Oral Montelukast Sodium versus Inhaled Fluticasone Propionate in Adults with Mild Persistent Asthma

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ABSTRACT

Objective: Asthma consensus guidelines recommend the use of a controller agent to control asthma symptoms and reduce inflammation in patients with mild asthma. The objective of this study was to compare montelukast to inhaled fluticasone on the percentage of asthma-free days in patients with mild persistent asthma during 48 weeks of active treatment.

Methods: This was a randomized, multicenter study with a 3-week single-blind run-in period, followed by a 12-week double-blind active treatment period, and a 36-week open-label active treatment period. Patients (aged 15 to 80 years) with mild persistent asthma as established by the Global Initiative for Asthma (GINA) guidelines were randomized to receive oral montelukast 10 mg (n=325) or fluticasone 100 µg (n=320) twice daily by metered-dose inhaler. An analysis of covariance model was used to analyze the primary endpoint of asthma-free days. Montelukast would be considered at least as effective as fluticasone if the treatment difference (average percentage of asthma-free days on fluticasone minus average percentage of asthma-free days on montelukast) was below 10% (3 days/month). Secondary endpoints were "as-needed" β-agonist use, days with symptoms, rescue-free days, asthma-specific quality of life, forced expiratory volume in 1 second (FEV_1), morning peak expiratory flow, asthma attacks, nocturnal awakenings, patient global assessment of asthma, blood eosinophil count, and safety and tolerability.

Results: Patients taking fluticasone had 6.44% (95% confidence interval [CI] 2.24, 10.64) more asthma-free days than did patients taking montelukast (<2 days/month/patient). The CI included the non-inferiority boundary of 10%. Both montelukast and fluticasone showed an improvement in asthma-related efficacy endpoints, except FEV_1, which was improved only for patients taking fluticasone. Both montelukast and fluticasone were well tolerated.

Conclusions: Both agents demonstrated efficacy for most of the primary and

secondary endpoints. Results for most endpoints were essentially equivalent; however, patients taking fluticasone had more asthma-free days and improved FEV_1 than did patients taking montelukast.

INTRODUCTION

Current therapeutic guidelines recommend inhaled steroids as first-line treatment for mild persistent asthma since airway inflammation is a significant part of the pathology.[1–5] Patients with mild asthma suffer from recurrent (though infrequent) symptoms and limitations in their activities. The cysteinyl leukotrienes LTC_4, LTD_4, and LTE_4 play an integral role in the pathophysiology of asthma.[6,7] Montelukast, a selective potent leukotriene-receptor antagonist given once daily, has been shown to effectively reduce symptoms of asthma in adults and in children (including those younger than 2 years of age). It has also been shown to reduce symptoms of allergic rhinitis.[8–14]

Traditionally, the efficacy of anti-asthma therapy is assessed by improvements in forced expiratory volume in 1 second (FEV_1), as well as home-monitored peak expiratory flow (PEF), patient-reported symptoms, and use of rescue medication; however, the correlation between these measures is often poor, suggesting that they measure different aspects of the disease.[15,16] Recently, emphasis has shifted to an evaluation of outcomes that impact patients' lives. Measures such as asthma-free days, asthma rescue medication-free days, and quality-of-life assessments show sensitivity and responsiveness in studies of mild asthmatic patients and help to define therapeutic effectiveness. Mild and moderate asthmatic patients taking montelukast have been reported to have experienced clinically important improvements in airway function, asthma exacerbations, asthma attacks, and symptoms.[8–10,17]

Although inhaled corticosteroids are effective in reducing symptoms of asthma, concerns about safety and non-compliance suggest that other agents that effectively reduce airway inflammation and are convenient to use may be a viable alternative.[18–21] In a previously published study, once-daily oral montelukast was similar to twice-a-day inhaled fluticasone in improving asthma rescue-free days and other symptoms of asthma in adults with mild asthma over 12 weeks of treatment.[17] The purpose of the present study was to compare the effects of oral montelukast versus inhaled fluticasone in increasing asthma-free days over a 12-week double-blind period and to evaluate the maintenance of treatment effect in a 36-week open-label period in patients with mild persistent asthma.

METHODS

Study Design

Protocol 905 was a 51-week, 3-period, randomized, double-blind, multicenter study at 77 sites in 22 countries in Europe, Asia, and South America. The study consisted of a 3-week run-in period (Period 1), a 12-week double-blind treatment period (Period 2), and a 36-week open-label treatment period (Period 3). During Period 1, patients received single-blind oral and inhaled placebo during the last 2 weeks of the 3-week period. During Period 2, patients were randomized using a computer-generated allocation schedule to receive either oral montelukast 10 mg (n=325) once daily at bedtime or fluticasone 100 µg (n=320) twice daily by metered-dose inhaler (MDI). This schedule incorporated the random switch of therapy for the 12-week double-blind period to the 36-week open-label phase for 10% of the patients while 90% remained on the initial therapy. Written informed consent approved by the respective

institutional review boards was obtained from all participants.

Inclusion Criteria

Patients with mild persistent asthma as defined by Global Initiative for Asthma (GINA) guidelines were included.[2] Patients were nonsmoking males and females, 15 to 80 years of age, with a history of asthma for at least 4 months, a baseline FEV_1 value 80% of predicted, and with either -agonist reversibility of at least 12% (FEV_1 or PEF) or a positive exercise challenge test within the previous month. Patients also had to have demonstrated daytime symptoms and short-acting -agonist use on at least 2 days—but not every day—of the first week of the run-in period. Patients were to be in need of, but not on, controller medication, and at the time of enrollment could only be taking -agonists.

Exclusion Criteria

Patients treated in an emergency department within 1 month, hospitalized for asthma within 3 months, or having unresolved symptoms and signs of upper respiratory tract infection within 3 weeks were excluded. Excluded medications included any form of corticosteroids within 1 month; cromolyn, nedocromil, or leukotriene-receptor antagonists within 2 weeks; theophylline, oral or long-acting -agonists, or inhaled anticholinergics within 1 week; or terfenadine, fexofenadine, loratadine, or cetirizine within 48 hours of the first visit. Patients starting immunotherapy within 6 months were excluded; however, a patient taking immunotherapy longer than 6 months prior to entry could be included if dosage was consistent throughout the duration of the study.

Evaluations

The primary endpoint was the comparison of the effect of 12 weeks of treatment with oral montelukast on the percentage of asthma-free days. An asthma-free day was defined as any day in which the patient had normal pulmonary function (PEF at least 80% of predicted), no symptoms (a score of 0 or 1 out of a possible 6 on the diary card question), no use of rescue medication (short-acting -agonists or other), no nocturnal awakenings, and no unscheduled doctor visits. Results with montelukast were compared with those for patients taking fluticasone.

Secondary endpoints included "as-needed" -agonist use, percentage of days with -agonist use, days with symptoms, percentage of asthma rescue medication-free days, asthma-specific quality of life, FEV_1, morning (AM) PEF, asthma attacks, nocturnal awakenings, patients' global assessment of asthma, blood eosinophil count, percentage of asthma rescue medication-free days in patients with normal lung function, and safety and tolerability over the 12-week period. Also evaluated was the treatment effect of oral montelukast and inhaled fluticasone over the 36-week open-label treatment period (Period 3) and the maintenance of treatment effect from Period 2 to Period 3.

A day with symptoms was any day with a symptom score of 2 or greater on the diary card question. An asthma rescue medication-free day was defined as any day a patient had no -agonist or corticosteroid use and no asthma-related health care resource use, such as an unscheduled office visit, an urgent or emergency care visit, or hospitalization. An asthma attack was defined as an unscheduled visit to the doctor's office, emergency room, or hospital or treatment with oral, intravenous, or intramuscular corticosteroids. Patients with normal lung function were defined as those with an AM PEF at least 80% of predicted.

Patients were instructed how to use the daily diary card which contained daytime asthma symptoms and nighttime awakening scales that had been previously shown to have acceptable evaluative measurement properties.[22] Daytime asthma symptoms were recorded in the evening before taking study medication and included an assessment of the daily asthma symptoms, such as, but not limited to, chest discomfort (tightness), wheezing, shortness of breath (breathlessness), and cough rated on a 7-point scale from 0 (symptoms none of the time) to 6 (symptoms all of the time). Patients recorded the total number of puffs of "as-needed" β-agonist used since arising. Nighttime symptoms were recorded in the morning upon arising, before taking any medication. Patients recorded whether they woke up during the night with symptoms of asthma and the total number of β-agonist puffs taken since going to bed. Patients also recorded the use of oral corticosteroid rescue medications and visits to the physician's office or hospital for episodes of worsening asthma. Patients measured PEF (best of 3 measurements) in the morning on arising using a commercial flow meter.

At the completion of the 12-week period, patients evaluated the change in asthma (global evaluation) by selecting the most appropriate response on a 7-point scale (very much better, moderately better, a little better, unchanged, a little worse, moderately worse, very much worse). An asthma-specific quality-of-life questionnaire was completed prior to randomization and at the end of the 12-week and 36-week periods or upon discontinuation of the trial.[23]

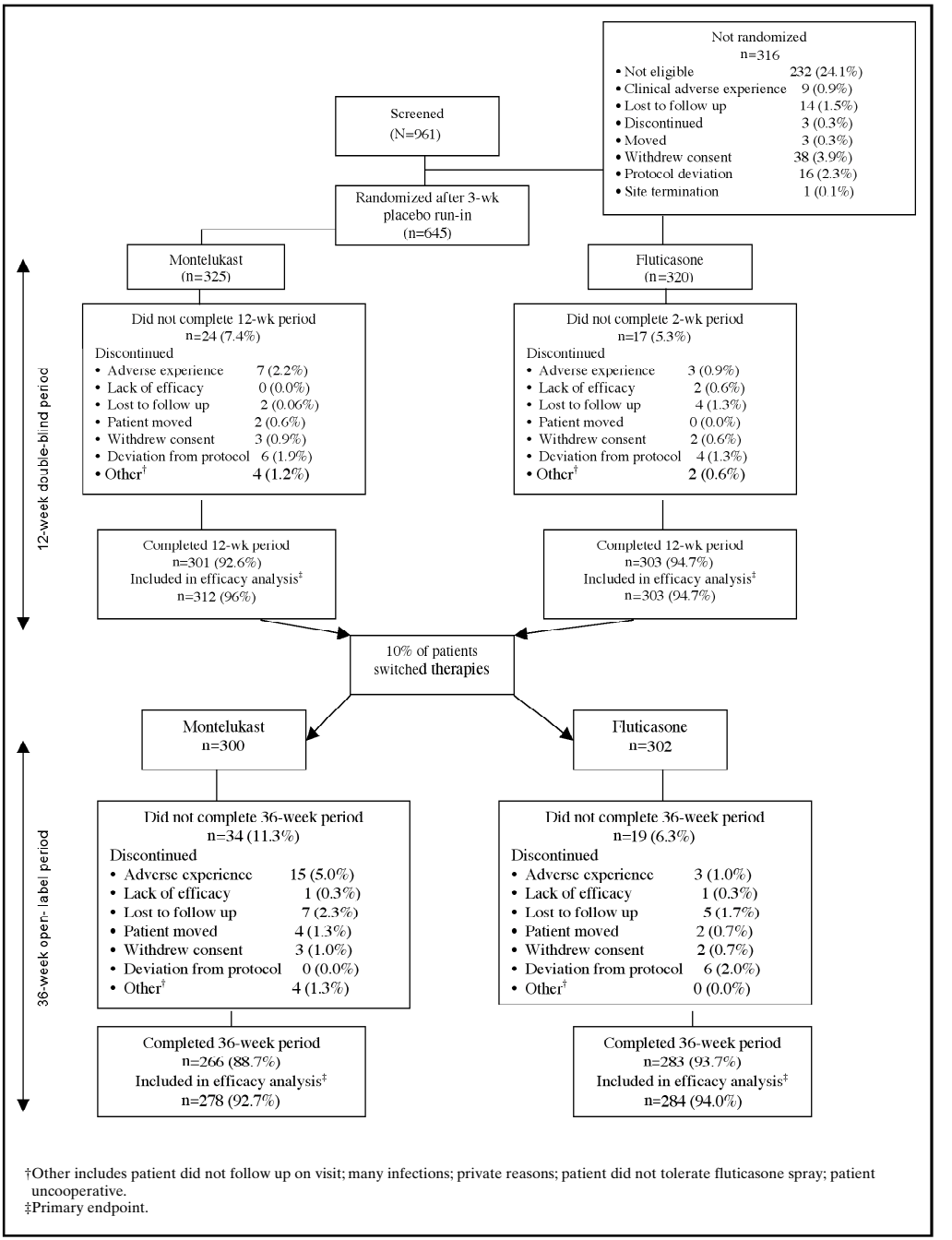
Statistical Methods

The primary analysis was a modified intention-to-treat approach in that all patients who have been treated for 1 day with at least one baseline measurement were included in the analysis. To assess whether montelukast was similar to fluticasone for the primary endpoint, it was determined that the two-sided 95% CI of the treatment difference (average percentage of asthma-free days on fluticasone minus the average percentage of asthma-free days on montelukast) for the 12-week double-blind period and the 36-week open-label period should lie below 10% (3 days per month). The 95% CI was constructed using the least-squares (LS) means from an analysis of covariance (ANCOVA) model with effects for treatment and center, using baseline asthma-free days as covariate. Treatment differences for secondary endpoints were explored using 95% CIs constructed using LS means. In addition, the treatment difference for secondary endpoints was tested using an analysis of variance (ANOVA) or ANCOVA models with effects for treatment and center using baseline as covariate (if available). Maintenance of treatment effect was explored for patients remaining on the same treatment throughout the whole 48 week active treatment duration (90% of patients).

The safety profile of montelukast and fluticasone was compared by statistical and clinical assessments of frequency of adverse experiences during the treatment periods.

Power and Sample Size

The study was designed with a sample size of 166 patients in each treatment group in order to provide 90% power to accurately assess the primary endpoint of asthma-free days during the 12-week period. A limit of 10% corresponds to a treatment difference of 3 days/month. A larger number of patients was recruited to ensure that there was a sufficient number of patients with mild asthma and whose symptoms corresponded to Step II of the GINA guidelines.



†Other includes patient did not follow up on visit; many infections; private reasons; patient did not tolerate fluticasone spray; patient uncooperative.
‡Primary endpoint.

Figure 1. Study design for evaluation of oral montelukast 10 mg and inhaled fluticasone 100 µg twice daily in patients with mild persistent asthma

RESULTS

Patients

Six hundred forty-five patients entered the 12-week double-blind treatment period; 325 were allocated to the oral montelukast group and 320 to the inhaled fluticasone group (Figure 1). The demographic characteristics of the patients were essentially and statistically similar between the two groups

Table 1. Demographic and Baseline Characteristics of Randomized Patients with Asthma Treated with Oral Montelukast 10 mg Once Daily at Bedtime or Inhaled Fluticasone 100 µg Twice Daily

Characteristic	Montelukast n=325	Fluticasone n=320
Age, yr	35.9 ± 14.3	36.6 ± 13.8
Gender, n (%)		
Male	126 (38.8)	113 (35.3)
Female	199 (61.2)	207 (64.7)
Race, n (%)		
Caucasian	208 (64.0)	196 (61.3)
Black	2 (0.6)	3 (0.9)
Asian	37 (11.4)	38 (11.9)
Hispanic	58 (17.8)	63 (19.7)
Other	20 (6.2)	20 (6.3)
Height (cm)	167.3 ± 10.1	165.9 ± 10.0
Weight (kg)	71.4 ± 15.6	69.3 ± 13.7
History of allergic rhinitis, n (%)	194 (59.7)	179 (56.1)
History of atopic dermatitis, n (%)	42 (12.9)	45 (14.1)
FEV_1, L (n)	3.14 ± 0.85 (324)	2.99 ± 0.81 (318)
FEV_1, % of predicted, (n*)	90.5 ± 12.2 (324)	88.2 ± 12.2 (318)
AM PEFR, L/min, (n*)	397.7 ± 102.2 (323)	390.7 ± 108.8 (314)
Asthma-free days, %, (n*)	22.6 ± 23.2 (320)	22.8 ± 23.6 (308)
-agonist, puffs/day, (n*)	1.28 ± 1.1 (305)	1.38 ± 1.3 (301)
Days with symptoms, % (n*)	47.0 ± 22.2 (324)	48.6 ± 21.6 (313)
Asthma rescue medication free days,† %, (n*)	45.3 ± 22.2 (311)	44.7 ± 23.0 (303)
Quality of life score, pooled domains, (n*)	4.98 ± 1.00 (324)	4.97 ± 0.95 (318)
Nocturnal awakenings, % (n*)	21.3 ± 26.5 (321)	23.1 ± 27.1 (309)
Blood eosinophils, $10^3/\mu L$ (n*)	0.29 ± 0.24 (319)	0.28 ± 0.22 (315)

*Number of patients with available information in this category.

†Defined as a day without -agonist use or other asthma-related medication or resource use and AM PEF at least 80% of predicted.

FEV_1 = forced expiratory volume in 1 second; AM PEF = peak expiratory flow measured in the morning.

Data are mean ± standard deviation unless otherwise specified.

(Table 1). Patients continuing into the open-label phase were generally similar to those not continuing into the open-label phase.

Of the 645 patients, 30 (13 in the montelukast group and 17 in the fluticasone group) were excluded from the modified intention-to-treat analysis for the primary endpoint of asthma-free days. Three patients were excluded from all efficacy analyses due to protocol violations, and 27 were excluded due to a lack of a valid baseline or treatment-period measurements. A total of 602 patients entered the open-label 36-week phase; 300 patients in the montelukast group and 302 in the fluticasone group (Figure 1).

Efficacy Evaluations

Asthma-Free Days

Throughout the trial, both montelukast and fluticasone significantly improved the primary endpoint asthma-free days

Table 2. Treatment Differences in Efficacy Endpoints for Oral Montelukast 10 mg and Inhaled Fluticasone 100 µg Twice Daily in Patients With Mild Persistent Asthma

End Point	Treatment Differences in the 12-Week Double-Blind Period				
	Montelukast		Fluticasone		LS Mean Treatment
	n*	Mean (SD)	n*	Mean (SD)	Difference (95% CI)†
Asthma-free days (%)	278	46.1 (36.1)	284	49.5 (37.0)	5.38 (0.07,10.69)
"As needed" β-agonist use‡§	218	–42.6 (79.4)	235	–52.5 (77.9)	–9.78 (–24.62, 5.06)
Days with β-agonist use (%)	268	28.6 (28.9)	281	24.9 (31.1)	–4.95 (–9.56, –3.4)
Days with symptoms (%)	280	23.9 (27.7)	290	19.2 (27.0)	–5.10 (–9.26, –0.94)
Asthma rescue medication-free days (%)	268	71.2 (29.1)	281	74.8 (31.1)	5.07 (0.42, 9.72)
Asthma rescue medication-free days with normal lung function (%)	278	50.2 (36.6)	285	52.8 (37.3)	4.83 (–0.45, 10.10)
FEV_1 (L, % change)	277	–2.04 (10.36)	284	1.52 (10.57)	3.14 (1.43, 4.85)
FEV_1 (% of predicted)‡§	277	–2.02 (9.27)	284	1.25 (9.20)	2.83 (1.33, 4.32)
AM PEF (L/min)‡§	279	22.8 (55.4)	291	32.4 (49.2)	9.35 (1.01, 17.68)
Nocturnal awakenings (%)	279	9.9 (18.3)	288	8.0 (15.8)	–2.73 (–5.33, –0.13)
Asthma specific Quality of Life score	208	0.66 (0.97)	237	0.83 (1.06)	0.11 (–0.04, 0.27)
Eosinophil count ($10^3/\mu L$)‡§	275	–0.04 (0.20)	285	–0.04 (0.20)	0.01 (–0.02, 0.03)

*Number of patients with data available in this category.

†Treatment difference = montelukast value – fluticasone value.

‡Includes only patients with baseline β-agonist use ≥ 0.5 puffs/day.

§Change from baseline.

CI = confidence interval, LS = least squares; SD = standard deviation.

from baseline (P < 0.001) (Figure 2). At 12 and 36 weeks, the number of asthma-free days was significantly greater for patients treated with fluticasone than for those treated with montelukast. The LS mean treatment difference was 6.44% in favor of fluticasone at 12 weeks (P=0.003) and 5.38% in favor of fluticasone at 36 weeks (P=0.047) (Table 2).

The maintenance of treatment effect was evaluated by slope analysis of the weekly measurements over the 12- and 36-week periods. There was a significant increase in asthma-free days relative to baseline for both montelukast and fluticasone (P=0.031). The difference in slopes (–0.11 [95% CI –0.24, 0.02]) between montelukast and fluticasone over the entire 48 weeks was not significant (P=0.094).

The subgroup analysis by gender, age, race, baseline β-agonist use, and years since diagnosis of asthma showed no significant treatment × subgroup effect except for evaluation by baseline β-agonist use. No treatment difference was evident in patients with low β-agonist use at baseline compared with the median (<0.92 puffs/day). In patients with high β-agonist use at baseline (> 0.92 puffs/day), a higher percentage of asthma-free days was seen for patients taking fluticasone compared with values at baseline (P=0.031).

Secondary Endpoints

Both montelukast and fluticasone significantly reduced average daily "as needed" β-agonist use in patients who had at least 0.5 puffs/day of β-agonist use at baseline (P=0.002) (Figure 3). At 12 weeks, patients on fluticasone had a significantly greater decrease in puffs/day

Treatment Differences in the 36-Week Open-Label Period				
Montelukast		Fluticasone		LS Mean Treatment
n*	Mean (SD)	n*	Mean (SD)	Difference (95% CI)†
312	37.5 (32.6)	303	43.7 (34.8)	6.44 (2.24, 10.64)
247	–27.4 (70.2)	244	–46.9 (57.6)	–18.84 (–30.09, –7.59)
303	36.8 (28.3)	296	30.8 (28.6)	–7.13 (–10.92, –-3.34)
316	29.5 (27.8)	308	23.6 (26.4)	–7.34 (–11.03, –3.65)
303	62.9 (28.5)	296	69.2 (28.6)	7.11 (3.31, 10.90)
312	41.2 (33.2)	303	47.9 (35.2)	7.32 (3.17, 11.47)
314	–0.33 (9.81)	309	2.73 (11.38)	2.60 (0.98, 4.22)
314	–0.55 (8.70)	309	2.15 (8.92)	2.17 (0.83, 3.51)
315	16.9 (42.3)	309	23.7 (39.9)	6.31 (0.08, 12.55)
313	14.8 (22.2)	304	9.9 (15.8)	–5.73 (–8.28, –3.17)
246	0.47 (0.85)	247	0.70 (0.92)	0.24 (0.11, 0.37)
275	–0.05 (0.23)	277	–0.04 (0.19)	–0.00 (–0.03, 0.03)

of □-agonist than did patients taking montelukast (P=0.001), but the difference was not significant in the 36-week period (P=0.196) (Table 2). Montelukast and fluticasone also significantly reduced the percentage of days with □-agonist use during the 12- and 36-week treatment periods (P<0.001). Treatment favored the fluticasone group at 12 weeks (P<0.001) and at 36 weeks (P=0.035) (Table 2). Both treatments significantly increased the percentage of asthma rescue medication-free days during both time periods for all patients and for patients with normal lung function (P □ 0.001). For percentage of asthma rescue medication-free days in all patients, treatment favored the fluticasone group at 12 weeks (P<0.001) and at 36 weeks (P=0.033). In patients with normal lung function, treatment favored fluticasone at 12 weeks (P=0.001) but not at 36 weeks (P=0.073) (Table 2).

Montelukast and fluticasone significantly reduced the percentage of days with symptoms relative to baseline (P<0.001). Treatment favored fluticasone at the 12-week (P<0.001) and 36-week (P=0.016) periods (Table 2). Montelukast did not change FEV_1 during either treatment period but did significantly improve AM PEF from values at baseline during both periods. The change from baseline in AM PEF during the 12-week double-blind period was 16.88 L/min for the montelukast treatment group and 23.66 L/min for the fluticasone treatment group, (P=0.047). At 36 weeks, AM PEF change from baseline was 22.80 L/min for the montelukast treatment group and 32.36 L/min for the fluticasone treatment group (P=0.028) (Table 2).

There was no significant difference

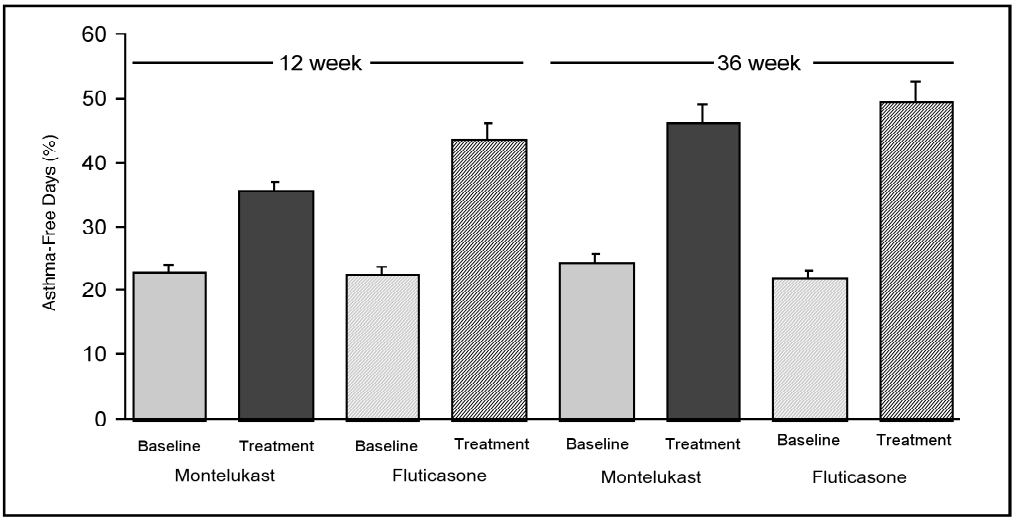


Figure 2. Percentage of asthma-free days for patients taking oral montelukast or inhaled fluticasone during the 12-week double-blind and 36-week open-label periods. Both treatment groups significantly increased the percentage of asthma-free days from baseline for the 48-week treatment period. The percent of asthma-free days was greater in the fluticasone group than in the montelukast group at both time periods

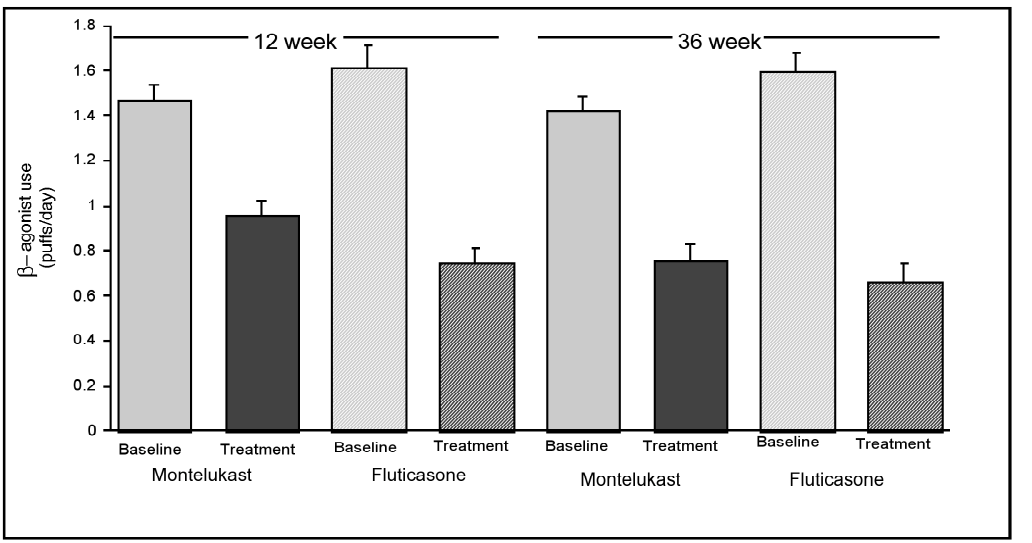


Figure 3. "As needed" β-agonist use in patients taking oral montelukast or inhaled fluticasone for the 12-week double-blind and 36-week open-label periods. Both treatment groups significantly reduced average daily β-agonist use over the 48-week active treatment period. Reduction in "as needed" β-agonists was greater in the fluticasone group than in the montelukast group during the 12-week period but not during the 36-week open-label period.

between montelukast and fluticasone during either period for the proportion of patients having an asthma attack. During the 12-week double-blind period, 7.7% of the patients in the montelukast group and 4.4% for the fluticasone group reported having an asthma attack (odds ratio 1.82; 95% CI 0.93, 3.56; P=0.083). During the 36-week period, 16.7% of the patients in the montelukast group and 14.5% in the fluticasone group reported an asthma

attack (odds ratio 1.18; 95% CI 0.75, 1.84; *P*=0.474).

Montelukast and fluticasone significantly reduced nocturnal awakenings compared with baseline values during the 12- and 36-week trial periods (*P*<0.001). The percentage of nights with awakenings due to asthma during the 12-week period was 14.83% for the montelukast group and 9.93% for the fluticasone group. During the 36-week treatment period, the mean percentage of nocturnal awakenings was 9.88% in the montelukast group and 8.00% in the fluticasone group. Patients taking fluticasone had fewer nights with awakenings in the 12-week (*P*<0.001) and 36-week time periods (*P*=0.040) compared with those taking montelukast (Table 2).

Both montelukast and fluticasone significantly improved overall quality of life and individual domains of activity, symptoms, emotional function, and environmental stimuli (*P*<0.001). The treatment effect for overall quality of life favored fluticasone at 12 weeks (*P* □ 0.01), but the difference between the treatments was not significant at 36 weeks (*P*=0.150). For the global evaluation, 29.8% in the montelukast group and 32.1% in the fluticasone group reported feeling moderately better, and 30.1% on montelukast and 39.4% on fluticasone reported feeling very much better than when they entered the study. The treatment difference was significant (*P*<0.001).

Montelukast and fluticasone significantly reduced peripheral blood eosinophil counts from baseline during both periods (*P*<0.001); the treatment difference was not significant during either period (*P*=0.894) (Table 2).

Safety

During the 12-week period, adverse experiences determined by the investigator to be possibly, probably, or definitely drug related occurred in 24 (7.4%) and 12 (3.8%) of patients in the montelukast and fluticasone groups, respectively. The most common clinical adverse experiences were asthma, which occurred in 4 (1.2%) patients taking montelukast and 1 (0.3%) patient taking fluticasone, and headache in 4 (1.2%) patients taking montelukast and 2 (0.6%) patients taking fluticasone. Eleven (1.7%) of the 645 patients discontinued therapy due to a clinical adverse experience: 7 (2.2%) in the montelukast group (including 2 patients who discontinued due to pregnancy) and 4 (1.3%) in the fluticasone group.

During the 36-week period, 19 patients (6.3%) in both groups had adverse experiences that were considered drug related. The most common adverse experiences were headache, reported by 3 (1.0%) patients taking montelukast and 1 (0.3%) patient taking fluticasone, and asthma, reported by 5 (1.7%) patients taking montelukast and 3 (1.0%) taking fluticasone. A total of 16 (2.7%) of 602 patients discontinued therapy due to pregnancy or a clinical adverse experience during the 36-week open-label period. There were no clinically meaningful differences between treatment groups and no discontinuations due to laboratory adverse experiences over the 48 weeks of active therapy.

DISCUSSION

In this study, montelukast and fluticasone significantly improved asthma-free days, the primary endpoint, as well as multiple parameters of asthma control over the 48 weeks of the active treatment period. However, the study did not support the non-inferiority hypothesis of montelukast compared with fluticasone in asthma-free days during the 12-week double-blind period. There was a statistically significant difference in the percentage of asthma-free days, favoring

fluticasone over montelukast. Although both treatments significantly improved β-agonist use and nocturnal awakenings, both of which are components of an asthma-free day, outcomes favored fluticasone for these clinical endpoints. These results differ from the equivalent efficacy established for montelukast compared with inhaled corticosteroids in previous studies.[17,20] The established non-inferiority boundary for montelukast was defined at a conservative level of no more than 3 days per month for the difference in asthma-free days compared with findings for fluticasone. However, since the 95% CIs included the boundary of 10%, the non-inferiority of montelukast to fluticasone could not be established. The mean difference in asthma-free days was less than 2 days per month per patient between the treatment groups.

The percentage of asthma rescue medication-free days was significantly improved, and asthma attacks were significantly reduced by montelukast and fluticasone during the 48-week active treatment period. Patients taking either montelukast of fluticasone had more than 75% of days per month with no symptoms and approximately 70% of days per month with no need for rescue medication. Symptoms such as the intensity of shortness of breath and use of rescue medication in mild asthmatics have been shown to correlate with quality of life, which was improved by both therapies.[24]

In a similar study, montelukast and fluticasone significantly improved asthma rescue-free days to the same degree in patients with an FEV_1 >86% predicted.[17] A similar analysis performed in the present study did not support this finding. The results of the previous study suggest that montelukast is as effective as fluticasone in patients with very mild asthma. However, asthma is a variable disease, and therapy will have to be tailored to the individual patient.

Goals of therapy are to prevent recurrent exacerbations of asthma and to minimize the need for emergency treatment.[1,2] Although this was a population of patients with mild asthma, attacks can occur in this subgroup, contributing significantly to the burden of uncontrolled asthma. In this study, asthma attacks were significantly and similarly reduced by both montelukast and fluticasone over the duration of the study, confirming results from a previous clinical trial that demonstrated that montelukast and beclomethasone reduced asthma attacks to a similar degree in patients with mild to moderate asthma.[20]

The improvements in multiple indices of asthma seen with montelukast did not correlate with FEV_1 over the active treatment periods. FEV_1 remained relatively unchanged in patients taking montelukast for 48 consecutive weeks; however, montelukast improved FEV_1 in other studies in adults with a broad range of asthma severities.[8] A subgroup analysis of clinical trials evaluating the effect of montelukast in patients with mild asthma reported an average improvement of 6.8% or greater in FEV_1 in trials of various durations of treatment.[25] Fluticasone significantly increased FEV_1 in the present study (2.73% after 12 weeks and 1.52% at 36 weeks). This level of change in FEV_1, although statistically significant, may not be clinically relevant. AM PEF was significantly improved for both montelukast and fluticasone.

Airway inflammation is an established feature of asthma and it is recognized that the eosinophil is a key cellular mediator of the inflammation associated with asthma.[26] Results from the present study demonstrated that montelukast and fluticasone significantly reduced peripheral blood eosinophils in mild asthmatic patients over the 48-week trial period. Reductions in periph-

eral blood eosinophils have been previously demonstrated in adult and pediatric patients treated with montelukast.[9,10,13,27] Reductions in peripheral blood eosinophils have been associated with improved asthma control and appear to be associated with improvements in clinical indices of asthma control in the present study.[28,29] Decreases in eosinophilia in the patients treated with montelukast or fluticasone in the current study underscore the importance of inflammation even in the mildest forms of asthma.

In summary, this clinical trial comparing once-daily oral montelukast to twice-daily inhaled fluticasone demonstrated that both treatments significantly improved the primary endpoint (asthma-free days) as well as other secondary endpoints during the 12-week double-blind and 36-week open-label trial periods. Both treatment approaches in this study maintained significant control of asthma symptoms, reduced asthma attacks to a similar degree, improved quality of life, reduced peripheral blood eosinophils over the 48-week trial period. Results from the 12-week trial favored fluticasone in several indices, these differences tended to diminish during the 36-week period.

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