Smoking Affects Response to Inhaled Corticosteroids or Leukotriene Receptor Antagonists in Asthma

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Rationale: One-quarter to one-third of individuals with asthma smoke, which may affect response to therapy and contribute to poor asthma control.

Objectives: To determine if the response to an inhaled corticosteroid or a leukotriene receptor antagonist is attenuated in individuals with asthma who smoke.

Methods: In a multicenter, placebo-controlled, double-blind, double-dummy, crossover trial, 44 nonsmokers and 39 light smokers with mild asthma were assigned randomly to treatment twice daily with inhaled beclomethasone and once daily with oral montelukast.

Measurements and Main Results: Primary outcome was change in prebronchodilator FEV₁ in smokers versus nonsmokers. Secondary outcomes included peak flow, PC₂₀ methacholine, symptoms, quality of life, and markers of airway inflammation. Despite similar FEV₁, bronchodilator response, and sensitivity to methacholine at baseline, subjects with asthma who smoked had significantly more symptoms, worse quality of life, and lower daily peak flow than nonsmokers. Adherence to therapy did not differ significantly between smokers and nonsmokers, or between treatment arms. Beclomethasone significantly reduced sputum eosinophils and eosinophil cationic protein (ECP) in both smokers and nonsmokers, but increased FEV₁ (170 ml, $p = 0.0003$) only in nonsmokers. Montelukast significantly increased A.M. peak flow in smokers (12.6 L/min, $p = 0.002$), but not in nonsmokers.

Conclusions: In subjects with mild asthma who smoke, the response to inhaled corticosteroids is attenuated, suggesting that adjustments to standard therapy may be required to attain asthma control. The greater improvement seen in some outcomes in smokers treated with montelukast suggests that leukotrienes may be important in this setting. Larger prospective studies are required to determine whether leukotriene modifiers can be recommended for managing asthma in patients who smoke.

Keywords: antiasthmatic agents; smoking adverse effects; corticosteroids; leukotrienes

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AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

The prevalence of smoking among patients with asthma is approximately the same as in the population at large. Those with asthma who smoke appear to have a blunted response to inhaled and oral corticosteroids. The best strategy for treating these patients is not known.

What This Study Adds to the Field

This study confirms the presence of corticosteroid insensitivity in patients with asthma who smoke, and suggests that leukotriene modifiers may be beneficial in these patients.

Despite the logical expectation that people with asthma would avoid exposure to cigarette smoke, studies suggest that the prevalence of active smoking among individuals with asthma is approximately the same as in the population at large. Thus, during 2005, the median adult smoking prevalence among all 50 states and the District of Columbia was 20.6% (1). Other studies, in the United States and abroad, have reported a smoking prevalence in individuals with asthma of 25 to 35% (2–8). A recent survey of patients with asthma presenting to emergency departments for treatment of asthma exacerbations found that 35% were smokers (9). Moreover, even nonsmoking patients with asthma may have significant exposure to passive smoke. In recent studies from northern Italy, Canada, and the United States, 42 to 58% of patients with asthma reported living with an active smoker or being exposed to cigarette smoke on a daily basis (10–12), and 17.5% of Southern California schoolchildren in the Children's Health Study reported regular exposure to secondhand smoke (13). If biological markers of environmental tobacco smoke exposure (e.g., serum cotinine) are used, up to 90% of patients with asthma have evidence of exposure (14).

Multiple outcomes are known to be worsened when patients with asthma are exposed to cigarette smoke. For example, acute exposure to cigarette smoke triggers bronchoconstriction and symptoms in people with asthma (2, 15). In addition, patients with asthma who smoke regularly have more severe respiratory symptoms, worse quality of life, more emergency department visits and hospitalizations (8, 16), and an accelerated loss of lung function, compared with patients with asthma who do not smoke (17).

Until recently, there has been little information regarding the effect of cigarette smoking on the response to asthma therapy

because most studies of asthma therapy have excluded subjects who smoke. Two recent studies of short-term administration of inhaled and oral corticosteroids have suggested that active smoking interferes with the response to corticosteroids (18, 19). A third, larger study suggested that smokers might benefit from higher doses of inhaled corticosteroid; however, the authors of that study cautioned that interpretation of their results is limited by small sample size and by a negative interaction test for a different effect of smoking in the low- versus high-dose inhaled corticosteroid group (20). To our knowledge, no study has tested other, noncorticosteroid asthma therapies in subjects who smoke, especially in the same cohort.

Leukotrienes have been implicated in the pathophysiology of asthma, and leukotriene-modifying drugs have been reported to be efficacious in the treatment of asthma (21–23). In addition, studies have shown a dose-related increase in urinary leukotriene E_4 (LTE_4) excretion in response to cigarettes in habitual smokers (24), an increase in 15-lipoxygenase activity in the airways of healthy smokers (25), and a smoking-induced increase in urinary LTE_4 in subjects with asthma, but not in subjects with chronic obstructive pulmonary disease (COPD) or normal subjects (26). These studies provide the rationale for studying montelukast in patients with asthma who smoke.

If patients with asthma who smoke do not respond to inhaled corticosteroids (or if they have a significantly blunted response), then the therapeutic ratio shifts significantly. In addition, the fiscal implications are enormous. If we assume that approximately 30% of the 17 million Americans with asthma smoke (2–9), and that approximately 60% have persistent asthma (27), requiring 1 canister of inhaled corticosteroid per month at approximately \$60 per canister, then the cost of administering inhaled corticosteroids to this population would be \$2.2 billion per year. We therefore performed this randomized, crossover trial to examine whether the response to a relatively long (8 wk) course of treatment with an inhaled corticosteroid or with a leukotriene receptor antagonist was blunted in subjects with asthma who smoke. The SMOG (Smoking Modulates Outcomes of Glucocorticoid Therapy) study was sponsored by the National Institutes of Health and conducted by the National Heart, Lung, and Blood Institute's (NHLBI's) Asthma Clinical Research Network (ACRN).

METHODS

Subjects

This study was conducted between January 2002 and February 2004 at the six clinical sites that comprise the NHLBI's ACRN. Steroid-naïve male and female subjects between the ages of 18 and 50 years with a history of asthma (28) were recruited. All were required to have prebronchodilator FEV_1 values of 70 to 90% of predicted and heightened airway reactivity as indicated by 12% or greater reversibility after albuterol inhalation or by PC_{20} (provocative concentration causing a 20% fall in FEV_1) methacholine of less than 8 mg/ml. Nonsmokers were required to have a total lifetime smoking history of less than 2 pack-years, and no smoking for at least 1 year. Subjects were enrolled as smokers if they were currently smoking 10 to 40 cigarettes/day, had a 2 to 15 pack-year smoking history, and a diffusing capacity of carbon monoxide (DL_{CO}) of 80% of predicted or greater. To avoid inclusion of subjects with COPD, exclusion criteria included age older than 50, smoking history of greater than 15 pack-years, active smoking of more than 40 cigarettes/day, and DL_{CO} less than 80% of predicted.

Study Design

The study design was approved by an NHLBI Protocol Review Committee and Data Safety Monitoring Board, and by the institutional review boards at each of the six ACRN clinical centers and the data coordinating center. This was a randomized, double-blind, double-dummy, crossover trial of treatment with an inhaled corticosteroid (hydrofluor-

oalkane [HFA]–beclomethasone dipropionate [BDP] or QVAR, 160 μ g, twice daily) or an oral leukotriene receptor antagonist (montelukast [Singulair], 10 mg, once daily) in subjects with mild to moderate asthma who were or were not current smokers. After a 2-week run-in period, to establish eligibility and adherence to study protocol and forms, subjects entered an 8-week single-blind placebo treatment period. Subjects with asthma who smoked and those who did not were then randomly assigned in parallel to receive either inhaled beclomethasone HFA or oral montelukast for 8 weeks. At randomization, smoking and nonsmoking subjects were matched according to sex, age, and FEV_1 % predicted, to ensure equal representation in the two groups. After the first 8-week treatment period, subjects entered a 6-week placebo wash-out period, followed by a second 8-week period with the alternate treatment. Spirometry, methacholine reactivity, and asthma-specific quality of life were measured, and sputum induction was performed at the beginning and end of each treatment period. Urinary cotinine levels were measured at the beginning of each treatment period to validate smoking history.

Study Procedures and Measurements

At the time of first contact, all subjects who smoked were counseled and encouraged to attempt smoking cessation. Those who declined were enrolled in the study. Counseling and written referral to smoking cessation programs were provided again at the end of the study.

Written, informed consent was obtained from all subjects using forms that contained standard elements approved by the NHLBI, and which were approved by the individual institutional review boards at each institution. Routine history and physical examination and demographic information were recorded at the beginning of the run-in period. Spirometry and diffusing capacity were measured using standard techniques (29, 30). To test reversibility, FEV_1 was measured before and 15 minutes after inhalation of up to 540 μ g of albuterol by a standardized procedure. Bronchial hyperresponsiveness was assessed by measuring the PC_{20} methacholine (31). Asthma-specific quality of life was assessed with a well-validated instrument (32). At the first visit, subjects were provided with an electronic peak-flow meter (AM1; Jaeger, Hoechberg, Germany) and a diary, and instructed in their twice-daily use. In addition, they received single-blind placebo medications. Pill bottles were fitted with an electronic Drug Exposure Monitor (eDEM) (Aardex Ltd., Zug, Switzerland), and metered-dose inhalers were fitted with a Doser device (MediTrack Products, Hudson, MA) to record opening of the pill container and actuation of the metered-dose inhaler, respectively. Sputum induction was performed as described previously (33). Personnel from all sites were trained and certified to perform sputum induction and to prepare slides for analysis, and quality control was maintained throughout the study by periodic overreading and grading of slides. All numerical counts for analysis were performed at a single site (University of California, San Francisco). Cotinine was measured by a reference lab (National Medical Services, Willow Grove, PA).

Statistical Analysis

Descriptive statistics for continuous variables at baseline included means and standard deviations (or medians and quartiles for skewed distributions). The principal outcome was the change in prebronchodilator FEV_1 over the 8-week inhaled corticosteroid treatment period, comparing the change in FEV_1 in the group of smokers with that observed in the nonsmokers. Secondary outcomes included A.M. and P.M. PEF, PC_{20} methacholine, daily symptom scores, and quality-of-life measures. To determine if differences between the smoking and nonsmoking groups reflected differences in the character of inflammation, we examined induced sputum for total and differential cell counts, and for concentrations of eosinophil cationic protein (ECP) and trypsin, as markers of airway inflammation, eosinophil activation, and mast cell activation, respectively. A mixed-effects linear model was applied that included a slope–intercept fit for the set of repeated measurements within each treatment period (Weeks 10–18 or 24–32), while accounting for (1) period and sequence effects from the crossover design and (2) correlations among the repeated measurements within one subject and within subject members of a matched pair (34). Contrasts were then constructed to estimate the mean change between the end and beginning of the treatment periods.

The sample size calculation was performed using estimates for the standard deviation for improvement of FEV₁ after inhaled corticosteroid from prior ACRN studies (35, 36). We calculated that 42 smokers and 42 nonsmokers would provide 90% statistical power for detecting a 10% improvement in FEV₁ in nonsmokers versus a 5% improvement in FEV₁ in smokers when inhaled corticosteroid was administered (primary outcome), and 73% power for detecting an 8% improvement in FEV₁ in nonsmokers versus a 4% improvement in FEV₁ in smokers when a leukotriene receptor antagonist was administered (secondary outcome). Our actual enrollment in this study was 83, providing 89% power for the inhaled corticosteroid comparison and 73% power for the leukotriene receptor antagonist, under the above assumptions.

Randomization and Blinding

Subject randomization was performed online via an Internet connection to the computer system at the data coordinating center. When a subject was deemed eligible for study entry, a clinical center staff member entered and verified the pertinent data and received a drug packet number to give the subject. The study was triple-blinded in that subjects, clinical center personnel, and data analysts were all blinded to treatment identity. Treatment medication for each subject was packaged together,

labeled with a unique number, and distributed to the clinical centers. The contents of the drug packages were known only to administrative personnel at the data coordinating center.

Role of the Funding Source

This study was funded by the NHLBI. The study was conceived, designed, implemented, conducted, analyzed, and interpreted by the investigators of the ACRN. The funding organization was not involved in the conduct of the study or in the collection, analysis, or interpretation of the data, nor did it have editorial authority or rights to decisions about publication. 3M, Inc., provided beclomethasone HFA inhalers and matching placebos, but had no input into the design, conduct, or interpretation of this study. Montelukast and matching placebo were purchased/prepared by the ACRN.

RESULTS

Participant Flow

A total of 182 subjects were screened for this study, and 141 entered the run-in at visit 1 (Figure 1). After 20 nonsmokers

Figure 1. Flow of participants through the study.

and 38 smokers were excluded (Figure 1), 44 nonsmokers and 39 smokers were randomized. Each matched pair was randomly assigned to treatment with either beclomethasone in the first treatment period followed by montelukast in the second, or the opposite sequence.

Subject Characteristics

Nonsmokers and smokers were well matched at baseline (Table 1). They did not differ significantly in any major demographic or physiologic characteristics. Subjects were, on average, 29 years old and had asthma for 10 years or more. The average baseline FEV₁ was 78 to 80% of predicted, with a mean increase after albuterol of 16 to 18%. Median baseline PC₂₀ methacholine was 1.00 to 1.25 mg/ml, and baseline DL_{CO} was normal in both groups. The smokers averaged 7 pack-years, had urinary cotinine levels of 975 (interquartile range, 575–1,000), and despite similar baseline spirometry, reversibility, and PC₂₀ methacholine measurements in the laboratory, had significantly lower daily A.M. peak flow, A.M. and P.M. symptom scores, and worse asthma quality of life compared with nonsmokers.

Treatment Endpoints

In the subjects with asthma who did not smoke, 8 weeks of treatment with inhaled beclomethasone was associated with significant increases in FEV₁ (170 ml), FEV₁% predicted (5%), PEF derived from spirometry (28 L/min), daily A.M. and P.M. PEF (12 L/min and 7 L/min, respectively), and PC₂₀ methacholine (0.63), and with a significant reduction in sputum eosinophils (–2.6%) (Table 2 and Figure 2). In contrast, in the subjects who smoked, the same treatment had no significant effect on any of these variables except for daily A.M. PEF and sputum eosinophils (Table 2 and Figure 2). In general, the changes in the physiologic outcomes in the smokers were in the same direction as in the nonsmokers, but were of smaller magnitude. The between-group differences were not statistically significant, although the greater

improvement in FEV₁ in nonsmokers trended toward significance ($p = 0.09$).

In smokers, but not nonsmokers, treatment with oral montelukast was associated with a significant increase in daily A.M. PEF (13 L/min) (Table 2, Figure 2B). When expressed as percentage of change from baseline, A.M. PEF increased 4.3 and 0.9% in smokers and nonsmokers, respectively, and the difference between groups was significant ($p = 0.02$). Montelukast also decreased daily PEF variability in subjects who smoked ($p = 0.003$), but improved Asthma Quality of Life score in subjects who did not smoke. Neither smokers nor nonsmokers had significant increases in their FEV₁ after 8 weeks of oral montelukast.

Analysis of the Doser devices, eDEM monitors, and diary cards demonstrated that adherence to inhaled and oral medication regimens was 77 to 92% and was not significantly different between smokers and nonsmokers ($p = 0.13$), and that concordance among the three methods of assessing adherence was good.

DISCUSSION

We compared the effects of monotherapy with an inhaled corticosteroid or a leukotriene receptor antagonist in two groups of subjects with mild asthma: one group who actively smoked cigarettes (total smoking history, ~ 7 pack years) and another group who did not. We found that smokers differed from nonsmokers in their responses to beclomethasone and montelukast. Treatment with inhaled beclomethasone was associated with a significant improvement in virtually every physiologic outcome in nonsmokers, whereas the only significant change in smokers was in A.M. PEF. Treatment with montelukast resulted in only small changes in physiologic outcomes in nonsmokers, whereas the change in A.M. peak flow was large in smokers compared with nonsmokers. We conclude that cigarette smoking alters the response to inhaled corticosteroids and leukotriene receptor antagonists in subjects with asthma.

TABLE 1. BASELINE CHARACTERISTICS OF ALL RANDOMIZED SMOG (SMOKING MODULATES OUTCOMES OF GLUCOCORTICOID THERAPY) STUDY SUBJECTS

Characteristic	Nonsmokers (n = 44)		Smokers (n = 39)		p Value
	Mean	SD	Mean	SD	
Age at Week 0	28.98	5.92	29.06	6.54	0.951*
Duration of asthma, yr	17.15	4.99	14.96	6.34	0.083*
Pack-years [†]	0.00	0.00, 0.00	7.00	4.00, 11.00	< 0.001 [‡]
Cotinine at Week 10 [†]	0.00	0.00, 0.00	975.00	575.00, 1,000.00	< 0.001 [‡]
DL _{CO} % predicted at Week 0	97.99	12.70	94.47	13.12	0.219*
FEV ₁ at Week 10, L	2.98	0.54	2.86	0.65	0.379*
FEV ₁ % predicted at Week 10	80.16	9.16	78.10	9.87	0.328*
Maximum reversibility at Week 2 [§]	18.27	10.15	16.41	10.77	0.421*
Methacholine PC ₂₀ at Week 10, mg/ml [§]	1.04	0.46, 3.72	1.25	0.52, 2.16	0.831 [‡]
A.M. peak flow 2-wk avg before Week 10, L/min	456.71	111.62	395.58	93.69	0.009*
A.M. symptom score 2-wk avg before Week 10	0.13	0.20	0.36	0.45	0.005*
P.M. symptom score 2-wk avg before Week 10	0.20	0.23	0.47	0.45	0.001*
AQOL overall score at Week 10	6.04	0.65	5.57	0.78	0.004*
Sputum epithelial cells at Week 10, %	12.59	10.91	16.07	13.33	0.231*
Sputum macrophages at Week 10, %	39.26	20.33	37.22	21.46	0.683*
Sputum eosinophils at Week 10, %	3.15	5.21	2.05	3.11	0.279*
Sputum neutrophils at Week 10, %	43.95	23.76	43.89	24.24	0.991*
Sputum lymphocytes at Week 10, %	1.05	0.84	0.76	0.78	0.139*

Definition of abbreviations: AQOL = Asthma Quality of Life; DL_{CO} = diffusing capacity of carbon monoxide; PC₂₀ = provocative concentration causing a 20% fall in FEV₁.

Week 10 = Randomization.

* *t* Test for differences between smoking groups.

[†] Median and first and third quartiles are reported.

[‡] Wilcoxon test for differences between smoking groups.

[§] Maximum reversibility and PC₂₀ imputed for right-censored observations.

TABLE 2. CHANGE OVER 8 WEEKS OF TREATMENT

Outcome	Treatment	Nonsmokers			Smokers		
		Estimate	95% CI	p Value	Estimate	95% CI	p Value
Spirometry FEV ₁ , L	Montelukast	0.08	(−0.01, 0.18)	NS	0.06	(−0.04, 0.17)	NS
	Beclomethasone	0.17	(0.08, 0.26)	0.0003	0.06	(−0.04, 0.16)	NS
Spirometry FEV ₁ , % predicted	Montelukast	2.14	(−0.43, 4.70)	NS	2.00	(−0.79, 4.79)	NS
	Beclomethasone	4.66	(2.12, 7.21)	0.0004	2.03	(−0.69, 4.75)	NS
Spirometry PEF _R , L/s	Montelukast	0.08	(−0.21, 0.36)	NS	0.30	(−0.02, 0.61)	NS
	Beclomethasone	0.46	(0.18, 0.75)	0.0015	0.17	(−0.13, 0.48)	NS
Diary A.M. peak flow, L/min	Montelukast	4.51	(−2.30, 11.32)	NS	12.64	(4.73, 20.55)	0.0019
	Beclomethasone	11.74	(5.08, 18.40)	0.0006	8.30	(0.80, 15.81)	0.0303
Diary PEF _R variability, %	Montelukast	−0.64	(−1.34, 0.07)	NS	−1.43	(−2.38, −0.48)	0.0035
	Beclomethasone	−0.58	(−1.27, 0.11)	NS	−0.63	(−1.62, 0.37)	NS
Methacholine log ₂ (PC ₂₀)*	Montelukast	0.00	(−0.63, 0.63)	NS	0.27	(−0.29, 0.82)	NS
	Beclomethasone	0.69	(0.05, 1.32)	0.0342	0.53	(−0.00, 1.07)	NS
Sputum eosinophils, %	Montelukast	−1.02	(−3.05, 1.01)	NS	0.99	(−2.26, 4.24)	NS
	Beclomethasone	−2.74	(−4.80, −0.69)	0.0098	−3.44	(−6.56, −0.32)	0.0314
Sputum neutrophils, %	Montelukast	−0.23	(−6.86, 6.40)	NS	−2.70	(−9.82, 4.43)	NS
	Beclomethasone	1.33	(−5.39, 8.05)	NS	−0.86	(−7.71, 6.00)	NS
AQOL average score	Montelukast	0.23	(0.04, 0.42)	0.0200	0.07	(−0.19, 0.32)	NS
	Beclomethasone	0.13	(−0.06, 0.32)	NS	0.12	(−0.13, 0.37)	NS
Log (ECP)	Montelukast	−0.19	(−0.50, 0.12)	NS	−0.46	(−0.75, −0.17)	0.0024
	Beclomethasone	−0.43	(−0.76, −0.11)	0.0091	−0.48	(−0.75, −0.21)	0.0007
Log (tryptase)	Montelukast	−0.14	(−0.58, 0.30)	NS	−0.23	(−0.78, 0.31)	NS
	Beclomethasone	−0.55	(−1.00, −0.09)	0.0194	−0.22	(−0.72, 0.28)	NS

Definition of abbreviations: AQOL = Asthma Quality of Life; CI = confidence interval; ECP = eosinophil cationic protein; NS = not significant; PC₂₀ = provocative concentration causing a 20% fall in FEV₁; PEF_R = peak expiratory flow rate.

* PC₂₀ imputed for right-censored observations and responses to diluent.

Consistent with many other studies, we found that treatment with inhaled beclomethasone resulted in significant improvements from baseline in many outcomes of asthma control and airway function in nonsmoking subjects with asthma. In contrast, we found that the only significant improvements from baseline in smokers were in A.M. PEF, sputum eosinophils, and sputum ECP. Although these differences in treatment response between the nonsmokers and smokers did not reach statistical significance, the consistency of the differences across outcomes and the consistency with prior data (18–20) provide convincing evidence that subjects with asthma who smoke have an attenuated response to inhaled corticosteroids. There are a number of potential mechanisms by which habitual cigarette smoking may induce insensitivity to corticosteroids. Experimental data suggest down-regulation of histone deacetylase (37) and/or enhanced neutrophil-mediated inflammation (38) in smokers. Increased levels of tumor necrosis factor- α (39, 40), or changes in the ratio of the glucocorticoid receptor (GR) isoform GR- α to GR- β (41–44), have also been suggested as explanations for steroid insensitivity. In fact, Livingston and colleagues have reported that the GR- α to GR- β ratio is reduced in peripheral blood mononuclear cells of cigarette smokers (45). Our study and others (24) suggest that production of cysteinyl leukotrienes may be important.

The increase in FEV₁ after inhaled beclomethasone seen in nonsmokers in this study averaged 5% and was less than the 10 to 20% reported in many published studies, including our own (35, 36, 46). Possible explanations for this result are that the subjects had mild asthma (although they had documented albuterol reversibility of $\sim$ 15%), or that they received too little inhaled corticosteroid. The subjects did, in fact, have baseline characteristics very similar to the subjects with mild persistent asthma studied in the Improving Asthma Control Trial (IMPACT) (47), in which the response to treatment with inhaled corticosteroid for 1 year was nearly identical (4%) to that obtained in the current study (5%). The inhaled corticosteroid chosen for this study, HFA-BDP (QVAR), is a chlorofluorocarbon (CFC)-free

preparation with corticosteroid in solution rather than suspension, a formulation believed to produce an extrafine aerosol that deposits more distally in the lung than CFC-BDP. Because of increased lung deposition of HFA-BDP relative to CFC-BDP, patients with asthma require half the daily dose to achieve the same degree of asthma control (48). Thus, the dose of 160 μ g twice daily used here can be considered equivalent to a dose of 320 μ g twice daily of CFC-BDP. This is not a low dose, and we think it unlikely that the smaller-than-expected response in nonsmokers is due to underdosing, especially since adherence, inferred from three separate measures, was close to 90%. An alternative explanation is that we recruited, by chance, a group of nonsmoking subjects with asthma whose response to HFA-BDP was modest. Subjects with asthma show considerable heterogeneity in their responsiveness to inhaled corticosteroids as demonstrated in a prior study in which approximately one-third of inhaled corticosteroid-naïve subjects had a poor response to this treatment (35).

Montelukast produced a statistically significant increase in A.M. PEF and a decrease in PEF variability in smokers, and these changes were significantly greater than its effects seen in nonsmokers. These findings may be explained by enhanced leukotriene synthesis or sensitivity in smokers. Urinary excretion of LTE₄ is closely correlated with the number of cigarettes smoked daily, and urinary LTE₄ levels increase significantly in nonsmokers who smoke six cigarettes in 12 hours (24). Gaki and associates have reported that smoking increases urinary LTE₄ in patients with asthma, but not in normal subjects or patients with COPD (26). Habitual smokers, such as those enrolled in our study, may therefore have chronically elevated leukotriene levels that may render them responsive to treatment with cysteinyl leukotriene receptor antagonists. Although the smokers with asthma had a significant response to montelukast in terms of A.M. peak flow and sputum ECP, other outcomes were not similarly improved. For example, in smokers, the effects of montelukast on FEV₁, PC₂₀ methacholine, asthma symptoms,

Figure 2. Effect of 8 weeks of double-blind treatment on FEV₁ (A), PEF (B), PC₂₀ methacholine (Mch) (C), and percentage of eosinophils in sputum (D). Solid bars, nonsmokers; open bars, smokers.

and asthma quality of life were not significantly greater than in nonsmokers. Nevertheless, our data for improvement in A.M. peak flow warrant follow-up in larger studies, including studies of the effects of leukotriene pathway modifiers on asthma exacerbation rates in smokers.

Relatively few studies have focused on the effects of cigarette smoking on outcomes of asthma control and airway inflammation in subjects with asthma. In this regard, we would emphasize some important observations made during the initial character-

ization visits of the study. First, despite smoking at least 10 cigarettes per day for an average of 7 years, smokers with asthma demonstrated, at baseline, albuterol reversibility and methacholine reactivity that were very nearly identical to nonsmokers. Second, despite similar FEV₁, FEV₁% predicted, reversibility, and response to methacholine, the subjects with asthma who smoked had significantly more symptoms (across all symptom domains), worse asthma-specific quality of life, and lower PEF measured daily at home than did the nonsmokers. These findings are consistent with previous studies that have described worse clinical status in subjects with asthma who smoke (8, 16, 17). Although several studies have reported that smokers with chronic airflow obstruction have fewer symptoms with induced bronchoconstriction than patients with asthma with similar obstruction (49, 50), perhaps due to depletion of neurotransmitters from sensory nerves (50), the ability to perceive induced bronchoconstriction could not be predicted by smoking history (49). Taken together, these data demonstrate that laboratory-based testing does not capture the impact of cigarette smoking on disease severity in asthma such as is captured by daily symptom diaries and quality-of-life measures. Third, the baseline sputum cell profiles did not differ based on smoking status: We found no differences in the percentages of eosinophils or neutrophils in induced sputum obtained at baseline. We expected to find increased sputum neutrophils in smokers because smoking has been associated with neutrophilic inflammation in the airways (38, 51), which improves with smoking cessation (51, 52), and inhalation of cigarette smoke has been shown to induce chemotactic attraction of neutrophils, probably through induction of release of interleukin-8 (53, 38). Our data may be explained by the relatively young age of the subjects with asthma in our study and their relatively modest smoking history; most studies demonstrating that cigarette smoke causes inflammation and remodeling have enrolled older subjects with high numbers of pack-years of smoking. These results suggest that sputum neutrophilia may be a marker of heavy smoking and may not be causally related to the development of steroid insensitivity in patients with asthma who smoke cigarettes habitually.

Taken together, our data and those of others suggest that corticosteroid resistance occurs in patients with asthma who smoke and should be considered when prescribing treatments for this asthmatic subgroup. For example, Tomlinson and colleagues have suggested that these patients may benefit from increased inhaled corticosteroid dose (20). In addition, for some asthma control outcomes, we found that the lung function response to montelukast was better in patients with asthma who smoke than in nonsmokers. These data are not sufficient to warrant a change in treatment algorithms, but indicate the need for larger studies to further explore the utility of inhibiting leukotrienes in patients with asthma who smoke cigarettes. Meanwhile, our data suggest the need for a specialized approach to patients with asthma who smoke. Clearly, ongoing counsel and assistance with smoking cessation are essential. In addition, because of differences in treatment response, further trials are warranted to establish the optimal management strategies for subjects with asthma who are unwilling or unable to stop smoking.

Conflict of Interest Statement: S.C.L. received \$9,000 in 2003 and \$3,000 in 2004 from Merck and \$2,000 in 2004 from Critical Therapeutics for serving on advisory boards, \$2,500 in 2004 from GlaxoSmithKline and \$5,500 in 2005 from Merck for participating as a speaker in scientific programs, and \$36,000 in 2003 from Abaris Pharma as a research grant for participating in a clinical trial. V.M.C. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. N.J.R. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. H.A.B. received payments in 2003 and 2004 from GlaxoSmithKline for service on a steering committee for a multicenter study, chairing and speaking at conferences, and directs a research project funded by the company at University of California, San Francisco, as well as receiving payments for honoraria and consulting from

Altana, Sanofi-Aventis, Boehringer-Ingelheim, Novartis, and Sumitomo. R.C. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. T.J.C. has a pending consultancy with Schering-Plough, is an advisory board member of Sanofi-Aventis, and received \$8,000 in lecture fees from Merck, \$6,000 in lecture fees from Genentech, \$5,000 in lecture fees from GlaxoSmithKline, and \$5,000 in lecture fees from Schering-Plough; he has pending sponsored grants from Schering-Plough and Merck, and \$50,000 in grants from GlaxoSmithKline, and received \$100,000 grants from the American College of Allergy, Asthma, and Immunology (ACAAI), and \$5,000 from Methapharm. He has received \$125,000 in research grants from AstraZeneca, \$325,000 in research grants from Boehringer-Ingelheim, \$75,000 in research grants from Novartis, \$50,000 in grants from Genentech, \$85,000 in research grants from Dyax, \$50,000 in research grants from Lev, \$25,000 in research grants from Protein Design Labs, \$25,000 in research grants from Centacore, and \$200,000 in research grants from Sanofi-Aventis. A.D. has served on advisory boards for AstraZeneca in October 2002 and for Aerocrine, Inc., in May 2002; Brigham and Women's Hospital received a research grant of \$55,000 for a clinical trial conducted in January 2005 with A.D. as the site investigator. E.D. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. J.E.F. was an employee of Sanofi-Aventis at the time of this study, a pharmaceutical company involved in developing an inhaled corticosteroid (ciclesonide). This inhaled corticosteroid may be viewed as a potential competitor to the study drug, beclomethasone HFA; however, ciclesonide remains an experimental drug (not approved by the Food and Drug Administration). He currently is an employee of Genentech, Inc. J.G.F. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. E.I. served as a consultant for Asthmatrix in 2005 and received between \$10,000 and \$20,000. A multicenter clinical research project at his institution is currently pending. He receives advisory board fees of less than \$10,000 from Merck, received speaker's fees from Merck between 2003 and 2005, and participated in a multicenter clinical research project with Merck in 2005. He received between \$10,000 and \$20,000 in speaker's fees from Genentech in 2005, serves on a Genentech advisory board, and his institution is conducting a multicenter clinical trial with Genentech. In the past 3 years, E.I. participated in multicenter clinical trials with AstraZeneca, Boehringer-Ingelheim, Centocor, GlaxoSmithKline, and Merck. He received a medical school grant from Merck for support and research for less than \$50,000. J.K. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. M.K. received \$6,000 in 2003 and \$5,000 in 2004 for speaking at conferences sponsored by Merck, \$2,000 in 2004 from GlaxoSmithKline for speaking, \$8,000 in 2003, \$6,000 in 2004, and \$3,000 in 2005 for speaking sponsored by Genentech/Novartis, \$3,000 in 2005 for speaking sponsored by Sepracor, \$3,000 from AstraZeneca for consulting in 2004 and 2005, \$3,000 from GlaxoSmithKline for consulting, and research grants from GlaxoSmithKline, Genentech, and Boehringer-Ingelheim. R.F.L. received speaker honoraria from GlaxoSmithKline, Merck & Co., Aventis, and AstraZeneca in the last 3 years; in 2002, this totaled \$22,000 and, in 2003, \$12,000; all the other yearly amounts for each company were under \$10,000. He also received consultant fees from AstraZeneca, Aventis, GlaxoSmithKline, and Novartis/Genentech; in 2004, he received \$11,000 from AstraZeneca while all the other amounts for all years totaled under \$10,000. F.T.L. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. R.J.M. received advisory board fees of less than \$10,000 per year and lecture fees of greater than \$10,000 per year from Ivax for 2003–2005, and received lecture fees of less than \$10,000 per year from Merck for 2003–2005. G.R.P. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. S.P.P. does not own any stock in pharmaceutical or other related companies except for shares in various mutual funds, but his wife is a member of an investment club that owns less than 50 shares each of various stocks. From 2003 to 2005, S.P.P. performed the following consultative or other work, including basic research studying asthma pathogenesis under the National Institutes of Health, NHLBI, Bethesda, MD: clinical trials studying new and existing therapies for asthma treatment under the National Institutes of Health, National Heart, Lung, and Blood Institute, and its Asthma Clinical Research Network, Bethesda, MD, and the American Lung Association; pharmaceutical company clinical trials, as a member of a Wake Forest University Clinical Trials Group supported by Abaris, AstraZeneca, Altana, Boehringer-Ingelheim, Centocor, Genentech, GlaxoSmithKline, Novartis, Pfizer, and Wyeth; consulting (usually review of scientific grant proposals, review of data concerning drugs used for the treatment of asthma, or scientific writing/editing) under the National Institutes of Health, Adelphi (*Respiratory Digest*, Associate Editor), American Thoracic Society (*AJRCCM*, Associate Editor), AstraZeneca Pharmaceuticals, Asthma Leadership Council, Discovery, Genentech, Novartis, Omnicare, RAND Corporation, *Respiratory Medicine* (Associate Editor), *Respiratory Research* (Associate Editor), and Sanofi-Aventis; and participating in physician education programs (including speakers' bureaus) sponsored by American College of Chest Physicians, American Lung Association, American Academy of Allergy, Asthma & Immunology, AstraZeneca Pharmaceuticals, Merck Pharmaceuticals, Genentech, Novartis, and Respiratory and Allergic Disease Foundation. C.A.S. received \$5,000 annually for speaking at conferences sponsored by GlaxoSmithKline and AstraZeneca from 2002 to 2005, \$5,000 annually (2003–2005) from GlaxoSmithKline and AstraZeneca for serving on advisory boards, and \$50,000 in grant support from GlaxoSmithKline for 2002–2004. S.J.S. served as a consultant and a member of an advisory board for GlaxoSmithKline, AstraZeneca, and Aventis for the last 3 years and received approximately \$6,000 per year from each company, from Merck for 2 years at \$5,000 per year, and also received research funds for clinical trial performances from AstraZeneca for \$90,000 for 2002–2004 and Ross Pharmaceuticals for \$1,200,000 for 2003–2005.

M.E.W. received less than \$5,000 a year for 2003–2005 from Merck, Novartis, and GlaxoSmithKline for consultancies, advisory boards, and lecture fees. J.V.F. currently serves as a consultant to Abgenix, and served as a consultant to Sanofi-Aventis and AstraZeneca in 2004.

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