

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: The American Lung Association Asthma Clinical Research Centers. Randomized comparison of strategies for reducing treatment in mild persistent asthma. *N Engl J Med* 2007;356:2027-39.

Randomized Comparison of Strategies for Reducing Treatment in Mild Persistent Asthma

On-Line Repository

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Methods

Subjects

Beginning on June 6, 2003, 1309 patients from the 19 clinical centers representing the American Lung Association's Asthma Clinical Research Centers¹⁶ were assessed for eligibility (**Figure 1A, main manuscript**). Of these, 522 were excluded before enrollment and 287 after enrollment, resulting in 500 patients who demonstrated an acceptable level of asthma control after 4 to 6 weeks of open-label treatment with fluticasone propionate 100 µg twice daily. Participants were randomly assigned to either continue inhaled fluticasone propionate 100 µg twice daily (n=169), or to montelukast 5 or 10 mg once daily (n=166), or to inhaled fluticasone/salmeterol 100/50 µg once daily (n=165) for 16 weeks in a double-masked treatment protocol. The last participant was randomized on April 13, 2005 and the study ended on July 31, 2005. The study design is illustrated in **Figure 1B** (main manuscript).

Protocol

Inclusion criteria for enrollment in the open label fluticasone (100 µg twice daily) run-in period:

- physician diagnosed asthma
- age 6 years or older
- forced expiratory volume in 1 second (FEV₁) of 60% or greater predicted pre-bronchodilator
- airway reversibility defined by:
 - 12% or greater β-agonist reversibility using up to 4 puffs albuterol (within last 2 years), OR
 - PC₂₀ FEV₁ methacholine (provocative concentration of methacholine producing a 20% fall in FEV₁) 8 mg/mL or less (within last 2 years)
- for women of childbearing potential: not pregnant, non-lactating, and agree to practice an adequate birth control method (abstinence, combination barrier and spermicide, or hormonal) for the duration of the study,
- for patients not on an asthma controller medication (long-acting beta-agonists, leukotriene antagonist or inhaled corticosteroid): symptomatic asthma evidenced by an Asthma Control Questionnaire (ACQ)¹⁶ score of 1.5 or greater
- not on chronic oral steroid therapy or oral corticosteroid use within past 4 weeks
- no febrile illness (>38.0°C or 100.4°F) within past 24 hours or upper respiratory infections within the past 2 weeks,
- non-smoker and less than 20 lifetime pack years of smoking,
- no hospitalization or urgent medical care visit for asthma within past 4 weeks
- no participation in an intervention research study within past 4 weeks,
- no concurrent diseases that, in the investigator's opinion, would interfere with participation in the study or that might put the participant at risk by participating,
- informed consent and ability to comply with study procedures.

Web supplement: **Randomized Comparison of Strategies for Reducing Treatment in Mild Persistent Asthma**

Participants were contacted by telephone after 2 weeks of open label fluticasone propionate treatment, and seen in the clinic after 4 weeks of treatment. Inclusion criteria for randomization into one of the three double-masked treatment arms were:

- successful completion of the fluticasone run-in period (*i.e.* completed at least 10 of the last 14 days of diary cards during fluticasone run-in period and received treatment with fluticasone for 21 days of the last 28 days)
- good asthma control as evidenced by all of the following during the last two weeks of run-in period:
 - pre-bronchodilator FEV₁ ≥ 80% predicted
 - Asthma Control Questionnaire¹⁷ score less than 1.5
 - rescue beta-agonist use less than 16 puffs per week (excluding use as a pre-medication for exercise; one nebulizer use was considered equivalent to 2 puffs of beta-agonist)
 - no hospitalization or unscheduled medical care visit for asthma
 - no oral corticosteroid use
 - no need for any additional asthma medication for asthma symptoms
- no febrile illness (>38.0°C or 100.4°F) within 24 hours

If participants did not meet all these criteria (if they failed the adherence criteria, for example), they were permitted to remain on open label fluticasone propionate for another two weeks in order to attempt to qualify for randomization.

Participants were randomized to receive one of the 3 study treatments with an allocation ratio (1:1:1). The randomization schedule was a permuted block design stratified by clinic and pediatric status (6-16 years, ≥ 17 years). The double-masked treatment period lasted 16 weeks, and patients visited the clinic after 2, 4, 8, 12, and 16 weeks of blinded treatment.

Study drugs included fluticasone propionate inhalation powder (Flovent Diskus®), 100 µg bid, montelukast (Singulair®) 5 mg qpm (children 6-14 years of age) or 10 mg qpm 15 years or older), and combination therapy with fluticasone propionate inhalation powder 100 µg and salmeterol 50 µg (as salmeterol xinafoate salt 72.5 µg equivalent to salmeterol base 50 µg) inhalation powder (Advair Diskus® 100/50) qpm. Placebo and matching montelukast tablets were prepared by GlaxoSmithKline using a sugar over-coating method. The bioavailability of the formulation is similar to the commercial presentation of montelukast. In published data the geometric mean ratios and 90% confidence intervals for area under curve (AUC₀₀) and C_{max} of the sugar over-coating formulations were all within the acceptable range (0.80-1.25).^{On-line Reference}

^A Diskus counters were checked at each visit to determine adherence to the treatment regimen. Participants and staff were masked to the study treatment. At randomization each participant was instructed to use two Diskus inhalers each day, one in the morning and the other in the evening. The inhalers either were two containing fluticasone for the fluticasone group, one containing fluticasone and salmeterol and one placebo inhaler for the fluticasone/salmeterol group, or two placebo inhalers for the montelukast group. Inhalers were labeled AM or PM and had yellow or blue dots, respectively, to ensure compliance to the protocol. Each participant also took a capsule (or chewable tablet for 5 mg dose) containing montelukast or placebo once a day in the evening. Treatment compliance was determined in two ways, from diary cards and by checking counters on inhalers and pill counts.

Outcome Variables

The primary outcome variable was the time to the occurrence of a treatment failure defined as any one of the following:

- hospitalization or unscheduled medical care visit for asthma
- use of systemic corticosteroids for asthma
- need for open label inhaled corticosteroids for asthma symptoms (as determined by treating or study physician)
- decrease in pre-bronchodilator FEV₁ > 20% below baseline (measured at randomization)
- decrease in morning peak expiratory flow (PEF) greater than 35% below baseline PEF on two consecutive days (baseline PEF was the mean PEF during the final 2 weeks of fluticasone run-in period)
- use of 10 or more puffs per day of rescue β -agonist for 2 consecutive days (excluding use as a pre-medication for exercise; one nebulizer use was equivalent to 2 puffs of β -agonist)
- participant refusal to continue study drugs because of lack of satisfaction with asthma treatment
- physician judgment that patient should be withdrawn from study treatment for safety reasons.

Secondary and exploratory outcomes included measures of pulmonary function¹⁹, asthma symptoms and medication use from participant treatment diaries (daily asthma symptom scores, nocturnal asthma awakenings, patient-related measures [including asthma specific quality of life as measured by the Mini-Asthma Quality of Life Questionnaire (Mini-AQLQ) and Pediatric Asthma Quality of Life Questionnaire (PAQLQ),^{20,21} asthma control scores based on the Asthma Control Questionnaire (ACQ),^{17,18} asthma symptoms as measured by the Asthma Symptom Utility Index (ASUI),²² treatment effectiveness as measured by the Asthma Therapy Assessment Questionnaire (ATAQ),^{On-line Reference B}], asthma symptom-free days, markers of inflammation in blood (eosinophils and serum eosinophil cationic protein [ECP]) and exhaled breath condensate (EBC), and in a subgroup of adult participants airway responsiveness (PC₂₀ FEV₁ for methacholine). In a post-hoc analysis, the percent of participants with Total Asthma Control and Well-Controlled Asthma as described by Bateman²³ was calculated for each week of the 16 weeks of double-blind treatment. Total Control was defined as a week in which patients met the following criteria: did not seek urgent care; did not take oral corticosteroids; did not use rescue medications for asthma; had no days with an asthma symptom score greater than 0; did not report any nocturnal awakenings; and did not have an AM peak flow rate less than 80% of the predicated value. Well-Controlled asthma was defined as a week in which patients met the following criteria: did not seek urgent care; did not take oral corticosteroids; did not use rescue medications for asthma; had fewer than 3 days with an asthma symptom score greater than 0; did not report any nocturnal awakenings; and did not have an AM peak flow rate less than 80% of the predicated value.

Statistical Analysis

Analyses were performed by intention-to-treat. Kaplan-Meier and Cox Proportional hazards regression techniques were used to evaluate time-to-treatment failure.^{24,25} Linear and logistic regression models with Generalized Estimating Equations (GEE) were used to evaluate differences among treatment groups for continuous or dichotomous outcomes, respectively.^{26,27}

All results of regression analyses presented are adjusted for clinic, pediatric status, and baseline value of the outcome where appropriate. Analyses of repeated measures (i.e., pulmonary function, asthma symptom scores) employed GEE to account for correlations among the measurements within one participant and were adjusted for follow-up time. Continuous data that were skewed towards zero were analyzed based on the ranks of the data so that outliers were not overly influential. Data were analyzed using SAS V8 and STATA V9 software.^{28,29}

Adverse Events

Four pregnancies occurred during the trial. One child was delivered 4 weeks early; all children were reported to be in good health. Twenty severe adverse events (SAEs) were reported during the trial, 6 in the run-in prior to randomization and 14 after randomization, 6 in patients randomized to fluticasone propionate, 4 in patients randomized to fluticasone/salmeterol, and 4 in patients randomized to montelukast. One event "burning in her mouth and throat tightening or swelling" was thought to be definitely related to study medication (open label fluticasone propionate). Two events (asthma exacerbation, decrease in peak expiratory flow rate) were thought to be possibly related to study medications. All of the rest of the adverse events except 1 (depression in which the role of study medication was not known), were judged to be unrelated to study medications. Of the 20 SAEs, 7 were either an asthma exacerbation or an increase in asthma symptoms/signs, 11 involved hospitalizations/emergency visits for unrelated surgical, traumatic or other events, 1 was an anaphylactic reaction to peanuts or peanut oil, and 1 was the reaction to study medication (fluticasone propionate) described above.

The frequency of common minor side effects is presented in **Table B**. The percentage of participants reporting minor side effects was similar among groups: ear nose and throat (91.5%), lower respiratory (18.2%), headache (70.2%), gastrointestinal (47.4%), musculoskeletal (40.9%), and non-specific fever (21.5%). There were fewer upper respiratory infection and viral respiratory infection reported in the montelukast group, and more patients reported nausea and vomiting and fever in the fluticasone propionate group.

References for Supplement

- A. Smith GA, Rawls CM, Kunka RL. An automated method for the determination of montelukast in human plasma using dual-column HPLC analysis and peak height summation of the parent compound and its photodegradation product. *Pharm Res* 2004; 21:1539-1544.
- B. Vollmer WM, Markson LE, O'Connor E, Sanocki L, Fitterman L, Berger M, Buist ASB. Association of asthma control with health care utilization and quality of life. *Amer J Respir Crit Care Med* 1999;160:1647-1652.

Table A - Adherence to Assigned Treatment According to Treatment Group

	Treatment Group		
	Fluticasone	Fluticasone +Salmeterol	Montelukast
Data Source	Adherence (%) Median [Interquartile Range] (N)		
Diary cards, run-in period	100 [92.9, 100] (169)	100 [92.9, 100] (165)	100 [92.9,100] (165)
Diary cards, follow-up	95.8 [92.1, 98.1] (166)	97.3 [97.0, 99.2] (160)	97.2 [93.8, 99.1] (165)
Drug dispensing records, run-in period	91.2 [75.6, 98.6] (167)	90.3 [81.1, 97.8] (164)	94.1 [81.0, 98.2] (166)
Drug dispensing records, follow-up period	93.2 [69.1, 98.6] (158)	93.3 [73.9, 99.1] (153)	90.5 [73.3, 98.2] (159)
Patient interview, follow-up period	98.2 [92.9, 100] (167)	97.6 [92.2, 100] (161)	98.2 [92.9, 100] (165)

Figure Per Cent of Patients Well Controlled Each Week According to Bateman²³

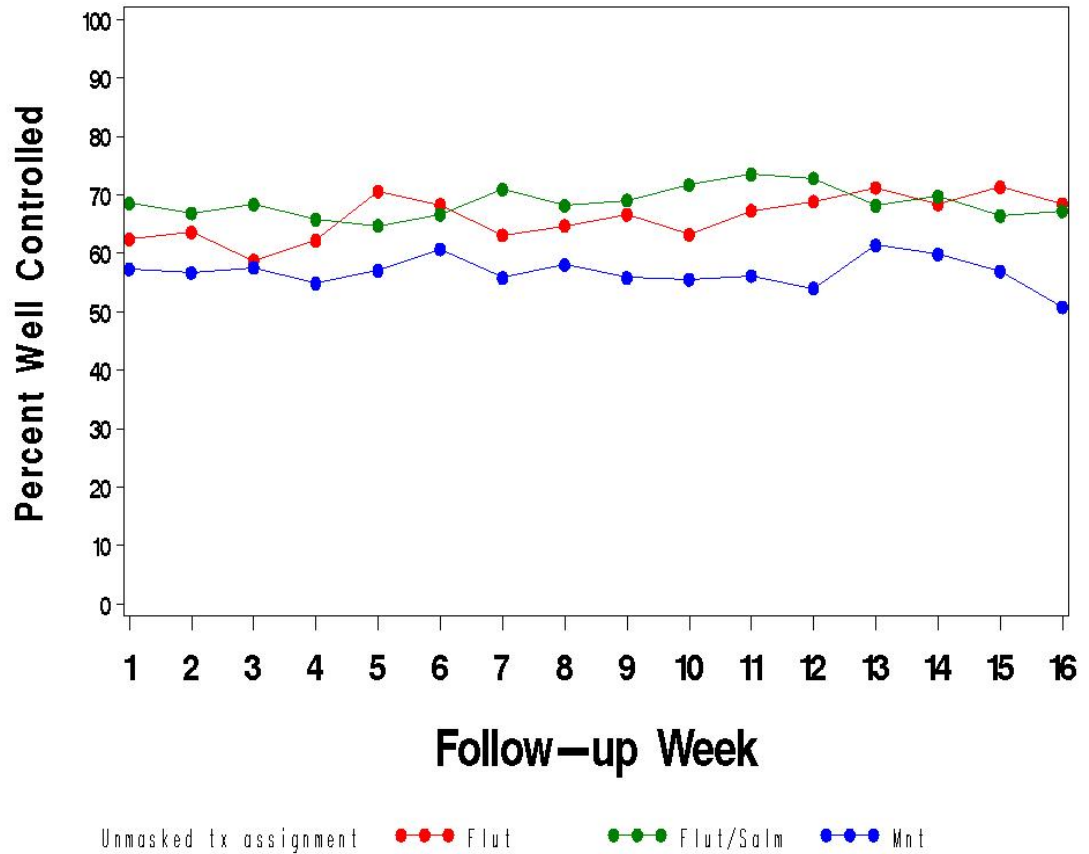


Figure Legend: The lines represent the percentage of patients with Well-controlled asthma during each week of follow-up by treatment assignment according to the definition used by Bateman et al²³ based on diary cards. Key: Flut=fluticasone bid; Flut/Salm=fluticason/salmeterol; Mnt=montelukast.

Table B - Occurrence of Adverse Events by Treatment Group

	Treatment Group			P-values [†]		
	Fluticasone	Fluticasone/ salmeterol	Montelukast	Flut/Sal vs Flut	Mnt vs Flut	Mnt vs Flut/Sal
N	168	161	165			
% Participants reporting event						
Ear, nose, & throat						
Upper respiratory infection	37.5	38.5	26.7	0.85	0.03	0.02
Pharyngitis	49.4	48.5	49.7	0.89	0.93	0.82
Rhinitis	71.4	73.9	67.3	0.65	0.36	0.18
Upper respiratory inflammation	50.0	45.3	42.4	0.31	0.16	0.69
Hoarsness/dysphonia	54.8	53.4	47.3	0.71	0.16	0.31
Sinusitis	39.9	31.1	30.9	0.08	0.07	0.97
Nasal congestion	80.9	80.1	77.0	0.77	0.39	0.57
Lower respiratory						
Viral respiratory infection	15.5	13.7	7.3	0.77	0.04	0.08
Influenza	8.9	9.9	4.8	0.75	0.15	0.08
Neurologic						
Headache	71.4	68.3	70.9	0.45	0.93	0.50
Gastrointestinal						
Diarrhea	24.4	19.3	21.2	0.25	0.50	0.64
Nausea and vomiting	33.0	23.0	21.2	0.03	0.01	0.79
GI distress	35.7	37.9	34.6	0.70	0.95	0.65
Non-specific						
Fever	26.9	22.4	15.2	0.33	<0.01	0.09
Musculoskeletal						
Musculoskeletal pain	37.5	43.5	42.8	0.28	0.39	0.85

[†]P-values derived from logistic regression model and were adjusted for clinic and pediatric status.