

# Improvement of Aspirin-Intolerant Asthma by Montelukast, a Leukotriene Antagonist

## A Randomized, Double-Blind, Placebo-Controlled Trial

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Leukotriene antagonists block the proinflammatory actions of leukotrienes (LT) and have been introduced as new treatments for asthma. Conventional therapy with glucocorticosteroids does not inhibit the biosynthesis of leukotrienes. We therefore tested whether addition of the leukotriene receptor antagonist montelukast was of therapeutic benefit in a group of aspirin-intolerant patients with asthma of whom 90% already were treated with moderate to high doses of glucocorticosteroids. Under double-blind conditions, 80 aspirin-intolerant patients with asthma were randomized to receive 4 wk oral treatment of either 10 mg of montelukast or placebo once daily at bedtime. Pulmonary function was measured as forced expiratory volume in 1 s (FEV<sub>1</sub>) once a week in the clinic and daily as morning and evening peak expiratory flow rate (PEFR). Asthma symptoms and use of rescue bronchodilator were also recorded daily. Asthma specific quality of life (QoL) was assessed before and after the treatments. The group receiving montelukast showed a remarkable improvement of their asthma, whereas the group given placebo showed no change. Thus, from equal baseline values, the mean difference between the groups over the 4-wk treatment period was 10.2% for FEV<sub>1</sub> and 28.0 L for morning PEFR (*p* for both < 0.001). The improved pulmonary function in the group receiving montelukast occurred at the same time as 27% less bronchodilator was used (*p* < 0.05), and it was associated with fewer asthma symptoms than in the group given placebo, including 1.3 nights more of sleep per week and 54% fewer asthma exacerbations (*p* < 0.05). There was also an improvement in asthma-specific QoL (*p* < 0.05). The therapeutic response to montelukast was consistent across patients with different baseline characteristics and did not correlate with baseline urinary LTE<sub>4</sub>. Addition of a leukotriene receptor antagonist such as montelukast improves asthma in aspirin-intolerant patients over and above what can be achieved by glucocorticosteroids.

**Keywords:** asthma therapy; leukotriene modifiers; glucocorticosteroids; airway inflammation

(Received in original form October 16, 2000; accepted in final form October 9, 2001)

The study was financed by an operating grant from Merck Research Laboratories and basic infrastructure funding by the participating institutions.

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Am J Respir Crit Care Med Vol 165, pp 9–14, 2002

DOI: 10.1164/rccm.2010080

Internet address: www.atsjournals.org

Following the discovery of leukotrienes (LT) as a group of potent arachidonic acid-derived inflammatory mediators (1), drugs that block the action or formation of leukotrienes have been developed. Such antileukotriene drugs are currently introduced worldwide as a new choice in the treatment of asthma (2, 3). However, the place of antileukotriene drugs in the treatment of asthma remains to be defined more precisely (2, 3). The current mainstay of asthma treatment consists of inhaled glucocorticosteroids. The goal is to control asthma, that is, reduce symptoms and asthma exacerbations and improve quality of life and lung function (4). However, patients with moderate to severe asthma are not always completely controlled even by high doses of inhaled glucocorticosteroids (5). In fact, recent studies have suggested that combinations of antiasthmatic drugs with different pharmacological effects may confer better asthma control than glucocorticosteroids alone (6–9).

This study evaluated the new alternative of adding a selective leukotriene receptor antagonist to a group of patients with aspirin-intolerant asthma and moderate to severe asthma requiring conventional controller therapy including glucocorticosteroids. Patients with aspirin-intolerant asthma have nonallergic intolerance to aspirin and related nonsteroidal antiinflammatory drugs (NSAIDs), chronic nasal afflictions, especially recurrent rhinosinusitis with nasal polyposis, and asthma. Their asthma is often inadequately controlled by conventional therapy (10, 11). The strategy to add an antileukotriene to the baseline therapy gains theoretical support from the findings that glucocorticosteroids do not inhibit leukotriene formation *in vivo* (12–15). The drug selected for the study, montelukast (16), is a competitive antagonist of the CysLT<sub>1</sub> receptor (17), which mediates the bronchoconstrictive and proinflammatory effects of cysteinyl-leukotrienes (LTC<sub>4</sub>, LTD<sub>4</sub>, and LTE<sub>4</sub>) (18). Montelukast has demonstrated efficacy in aspirin-tolerant asthma (19, 20), and a relatively long pharmacodynamic effect allows for once daily oral administration (16).

## METHODS

The study was conducted at eight centers in Europe and two in the United States. Approvals were obtained from the respective ethics committees and regulatory agencies, and the patients gave informed consent. Patients had the diagnosis of aspirin-intolerant asthma with characteristic symptoms of chronic rhinosinusitis, asthma, and aspirin intolerance. The intolerance was diagnosed by history and positive oral (36%), inhaled (56%), or nasal (8%) challenges with aspirin. The patients used short-acting  $\beta$ -agonists as needed. Baseline treatment

included glucocorticosteroids and theophylline (Table 1), but the doses had not been changed during the last 3 mo and the last week before the prestudy visit, respectively. None of the patients used long-acting antihistamines, long-acting  $\beta_2$ -agonists, or inhaled antimuscarinics either during the study or in the 2 wk before entering the study. For inclusion in the study, the patients were required during a 2-wk single-blind run-in period to demonstrate (1) at least 12% improvement in FEV<sub>1</sub> following inhalation of  $\beta$ -agonists; (2) mild daytime asthma symptoms (20% of the maximum score [at least 64 of 336 points] according to a previously validated symptom scoring system [21]); and (3) a daily average use of at least one puff of  $\beta$ -agonist. Those who met these three criteria were randomized according to a computer-generated allocation scheme to receive montelukast 10 mg or placebo, orally once daily at bedtime. There were no significant differences between the baseline characteristics of the two groups (Table 1).

During 4 wk of double-blind treatment, morning and evening (before intake of study drug) peak expiratory flow rate (PEFR; Mini-Wright), day (0–6 for four variables) and night (0–4) symptoms, and use of  $\beta$ -agonist were recorded daily on diary cards (21). The patients were seen by study nurses and physicians once a week. Forced expiratory volume in 1 s (FEV<sub>1</sub>) was determined between 6 A.M. and 9 A.M. using a standardized spirometer (Puritan-Bennett PB 100/110; Nellcor, Kansas City, KS) and results were transmitted electronically to a central database. The Asthma Specific Quality-of-Life Questionnaire (22) was completed at the baseline randomization visit and at the last study visit. Blood was collected for routine chemistry and hematology before the run-in period, at the time of randomization and at the last study visit. Duplicate samples of urine were collected at the randomization and at the last study visit, and levels of LTE<sub>4</sub> were determined as described (23).

The primary efficacy analysis used the intention-to-treat approach including all randomized patients with measurements at baseline and at least once during the double-blind period. The baseline values were the average of all recordings during the 2-wk run-in period. The average treatment response during the double-blind period was assessed by analysis of variance (ANOVA) in a model that included factors for treatment and study center. Quantitative interactions between the

study end points and demographic subgroups and concomitant asthma therapy, and the difference between montelukast and placebo groups were assessed using ANOVA. The results were expressed as least square mean with 95% CI unless otherwise stated. All statistical tests were between groups and two tailed, and a p value of less than or equal to 0.05 was considered to indicate significant differences. The study was designed with a 90% power to detect a mean between group difference in FEV<sub>1</sub> of 12 percentage points in percent change from baseline. Effects on nocturnal awakenings were assessed in the group of patients demonstrating at least two nights of awakenings per week during the run-in period. Asthma exacerbations and days with asthma control were defined by a previously described and validated algorithm (19). All patients were included in both efficacy and safety analysis.

## RESULTS

Montelukast significantly improved FEV<sub>1</sub> as well as morning and evening PEFR ( $p < 0.001$ ) (Figure 1). The mean difference in FEV<sub>1</sub> between treatments during the 4-wk period was 10.2% (4.9, 15.5). Likewise, the mean difference between treatments for morning and evening PEFR was 28.0 L/min (14.4, 41.6) and 23.1 L/min (9.5, 36.7), respectively. The effect of montelukast on pulmonary function was manifested within 1 d of treatment as shown by the morning PEFR recordings (Figure 1).

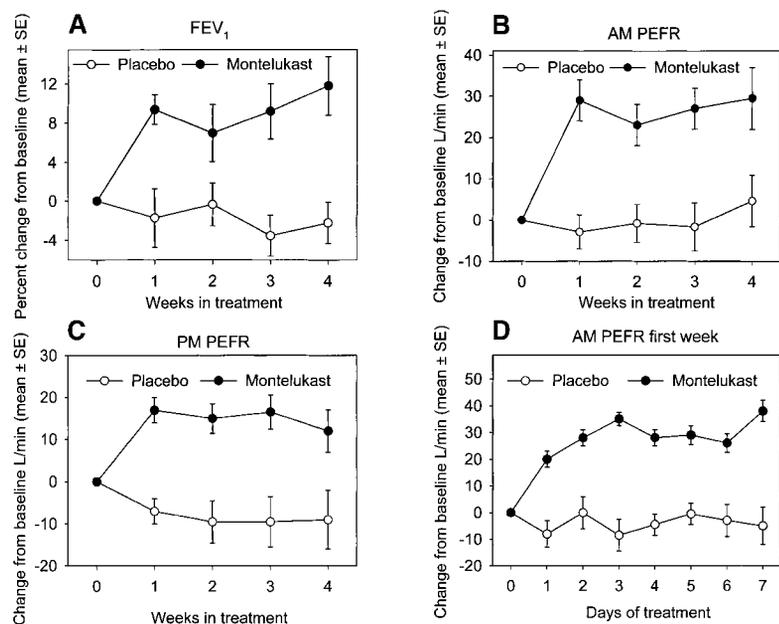
The distribution of the improvement in pulmonary function among the patients is displayed for FEV<sub>1</sub> in Figure 2. In the group receiving montelukast, 52.5% of patients improved their FEV<sub>1</sub> by 5% or more, as compared with 27.5% of subjects in the group on placebo (Figure 2). In fact, 12.5% of the patients in the montelukast group improved by 25% or more, whereas none in the placebo group displayed this magnitude of response. Moreover, in the montelukast group only 7.5% of the subjects showed a decrease in FEV<sub>1</sub> by more than 5% as

TABLE 1. THE BASELINE CHARACTERISTICS OF THE PATIENTS

	Montelukast (40 Patients)	Placebo (40 Patients)*
Age (median; range), yr	48.5 (23–72)	47.0 (22–69)
Sex	25 females (62.5%)	29 females (72.5%)
Duration of asthma (median; range), yr	14.7 (1.3–48.1)	14.2 (1.3–33.2)
Smoking history (median; range), pack-years	0 (0–8)	0 (0–7)
FEV <sub>1</sub> (mean $\pm$ SD), L	2.19 $\pm$ 0.67	2.19 $\pm$ 0.69
FEV <sub>1</sub> percent predicted (mean $\pm$ SD)	69.7 $\pm$ 13.5%	69.6 $\pm$ 12.3%
Morning PEFR (mean $\pm$ SD), L/min	343.6 $\pm$ 95.9	343.3 $\pm$ 107.0
$\beta$ -Agonist use (mean $\pm$ SD), puffs/d	3.8 $\pm$ 2.9	4.2 $\pm$ 2.9
Blood eosinophils (mean $\pm$ SD), per $\mu$ l	330 $\pm$ 290	380 $\pm$ 270
Urinary LTE <sub>4</sub> (mean $\pm$ SD), pg/mg creatinine	489 $\pm$ 488	773 $\pm$ 929
Glucocorticosteroid user	36 patients (90%)	34 patients (85%)
Specifications		
Inhaled only (range 400–2,000 $\mu$ g/d)	22 patients (55%), median dose 800 $\mu$ g/d	19 patients (47.5%), median dose 800 $\mu$ g/d
Oral only (range 4 and 16 mg/d)	2 patients (5%), median dose 10 mg/d	No patient
Inhaled and oral (range 400–1,600 $\mu$ g/d and 2–20 mg/d)	12 patients (30%), median doses 800 $\mu$ g/d and 5.2 mg/d	15 patients (37.5%), median doses 800 $\mu$ g/d and 4.3 mg/d
Theophylline user (range 150–800 mg)	16 patients (40%), median dose 600 mg/d	18 patients (45%), median dose 600 mg/d

Definition of abbreviations: LTE<sub>4</sub> = leukotriene E<sub>4</sub>; PEFR = peak expiratory flow rate.

\* One patient in the placebo group did not complete the study because of severe headaches.



**Figure 1.** Effects of 4 wk once daily oral treatment with placebo ( $n = 39$ ) or 10 mg montelukast ( $n = 40$ ) on pulmonary function in aspirin-intolerant patients with asthma maintained on baseline treatment including moderate to high doses of glucocorticosteroids (see Table 1). (A) FEV<sub>1</sub> measurements (mean  $\pm$  SE) at weekly clinic visits. The average FEV<sub>1</sub> percent change from baseline during the 4 wk was 8.6% and  $-1.8\%$  for montelukast and placebo, respectively ( $p < 0.001$ ). (B, C) Weekly averages (mean  $\pm$  SE) for morning and evening PEFr during the 4 wk of treatment. The morning PEFr increased by 26.2 L/min in subjects given montelukast ( $p < 0.001$ ) but decreased by 1.9 L/min in those given placebo (ns). The baseline values were equal (Table 1). The evening PEFr was increased by 14.8 L/min in the montelukast group from a baseline of 367 L/min, whereas it decreased from a baseline of 369 L/min by 8.3 L/min in the group receiving placebo. (D) Morning PEFr (mean  $\pm$  SD) during the first week of treatment. The difference from baseline in the group receiving montelukast is significant from Day 1 and onward.

compared with 35% in the group given placebo (Figure 2). Closely similar data were obtained for the distribution of other measures of pulmonary function and other end points (not shown).

Daytime asthma symptoms decreased from baseline by 12.7% in the group treated with montelukast as compared with 1.3% in the placebo group ( $p = 0.069$  for the difference between the groups) (Figure 3). In the montelukast group, rescue use of inhaled  $\beta$ -agonist decreased by 27.7% from baseline, whereas it decreased by 1.6% in the placebo group ( $p < 0.05$  for the difference between the groups) (Figure 3). From a baseline of 5.5 (2.1, 7.0) awakenings per week in the subgroup ( $n = 39$ ) displaying nocturnal symptoms during the run-in period, the montelukast-treated group had a reduction of awakenings by 35% in comparison with 5.6% for the placebo group (Figure 3). The difference between the groups was 1.29 additional night ( $-2.61, 0.03$ ) of sleep after montelukast ( $p = 0.055$ ) (Figure 3).

The montelukast group had 8.3% days of asthma exacerbations (mean change from baseline) as compared with 21.7% for placebo (Figure 4). The difference in incidence was 13.5% ( $-22.0, -5.1$ ;  $p < 0.05$ ). Likewise, the montelukast group had 53.6% days of asthma control (mean change from baseline),

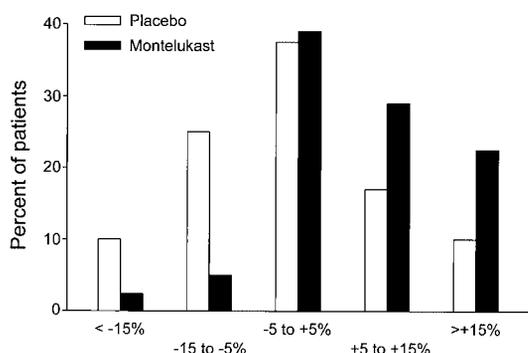
whereas the placebo group had 36.3% ( $p = 0.057$  for the difference) (Figure 4).

There was a significant improvement of pooled asthma-specific QoL after 4 wk of treatment with montelukast compared with placebo, and the most responsive domain was emotions (Figure 5). The mean change from baseline for the average of the four QoL domains during the treatment periods was 0.08 ( $-0.25, 0.41$ ) for placebo and 0.45 (0.15, 0.75) for montelukast ( $p < 0.05$ ).

The treatment effect was consistent across subgroups defined according to age, sex, history of allergic rhinitis or exercise-induced bronchoconstriction, as well as in relation to baseline treatments with theophylline and glucocorticosteroids (not shown). There were, however, no significant interactions between treatment effects and different baseline variables such as FEV<sub>1</sub>, daytime symptom score, or  $\beta$ -agonist use. Both groups of patients excreted high levels of LTE<sub>4</sub> in the urine (Table 1), but there were no correlations in the montelukast group between baseline urinary LTE<sub>4</sub> and treatment effect as assessed by change in FEV<sub>1</sub> (Figure 6), daytime symptom score (not shown), or  $\beta$ -agonist use (not shown). Neither did urinary LTE<sub>4</sub> levels change significantly during the course of either treatment. The mean changes were 112 pg/mg creatinine and  $-89$  pg/mg creatinine for the montelukast and placebo groups, respectively ( $p = 0.167$  compared with placebo).

The peripheral blood eosinophil counts decreased by 50 cells/ $\mu$ l ( $-170, 80$ ) compared with an increase of 80 cells/ $\mu$ l ( $-60, 220$ ) in the placebo group. This difference, however, was not significant ( $p < 0.1$ ).

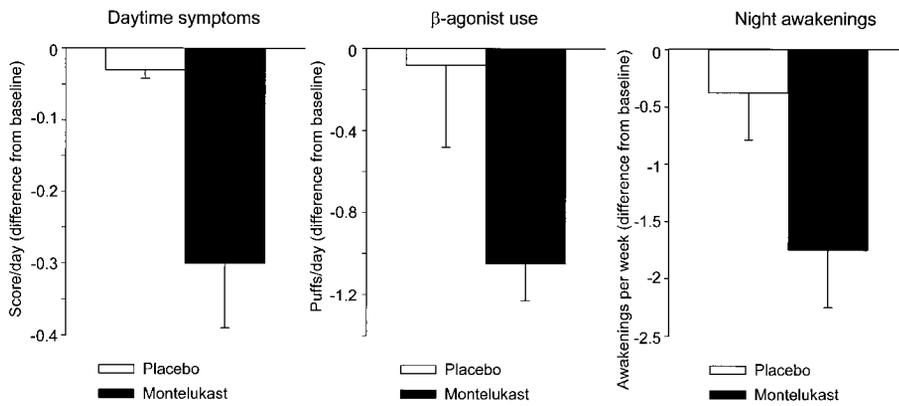
All patients completed the study except for one in the placebo group who discontinued due to severe headaches. There were no significant adverse events during the study. There was no difference between treatment groups with respect to occasional alanine aminotransferase (ALT) or aspartate aminotransferase (AST) values above the upper limit of normal (placebo seven cases, montelukast five cases).



**Figure 2.** Percent of patients in different intervals with respect to change in FEV<sub>1</sub> from baseline.

## DISCUSSION

This study in a group of 80 aspirin-intolerant patients with asthma demonstrated that addition of the leukotriene recep-



**Figure 3.** Change from baseline for both treatment groups in daytime symptoms (baseline scores 2.27 and 2.37 for placebo and montelukast), use of rescue medication (baseline values in Table 1), and night awakenings (see text for baseline value).

tor antagonist montelukast improved pulmonary function and control of asthma over and above what was achieved by treatment with conventional antiasthmatic controller therapy. The baseline treatment included inhaled, inhaled and oral, or only oral glucocorticosteroids in 90 and 85% of the patients receiving montelukast and placebo, respectively. In addition, 40–45% of the subjects used oral theophylline twice daily. The patients were considered to be clinically stable on optimal doses of glucocorticosteroids, and this view is supported by the absence of significant changes in the group given placebo.

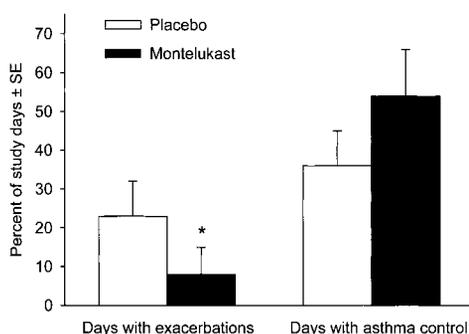
Nevertheless, there were remarkable improvements in the different outcome variables in the group that received montelukast. Pulmonary function increased by about 10%, with similar effects on daily PEFR and weekly FEV<sub>1</sub>, while 27% less rescue medication ( $\beta$ -agonist) was used in the montelukast group. There was a striking 54% decrease in the incidence of asthma exacerbations in the montelukast group. When judged from the diary cards, improvement was observed within 1 d of commencing montelukast treatment and maintained throughout the 4-wk treatment period. In fact, there was a nonsignificant trend for greater improvements in pulmonary function at the end of the 4-wk observation period as compared with the first 2 wk (Figure 1). The patients also reported fewer asthma symptoms and increased asthma-specific quality of life scores on montelukast. Furthermore, subjects with nocturnal asthma given montelukast slept more than one night extra per week (1.32) compared with the placebo group. As in other trials with antileukotrienes (19), it was not possible to identify predictors of the therapeutic response from the patients' baseline characteristics, including the level of urinary LTE<sub>4</sub> (Figure 6).

On the whole, as shown for pulmonary function in Figure 2, there was a marked shift in the response pattern among the

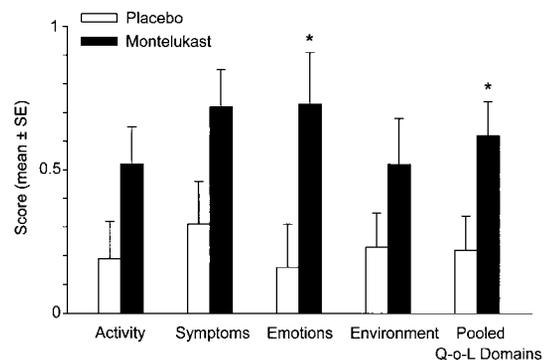
subjects given montelukast, with less than 10% showing deterioration during the active treatment and more than 50% of the patients improving their FEV<sub>1</sub> by more than 5% (and 22.5% improving by more than 15%). In the placebo group, there was a normal distribution of responses with about one-third of patients showing deterioration (more than 5% decrease in FEV<sub>1</sub>), one-third showing no change (change between +5% and -5%), and one-third showing improvement (more than 5% increase in FEV<sub>1</sub>). Furthermore, if there were well-defined subgroups of responders or nonresponders, the treated group would be expected to show a bimodal curve for distribution of responses. The homogeneous shift in the distribution of responses after montelukast provides no clear indication that there should be such subgroups, at least during a 4-wk trial. That assumption would also seem to be supported by the failure to identify predictors of the therapeutic response, including baseline urinary LTE<sub>4</sub>. Closely similar results for the distribution of responses have been obtained in other trials with montelukast (19, 24) as well as for other asthma medications such as beclomethasone (24).

Previous studies with montelukast and other antileukotrienes have shown decreased levels of circulating eosinophils over the first 6–8 wk of treatment (19, 25). It is of interest that there was already a trend for a reduction of eosinophils after 4 wk of treatment in this trial, despite relatively low levels of eosinophils at baseline. It should be acknowledged that with 80 patients, the study was not powered to analyze the effect of montelukast on eosinophil numbers.

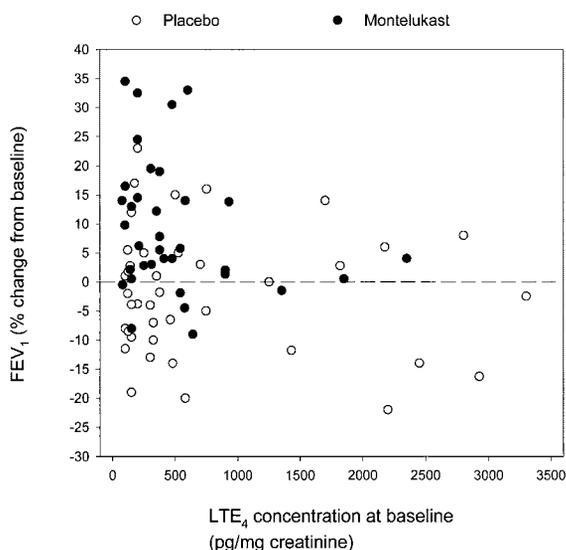
The pronounced effects of montelukast in our study may relate to the aspirin intolerance as such. The therapeutic response appears to be greater than that observed when beclomethasone



**Figure 4.** Change from baseline for both treatment groups with respect to days of asthma exacerbations and asthma-free days (see METHODS section for definitions). \*Significant difference ( $p < 0.01$ ).



**Figure 5.** Quality of life scores after both treatments. The scores are shown as the change from baseline values. \*Significant differences ( $p < 0.05$ ).



**Figure 6.** Scatterplot of baseline urinary LTE<sub>4</sub> versus percent change in FEV<sub>1</sub> during the treatment.

and montelukast were combined in a group of aspirin-tolerant patients with asthma with baseline characteristics being closely similar to those of the patients in this study (26). Patients with aspirin-intolerant asthma are indeed known to have increased production of cysteinyl-leukotrienes (27, 28), and this may be due to upregulation of the LTC<sub>4</sub> synthase (29) and genetic predisposition (30). Aspirin-intolerant patients with asthma have also been reported to be more sensitive to inhalation of leukotrienes than other patients with asthma (31). The latter finding may contribute to explaining why we were unable to find a direct relation between production of leukotrienes, measured as urinary LTE<sub>4</sub>, and the therapeutic response. Future assessments presumably need to take into account leukotriene responsiveness as well, estimated, for example, as sensitivity to inhaled LTD<sub>4</sub>.

Recent trials, however, suggest additive effects between anti-leukotrienes and glucocorticosteroids also in aspirin-tolerant patients with asthma (26, 32, 33). Before it can be concluded that leukotrienes are particularly important mediators in patients with aspirin-intolerant asthma, the effects of anti-leukotrienes in aspirin-intolerant and aspirin-tolerant patients with asthma must be compared using the same study design in patients matched for disease severity and baseline treatment.

Some of us previously reported that addition of the leukotriene biosynthesis inhibitor zileuton improved asthma in aspirin-intolerant patients with asthma (34). The effects of the selective CysLT<sub>1</sub> antagonist montelukast on pulmonary function in the reported study appears to be larger than those observed with zileuton. However, these are comparisons between studies and the groups had dissimilar baseline pulmonary function and possibly variations in reserve for improvement. Nevertheless, because montelukast selectively antagonizes the cysteinyl-leukotrienes, whereas zileuton also inhibits the formation of leukotriene B<sub>4</sub>, the findings together lend support to the notion that the cysteinyl-leukotrienes are the primary mediators of airway obstruction in asthma (3).

In conclusion, the study shows that a group of relatively severe patients with asthma maintained on moderate to high doses of glucocorticosteroids may improve further by the addition of a leukotriene receptor antagonist. Mechanistically, the therapeutic response to montelukast as well as the main-

tained high urinary excretion of LTE<sub>4</sub> provide further evidence that glucocorticosteroids do not inhibit the synthesis of leukotrienes. Although different study designs preclude direct comparisons, it is of interest that the improvements in pulmonary function in the present study were at least as great as those observed when other antiasthmatic agents have been added to glucocorticosteroids (6–9). Our findings reinforce the concept that a combination of drugs with different modes of action may produce better control of asthma than treatment with glucocorticosteroids alone. Better medical control of moderate to severe asthma is likely to have economical consequences for society as the patients with more severe asthma account for a disproportionately greater share of health costs due to hospitalization or absence from work or school (35).

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