptoms and use of medication — % of diary-care days						
No. of patients	165	160	165			
Percentage of days symptom-free — mean (95% CI)	85.8 (82.8–89.6)	82.7 (78.9–86.6)	78.7 (74.9–82.4)	0.48	0.10	0.35
Percentage of days with rescue-inhaler use — mean (95% CI)	18.2 (14.1–22.3)	17.1 (12.8–21.3)	22.9 (18.8–27.0)	0.69	0.09	0.06

* P values and 95% confidence intervals (CIs) were derived from multiple linear regression models with robust variance estimates. All models included adjustments for clinic, age, and — for continuous outcomes — baseline values of pulmonary function and asthma-control scores. Symptom-free days were analyzed as ranked data. FEV₁ denotes forced expiratory volume in 1 second, FVC forced vital capacity, and PEF peak expiratory flow rate.

† Predicted values for pulmonary function were from Hankinson et al.¹⁹

‡ Higher values indicate less-severe asthma. Asthma Symptom Utility Index (ASUI) scores range from 0 to 1. Mini-Asthma-Specific Quality-of-Life Questionnaire (mini-AQLQ) scores range from 1 to 7.

§ Asthma Control Questionnaire (ACQ) scores range from 0 to 6, with higher values indicating more-severe asthma.

suggests that our study protocol was safe and also sensitive for assessing step-down therapy.

The fact that 30.3% of patients had treatment failure in the montelukast group implies that approximately 70% of the patients continued to have

good asthma control. Similarly, according to a more stringent criterion, each week most patients (50.8 to 61.4%) assigned to montelukast had well-controlled asthma. The high percentages of symptom-free days in all three treatment groups (78.7%

for montelukast, 85.8% for fluticasone, and 82.7% for fluticasone plus salmeterol) also suggest that most patients fared well.

An interesting finding was that there were relatively few upper respiratory infections in the montelukast group. This may have been due to a misdiagnosis of allergic rhinitis, for which montelukast is effective, or possibly to a more specific effect on leukotriene production due to viral infection.³³ Alternatively, the chronic use of inhaled corticosteroids may reduce immunity, thereby predisposing patients to infection.

In a recent trial involving patients with mild persistent asthma, there were minimal differences in asthma control between those receiving an inhaled corticosteroid twice daily only as needed, guided by a symptom-based action plan, and those receiving either a leukotriene modifier twice daily or an inhaled corticosteroid twice daily.³⁴ The results of our study suggest another strategy, which is less complex for patients to follow. For patients whose asthma is well controlled with the twice-daily use of an inhaled corticosteroid, the use of once-daily fluticasone plus salmeterol or once-daily montelukast could be considered. If treatment failure occurs, treatment could be modified accordingly.

Whether the better outcomes found in our fluticasone-salmeterol group offset the convenience of a once-daily oral formulation (montelukast) depends on the preferences of patients and physicians as well as on cost. Recent studies have raised concerns about the potential adverse effects of long-acting beta-agonists and inhaled corticosteroids.³⁵⁻³⁷ Individual patients and their physicians must choose a treatment regimen for asthma that balances efficacy with actual or perceived risks and

maximizes adherence. No single approach will provide the best combination of these factors for all patients with asthma.

In summary, we found that patients whose asthma is well controlled with the use of twice-daily fluticasone can be safely switched to step-down treatment with once-daily fluticasone plus salmeterol. Oral montelukast is not as effective, although it provided good asthma control for most patients.

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APPENDIX

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