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Montelukast or salmeterol combined with an inhaled steroid in adult asthma: design and rationale of a randomized, double-blind comparative study (the IMPACT Investigation of Montelukast as a Partner Agent for Complementary Therapy-trial)

L. BJERMER[*], H. BISGAARD[†], J. BOUSQUET[‡], L. M. FABBRI[§], A. GREENING[¶], T. HAAHTELA[**], S. T. HOLGATE[††], C. PICADO[‡‡] AND J. A. LEFF[§§]

[*]*Department of Lung Medicine, University Hospital, Trondheim, Norway*
[†]*Department of Pediatrics, Copenhagen, University Hospital, Rigshospitalet Copenhagen, Denmark*
[‡]*Service des Maladies Respiratoires, CHU, Hopital Arnaud de Villeneuve, Montpellier, France*
[§]*Department of Respiratory Diseases, University of Modena, Modena, Italy*
[¶]*Respiratory Medicine Unit, Western General Hospital, Edinburgh, U.K.*
[**]*Department of Allergology, Helsinki University Hospital, Finland*
[††]*Respiratory Cell and Molecular Biology Research Division, Southampton General Hospital, Southampton, U.K.*
[‡‡]*Institut de Pneumologia, Clinical Hospital, University of Barcelona, Spain*
[§§]*Merck and Co., Inc., Whitehouse Station, New Jersey, U.S.A.*

Asthma patients who continue to experience symptoms despite taking regular inhaled corticosteroids represent a management challenge. Leukotrienes play a key role in asthma pathophysiology, and since pro-inflammatory leukotrienes are poorly suppressed by corticosteroids it seems rational to add a leukotriene receptor antagonist (LTRA) when a low to moderate dose of inhaled corticosteroids does not provide sufficient disease control. Long acting β_2-agonist (LABA) treatment represents an alternative to LTRAs and both treatment modalities have been shown to provide additional disease control when added to corticosteroid treatment. To compare the relative clinical benefits of adding either a LTRA or a LABA to asthma patients inadequately controlled by inhaled corticosteroids, a randomized, double-blind, multi-centre, 48-week study will be initiated at approximately 120 centres throughout Europe, Latin America, Middle East, Africa and the Asia–Pacific region in early 2000. The study will compare the oral LTRA montelukast with the inhaled LABA salmeterol, each administered on a background of inhaled fluticasone, on asthma attacks, quality of life, lung function, eosinophil levels, healthcare utilization, and safety, in approximately 1200 adult asthmatic patients. The requirements for study enrolment include a history of asthma, FEV_1 or PEFR values between 50% and 90% of the predicted value together with $\geq$12% improvement in FEV_1 after β-agonist administration, a minimum pre-determined level of asthma symptoms and daily β-agonist medication. The study will include a 4-week run-in period, during which patients previously taking inhaled corticosteroids are switched to open-label fluticasone (200 μg daily), followed by a 48-week double-blind, treatment period in which patients continuing to experience abnormal pulmonary function and daytime symptoms are randomized to receive montelukast (10 mg once daily) and salmeterol placebo, or inhaled salmeterol (100 μg daily) and montelukast placebo. All patients will continue with inhaled fluticasone (200 μg daily). During the study, asthma attacks, overnight asthma symptoms, and morning peak expiratory flow rate will be assessed using patient diary cards; quality of life will also be assessed using an asthma-specific quality-of life questionnaire. The results of this study are expected to provide physicians with important clinical evidence to help them make a rational and logical treatment choice for asthmatic patients experiencing breakthrough symptoms on inhaled corticosteroids.

Key words: leukotriene receptor antagonists; montelukast; Singulair; inhaled steroids; fluticasone; long-acting β-agonists; salmeterol; asthma; airway inflammation.

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Correspondence should be addressed to: Leif Bjermer, MD Dept. of Lung Medicine, University Hospital, N-7006 Trondheim, Norway. Fax: +47 73 867424; E-mail: Leif.Bjermer@medisin.ntnu.no

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Introduction

National and international guidelines recommend inhaled corticosteroids (ICS) as first line therapy for patients with moderate to severe persistent asthma (1–3). However, although ICS improve lung function, symptoms, and reduce asthma exacerbations (4–8), many asthma patients receiving these agents continue to experience symptoms presumably due to underlying inflammation. Pro-inflammatory leukotriene levels are poorly suppressed by corticosteroids (9) and since these patients are already taking ICS, it is possible that there is a leukotriene-driven component of inflammation in these patients.

Currently, there are two approaches to treat asthma patients who continue to experience symptoms on ICS: increase the dose of ICS or add a second therapeutic agent such as an inhaled long-acting β-agonist (LABA) or oral leukotriene receptor antagonist (LTRA). Clinical evidence to support the use of increased doses of ICS is variable, with several studies reporting inconsistent effects of higher steroid doses on control of asthma symptoms (10–13). In addition, higher doses of ICS may be associated with side-effects such as adrenal suppression, growth retardation in children, osteoporosis, cataracts, skin thinning and easy bruising (14–16).

Recent studies have suggested that addition of LABAs to ICS are more effective in improving asthma symptoms and lung function than increasing the dose of ICS (17–20). However, concerns have been raised since chronic treatment with LABA results in development of tolerance (21–26), even in those patient treated with ICS (27–29). Another potential concern is the risk of masking underlying airway inflammation, thereby allowing an exacerbation of asthma to go unrecognized (30).

Montelukast, a cysteinyl leukotriene receptor antagonist, represents an alternative therapeutic option for patients who continue to experience symptoms on ICS. The anti-asthmatic effect is well documented and today there are data from more then 5000 patients (over 2 years of age) treated in clinical trials. World-wide more than 2 million patients have been treated. Montelukast, with or without co-administration of corticosteroids, has been shown to reduce asthma exacerbations and attacks in adults and children (31–34). Moreover, regular treatment with montelukast does not seem to induce tolerance (35,36).

The exact role of leukotrienes in asthma inflammation is not known. Leukotrienes increase mucus production and reduce mucociliary clearance (37). They facilitate adhesion and chemotaxis by inflammatory cells, especially eosinophils (14,38). They also act directly on bronchial smooth muscle cells causing contraction, and stimulate myofibroblasts to differentiate and to form subepithelial fibrosis. Effects on inflammatory cells carrying the $CysLT_1$ receptor may also affect other inflammatory cells in an indirect way, for example, by altering cytokine expression and release.

Montelukast has been shown to have significant effects on parameters of asthmatic inflammation by blocking the action of leukotrienes, key mediators of airway inflammation not inhibited by steroids (9,39–41). Studies in children and adults demonstrate montelukast decreases eosinophil counts in peripheral blood, sputum and lung tissue, and reduces exhaled nitric oxide (NO) levels, a non-invasive marker of airway inflammation in asthmatics (31–33, 42,43,93). Further, montelukast in combination with beclomethasone dipropionate has recently been shown to produce additive reductions in peripheral blood eosinophils and exacerbations compared with either agent administered individually (44). Treatment with a LTRA has the potential benefit of both preventing bronchoconstriction, acting as a bronchodilator (45) and having anti-inflammatory activity. The bronchodilator effect is smaller than that seen after β_2-agonist treatment. However when LTRAs are added to a β_2-agonist additional effects have been noted (46). This finding suggests that montelukast and ICS may offer different, yet complementary, anti-inflammatory effects in asthma patients incompletely controlled on ICS alone.

To determine whether the addition of a LTRA has an advantage over the addition of a LABA for patients inadequately controlled by ICS alone, we have initiated a controlled clinical trial to compare the relative clinical benefits of montelukast and salmeterol, administered on a background of inhaled fluticasone propionate, on asthma attacks, quality of life, eosinophil levels, healthcare utilization and safety. Beginning in early 2000, this randomized, double-blind, multi-centre clinical trial will involve approximately 1200 adult asthmatic patients not sufficiently controlled by ICS. The purpose of this report is to summarize the background, rationale and design of this unique comparative study, which is expected to have important clinical ramifications for the successful management of asthma in the new millennium.

Study design

This is a randomized, double-blind, double-dummy, parallel-group, multi-centre study ranging over 48-weeks after an initial 4-week run-in period. The study has been designed and powered to compare the efficacy and safety of montelukast and salmeterol, when added to ICS therapy (fluticasone propionate), in preventing asthma attacks in adult asthmatic patients. The study involves approximately 1200 male or female patients aged 15–65 years with persistent asthma. Enrolment will begin in early 2000 at $\sim$120 asthma centres throughout Europe, Latin America, Middle East, Africa, and the Asia–Pacific regions, and the study is expected to take approximately 24 months to complete.

The requirements for study enrolment include a history of asthma, FEV_1 values between 50% and 90% of the predicted value [age 15–17, Hsu (47), age $\geq$18, Crapo (48)] together with $\geq$12% improvement in FEV_1 or PEFR after β-agonist administration, a minimum pre-determined level of daytime and night-time inhaled short-acting β-agonist use, and a minimum asthma symptom score. All female patients are required to have a negative urine pregnancy test at screening. Patients will be excluded if they have had emergency treatment for asthma within 1 month of the first visit, hospitalization for asthma within 3 months,

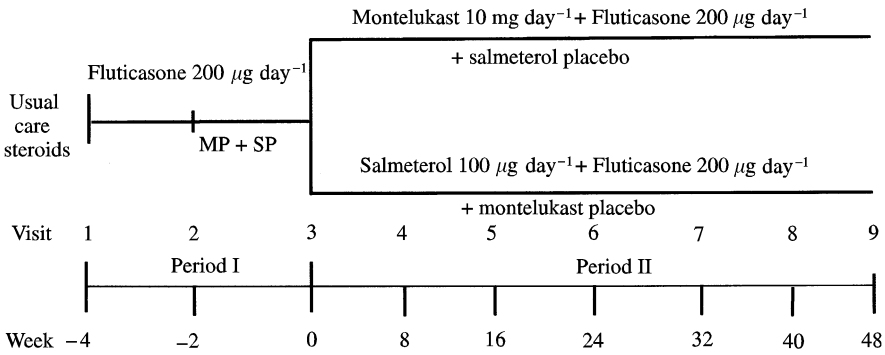

FIG 1. Treatment plan for the randomized, double-blind study comparing the efficacy and safety of montelukast and salmeterol, when added to inhaled steroid therapy (fluticasone), in preventing asthma attacks in adult asthmatic patients. MP: montelukast placebo; SP: salmetesol placebo.

unresolved upper respiratory tract infection within 3 weeks, or an active sinus infection.

Study objectives

The primary objective is to compare the effect of montelukast with salmeterol, administered concomitantly with inhaled fluticasone propionate, on the percentage of patients experiencing at least one asthma attack. For the purpose of this study, an asthma attack is defined as treatment with a course of oral corticosteroids or an unscheduled visit to the doctor's office, emergency room, or hospitalization. An indication for systemic steroid treatment is based upon either objective criterion as increase in symptoms or lung function deterioration, or according to judgement by the responsible investigator. The patients are instructed to contact the doctor if PEFR is 30% below baseline on three consecutive mornings (or $<200\,l\,min^{-1}$), or if symptoms increase with need for frequent β_2-agonist use (interval less than 3 h). Secondary objectives of the study include peripheral blood eosinophil counts, asthma-specific quality of life, nocturnal awakenings, healthcare resource utilization and morning PEFR. In addition, the study will compare the tolerability profile of montelukast and salmeterol in combination with inhaled fluticasone.

Treatment and follow-up

The study will begin with an initial 4-week run-in period (Period I, Fig. 1). During this phase, patients taking ICS, but with abnormal pulmonary function and daytime symptoms, will be placed on open-label fluticasone propionate (200 μg daily via Discus® dry powder inhaler). During the last 2 weeks of Period I, patients will also receive, in a single-blind manner, salmeterol placebo metered dose inhaler (MDI) and montelukast placebo tablets.

The initial run-in period will be followed by a 48-week, double-blind treatment period (Period II). At the beginning of Period II, patients who continue to be inadequately controlled (based on FEV_1, peak flow, β-agonist use and daytime symptoms) will be randomized to receive either active montelukast (10 mg once daily) or salmeterol (100 μg daily) in addition to fluticasone propionate 200 μg daily. All patients will be instructed to take their study tablet once daily at bedtime, with or without food, and to inhale one puff of the fluticasone pMDI twice daily and two puffs from the salmeterol or placebo pMDIs twice daily; in the morning upon arising and at bedtime. Patients will be allowed to (consistently) use a spacer device if desired. Patients will also be carefully instructed to use their inhaled short-acting β-agonist on an as needed basis and to avoid habitual use in the absence of symptoms. Both groups will receive montelukast or placebo tablets and salmeterol or placebo pMDIs in a double blind, double-dummy manner, so that patients, study site staff and sponsor staff will be blinded with respect to treatment allocation.

Patients will record asthma attacks, overnight asthma symptoms, and peak expiratory flow rate on diary cards. Overnight asthma symptoms will be assessed by the following question: did you wake up with asthma? Patients return the diary cards at clinic visits scheduled at approximately 8-week intervals for the 48 weeks of Period II. The study co-ordinators at each study site will be responsible for reviewing the diary cards for completeness and accuracy with the patient. Patients will be contacted frequently (at least every month) during the 48-week study to ensure accurate and complete recordings on the diary card.

The quality of life of asthma patients will be assessed during the study at weeks 0, 16, 32 and 48 using a validated Asthma-Specific Quality-of Life Questionnaire, available in a number of languages (49). This self-administered

TABLE 1. Principal inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
• Aged 15–65 years • Clinical history of chronic asthma for at least 1 year • Regular use of inhaled corticosteroids over the prior 8 weeks • FEV_1 values between 50% and 90% of the predicted value, together with $\geq$12% improvement in FEV_1 or PEFR after β-agonist administration • Minimum predetermined level of daytime and night-time inhaled short-acting β-agonist use ($\geq$one puff/day^{-1}) and minimum asthma symptom score (biweekly score of at least 56) • Current asthma treatment includes only short-acting β-agonists and inhaled corticosteroids*	• Received emergency treatment for asthma within 1 month of the first visit • Hospitalization for asthma within 3 months • Unresolved upper respiratory tract infection within 3 weeks • Active sinus infection within 1 week • Received the following asthma medications: oral corticosteroids within 1 month, cromolyn, nedocromil, leukotriene-receptor antagonists, long-acting or oral β-agonists, inhaled anticholinergics within 2 weeks, theophylline, terfenadine, fexodfenadine, loratadine, or cetirizine within 1 week

*Budesonide 200–1000 μg day^{-1} or equivalent.;

questionnaire consists of a series of questions pertaining to four asthma-specific quality of life domains (activity, symptoms, environment and emotions).

Safety

Safety and tolerability will be monitored throughout the study. Investigators will evaluate clinical adverse experiences in terms of intensity (mild, moderate or severe), duration, seriousness, outcome and relationship to test drugs.

Statistical considerations

To determine how many patients were required for the comparison of montelukast/fluticasone to salmeterol/fluticasone, a sample size estimate was performed based on estimates of the percentage of patients with asthma attacks derived from a previous beclomethasone/montelukast study (44) and the FACET trial (17). With 480 patients per group, the trial will have at least 80% power to statistically demonstrate that the risk of experiencing at least one asthma attack with montelukast/fluticasone is less than 1·33 times the same risk with salmeterol/fluticasone.

The primary efficacy analysis will be based on the intention-to-treat principle, although a per-protocol analysis will also be performed, taking into account missing data points and clinically important protocol deviations. Comparability of baseline characteristics between the treatment groups will be evaluated with respect to age, gender, race, disease history including disease duration, weight and height. The ratio of the percentage of patients with asthma attacks in the montelukast/salmeterol groups will be calculated using a generalized linear model with binomial distribution and logarithmic link. The treatment effect will be summarized by the risk ratio and its 95% confidence interval, calculated by the profile likelihood method. The montelukast/fluticasone combination will be considered statistically superior to the salmeterol/fluticasone combination if the upper limit of the two-sided confidence interval is less than 1·0. If the upper limit is less than 1·33, the montelukast/fluticasone combination will be considered non-inferior to the salmeterol/fluticasone combination. If the lower limit is more than 1·33, the montelukast/fluticasone combination will be considered statistically inferior to the salmeterol/fluticasone combination. As a secondary analysis, the number of asthma attacks will be analysed by Poisson regression using robust variance estimates (via GEE option in PROC GENMOD).

Organizational structure

At each study site, the principal investigator will be responsible for the care of enrolled patients and the accurate collection of clinical data, particularly in relation to the occurrence of asthma-related events. Specially trained clinical monitors will provide support to the principal investigators and collect data during the trial. A Steering Committee will have overall scientific responsibility for the study and for reports generated from study data. This committee will meet periodically to ensure that all procedures are standardized at study sites. Merck Research Laboratories in collaboration with the Steering Committee will process data.

Discussion

Physicians are frequently faced with the challenge of selecting a safe and effective therapeutic option to manage asthma patients who continue to experience symptoms while taking ICS. Currently, the therapeutic approaches to manage these patients include either increasing the dose of ICS or the addition of a second therapeutic agent, such as an inhaled LABA (e.g. salmeterol), a chromone (e.g. cromolyn and nedocromil), theophylline, or an oral LTRA. However, there have been few comparative studies on the relative efficacy and safety of these therapeutic options in this clinical setting, forcing practitioners to make management decisions based on anecdotal evidence, personal clinical experience, or extrapolation of clinical data from other studies. To help physicians in their decision to select the most effective and safest therapeutic approach for asthmatic patients uncontrolled on ICS alone, we have designed the present study to compare, in a controlled, randomized, double-blind manner, the effects of adding montelukast or salmeterol to a background of inhaled fluticasone on asthma attacks, quality of life, eosinophil levels, lung function and healthcare utilization.

Traditionally, surrogate markers of asthma control such as FEV_1 and peak expiratory flow rate have assessed effectiveness of preventative therapies for asthma control. However, there is a lack of clinical data validating the relationship between these surrogate endpoints and clinical outcomes such as prevention of asthma attacks. Salmeterol can be expected to have a slightly better bronchodilating potential than montelukast (50). However, recent experiences from the FACET study clearly shows that lung function may not be directly related to the risk of developing asthma attacks. Although the combination of low dose budesonide and formoterol gave the better lung function, increasing the steroid dose was superior in decreasing the numbers of severe exacerbations (17).

The ability of anti-asthmatic therapies to prevent asthma attacks is important from the perspective of decreasing morbidity and mortality, improving the quality of life of asthma patients, and diminishing the economic costs of the disease by reducing the need for emergency room visits and hospitalizations. For this reason, the percent of patients with at least one asthma attack, defined as worsening asthma requiring unscheduled doctor visits, hospitalization, or use of oral corticosteroids, was chosen as the primary endpoint in the present study.

A 10-mg dose of montelukast (once daily at bedtime) was selected for this study on the basis of previous dose-ranging studies (34,51). These studies, which used bedtime dosing to achieve peak plasma drug concentrations in the early morning when asthma characteristically worsens, demonstrated that montelukast 10 mg represents an optimal dose for improving asthma endpoints in chronic asthma patients; higher dosages have not been shown to provide further benefits. Further, this dose has been shown to achieve maximal inhibition of exercise-induced bronchoconstriction (52). Salmeterol xinafoate 50 μg twice daily was selected for this study in accordance with the manufacturers prescribing instructions. This dose produces clinically significant bronchodilator effects up to 12 h after a 50 μg dose in asthmatic patients. A study duration of 48 weeks was chosen to reflect the fact that asthma is a more or less persistent inflammatory disorder of the airways and to ensure that an adequate number of events occurred for a valid statistical comparison between study groups.

It is now well accepted that chronic inflammation of the airways, involving infiltration of multiple inflammatory cells such as mast cells, antigen-presenting cells such as dendritic cells, and macrophages, eosinophils, neutrophils and lymphocytes, represents a major pathogenic component of asthma (53). These inflammatory cells are responsible for elaborating a broad array of mediators and cytokines in the bronchial epithelium that ultimately give rise to the clinical hallmarks of asthma (14). Leukotrienes, in particular, represent important mediators of the inflammatory process, producing bronchoconstriction, mucosal secretion, cellular infiltration and increased vascular permeability (38,54–57).

Recognition of the fundamental inflammatory nature of asthma has resulted in a shift in the focus of asthma therapy from reliance on bronchodilators to emphasis on anti-inflammatory agents (53). According to the Global Strategy for Asthma Management and Prevention (3), anti-inflammatory agents, particularly ICS, are currently the most effective long-term preventative medications for persistent asthma. However, while ICS effectively improve lung function and symptom control, and decrease asthma exacerbation's (4,6–8,17), many patients receiving ICS continue to experience symptoms. Although low dosages of ICS are generally considered safe, increased dosages of ICS are associated with a variety of potential side-effects, including adrenal suppression, growth retardation in children, osteoporosis, cataracts, skin thinning, and easy bruising (14,15,16,58,59). Further, although ICS produce broad inhibition of pathways contributing to airway inflammation (53), these agents fail to block the production of cysteinyl leukotrienes that appear to play an important role in the pathophysiology of asthma (9,41).

Recent studies in adult asthmatics have shown that addition of the LABA salmeterol to existing ICS therapy (beclomethasone) is more effective in controlling asthma than increasing the dose of ICS (18–20). In addition, asthma patients receiving a combination of LABA (formoterol) and ICS showed a reduced rate of asthma exacerbations (17). Not all studies, however, have reported more effective asthma control when salmeterol is added to ICS therapy. For example, a recent long-term study in children with moderate asthma reported no additional benefit of adding salmeterol or increasing the daily dose of beclomethasone (60). Further, a recent review of LABA in children suggests they are effective bronchodilators and bronchoprotective agents when used as single doses, but not when used chronically (92).

Both salmeterol and formoterol are designed for use as maintenance treatment and to achieve maximal clinical benefit, these agents should be taken regularly rather than on an as-needed basis (61). Concerns have been raised that chronic treatment with β_2-agonists is associated with a deterioration in asthma control, lung function and airway

hyperresponsiveness in some patients (62,63). Development of tolerance to the protective effect of β_2-agonists on bronchoconstrictor stimuli (e.g. exercise, metacholine or allergen) has been reported in multiple studies (21,22,24,25,27), although the bronchodilating effect of these agents appear to be unaffected during chronic administration (64,65). For example, in a study of the effects of salmeterol on hyperresponsiveness in patients with mild asthma, Cheung *et al.* reported that regular treatment with salmeterol led to tolerance of its protective effects against the bronchoconstrictor stimulus metacholine, despite well-maintained bronchodilation (22). Further, the development of tolerance to β-agonists appears to be unaffected by co-administration of inhaled corticosteroids (27–29,66). This finding suggests that asthma patients may experience short-term bronchodilation with β-agonists but they may be susceptible to episodes of acute bronchoconstriction induced by newly encountered provocative stimuli (67). However, recent studies indicate that regular treatment with long-acting β_2-agonist may not be associated with increased risk for worsening of disease control (68), even in those steroid-naive patients treated with salmeterol only (69).

It has been proposed that tolerance development by β_2-agonist treatment also should be associated with a decreased ability to control the underlying asthmatic inflammation. Thus, the bronchodilation and the symptom-relieving effects of long-acting β_2-agonist treatment may mask a progressive worsening inflammation of the airways in asthma patients, thereby potentially delaying awareness of an exacerbation of asthma (30,70). Whether the lack of effect on inflammatory cells and markers will translate into sub-optimal outcomes is not yet clear (71–76). There are conflicting data on the interactive effect between β_2-agonist and steroid treatment. One report suggests that β-agonists in general, at high doses, may interfere with the anti-asthma effects of inhaled steroids, possibly leading to steroid resistance (77). However, other *in vitro* studies indicate that β_2-agonist treatment, conversely, may enhance the effect by steroids through activation of the glucocorticoid receptor (78). Interestingly a recent report suggests formoterol may decrease tissue eosinophils under some conditions (79).

Administration of theophylline, cromolyn, or nedocromil is also a potential therapeutic option to manage asthmatic patients who remain symptomatic on ICS. Theophylline is inexpensive compared to both LTRAs and LABAs and has proved to be effective at a low dose combined with ICS treatment (80). However, theophylline is no longer commonly used as first-line therapy primarily because of modest clinical benefit, a narrow therapeutic window, need to monitor drug levels, reports of serious adverse reactions, and the potential for drug interactions with commonly used medications (81–83). Cromolyn and nedocromil represent mild to moderate anti-inflammatory medications that may be used as initial choice for long-term control therapy (84). However, there are, as yet, no convincing long-term, controlled studies demonstrating that administration of either in combination with ICS is helpful in managing asthma patients. For example, a study by Toogood *et al.* found that adding cromolyn to an established ICS regimen failed to produce a discernible steroid-sparing effect or other clinical advantage (85).

Montelukast represents an alternative therapeutic option for asthma patients who continue to experience symptoms on ICS. Montelukast provides protection against exercise-induced bronchoconstriction for up to 20–24 h after dosing (52,86). These protective effects are maintained for a period of at least 12 weeks (35). The absence of tolerance with montelukast after long-term therapy contrasts with that seen with other therapies, including the short-acting inhaled β-agonist albuterol, the LABA salmeterol, and the ICS beclomethasone, where reduced effects have been reported to develop after 1 week, 4 weeks and 3 months of therapy, respectively (21,24,87,88,92). In a direct, double-blind, randomized comparative study of montelukast and salmeterol in 197 asthmatic men and women aged 15–45 years, montelukast was shown to provide significantly greater inhibition of exercise-induced bronchoconstriction than salmeterol (36). Maintenance of a bronchoprotective effect during long-term therapy is particularly important since it has been estimated that between 40 and 90% of asthmatic patients may be susceptible to developing exercise-induced symptoms (89,90).

Asthma is often characterized by the presence of activated eosinophils in the lower airways, and when present, they have been reported to impact the chronicity and severity of asthma (39,91). There is now growing evidence to indicate that the cysteinyl leukotrienes play an important role in the migration of eosinophils into the airways (38,39). By blocking the actions of leukotrienes, montelukast has been shown to have significant effects on parameters of asthmatic inflammation, including decreases in eosinophil counts in peripheral blood, sputum, and lung tissue, in both children and adults (14,31–33,42,93). In a recent 16-week, double-blind, randomized study, montelukast once daily was shown to reduce peripheral blood eosinophil counts to a similar extent as inhaled beclomethasone, and to provide additional control when the two agents were combined (44). Although the precise mechanism of the anti-inflammatory properties of montelukast in asthma is still under investigation, recent studies suggest that montelukast may decrease the release of endothelin-1 during eosinophilic airway inflammation, as well as inhibit the expression of IL-5 RNA and secretion of cysteinyl leukotrienes by mononuclear cells (40).

Since optimal control of inflammation is critical in managing chronic asthma, the addition of montelukast as a second anti-inflammatory agent to ICS may represent a logical therapeutic option. The combination of these two agents offers different yet additive, anti-inflammatory effects since montelukast attenuates the effects of cysteinyl leukotrienes, important pro-inflammatory mediators not inhibited by inhaled steroids (9,41). In this regard, the present randomized, double-blind study has been designed to determine whether two anti-inflammatory agents has an advantage over a bronchodilator and an anti-inflammatory agent for asthma patients inadequately controlled by ICS. It is anticipated that the results of this important study will provide physicians with new clinical evidence to help them

make a rational and logical treatment choice for asthmatic patients experiencing breakthrough symptoms on ICS.

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