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Montelukast

A Review of its Therapeutic Potential in Persistent Asthma

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Data Selection

Sources: Medical literature published in any language since 1966 on montelukast, identified using AdisBase (a proprietary database of Adis International, Auckland, New Zealand), Medline and EMBASE. Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

Search strategy: AdisBase, Medline and EMBASE search terms were 'montelukast', 'MK-476', 'MK-0476', 'L-706631', 'Singulair' and 'asthma'. Searches were last updated 20 Mar 2000.

Selection: Studies in patients with asthma who received montelukast. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: Asthma, montelukast, pharmacodynamics, pharmacokinetics, therapeutic use.

Contents

Summary

Abstract

Montelukast is a cysteinyl leukotriene receptor antagonist used to treat persistent asthma in patients aged ≥6 years.

The drug has a rapid onset of action. Improvements in lung function and reductions in as-needed β_2-agonist usage are apparent within 1 day of initiating montelukast treatment in adults and adolescents (aged ≥15 years treated with 10 mg/day) or children (aged 6 to 14 years treated with 5 mg/day) with persistent asthma as shown in clinical trials.

In two 12-week, multicentre, randomised, double-blind studies in adults and adolescents aged ≥15 years with persistent asthma [forced expiratory volume in 1 second (FEV_1) = 50 to 85% predicted] there was significantly ($p \leq 0.05$) greater improvement in FEV_1, symptom scores, peak expiratory flow (PEF), as-needed β_2-agonist use, peripheral eosinophil counts and health-related quality of life (QOL) in patients treated with montelukast 10 mg/day than in recipients of placebo. Improvements were significantly greater in patients treated with inhaled beclomethasone 400 μg/day than in recipients of montelukast 10 mg/day in 1 of these studies. Nonetheless, 42% of montelukast recipients experienced ≥11% improvement in FEV_1, the median improvement in this parameter in beclomethasone-treated patients.

In an 8-week multicentre, randomised, double-blind, study in children aged 6 to 14 years with persistent asthma (FEV_1 50 to 85% predicted), montelukast 5 mg/day produced significantly greater improvements in FEV_1, clinic PEF, as-needed β_2-agonist use, peripheral eosinophil counts, asthma exacerbations and QOL scores than placebo.

The combination of montelukast 10 mg/day plus inhaled beclomethasone 200μg twice daily provided significantly better asthma control than inhaled beclomethasone 200μg twice daily in adults with poorly controlled asthma (mean FEV_1 = 72% predicted) despite 4 weeks treatment with inhaled beclomethasone. Patients receiving the combination experienced significant improvements in FEV_1 and morning PEF, significant reductions in daytime symptom scores, as-needed β_2 agonist usage and night-time awakenings with asthma, and had significantly

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lower peripheral blood eosinophil counts after 16 weeks in this multicentre, randomised, double-blind, placebo-controlled study.

Among adults (FEV_1 ≥70%) treated with montelukast 10 mg/day for 12 weeks, inhaled corticosteroid dosages were titrated downward by 47% (*vs* 30% in placebo recipients), 40% of patients were tapered off of inhaled corticosteroids (*vs* 29%), and significantly fewer patients (16 *vs* 30%) experienced failed corticosteroid rescues in a multicentre, randomised, double-blind study.

During clinical studies, the frequency of adverse events in montelukast-treated adults, adolescents and children was similar to that in placebo recipients.

In conclusion, montelukast is well tolerated and effective in adults and children aged ≥6 years with persistent asthma including those with exercise-induced bronchoconstriction and/or aspirin sensitivity. Furthermore, montelukast has glucocorticoid sparing properties. Hence, montelukast, as monotherapy in patients with mild persistent asthma, or as an adjunct to inhaled corticosteroids is useful across a broad spectrum of patients with persistent asthma.

Pharmacodynamic Properties

Cysteinyl leukotrienes [leukotriene C_4 (LTC_4), D_4 (LTD_4) and E_4 (LTE_4)] are important pro-inflammatory mediators in asthma. Montelukast is a competitive antagonist of these substances at the cysteinyl leukotriene type 1 ($cysLT_1$) receptor. The affinity of montelukast (50% inhibitory concentration = ≥2.3 nmol/L) for the cloned human $cysLT_1$ receptor was 2.5 to 5-fold lower than that of LTD_4 and was generally similar to that of other commercially available $cysLT_1$ receptor antagonists.

Montelukast 5 mg/day for ≥2 weeks reduced nitric oxide levels in exhaled air, a marker of inflammation, by ≥20% in children with mild asthma.

Peripheral blood eosinophil levels were significantly reduced from baseline in adult and paediatric patients treated with clinically relevant dosages of montelukast for ≥4 weeks.

Over a broad dose range (5 to 250mg), and at both peak and trough plasma concentrations, montelukast inhibited acute LTD_4-induced bronchoconstriction in patients with asthma. Moreover, the onset of the antagonist effect of montelukast was readily apparent after absorption of a single dose.

Significant improvements in FEV_1 were noted within 15 minutes of administration of montelukast 7mg intravenously.

Single oral doses of montelukast 100 or 250mg produced significant improvements in forced expiratory volume in 1 second (FEV_1) within 1 hour of drug administration in patients with asthma including those receiving ongoing inhaled corticosteroids. Importantly, these improvements did not preclude a bronchodilator response to inhaled salbutamol (albuterol).

After 2 doses, montelukast 10 mg/day provided a significant protective effect against both early (EAR) and late asthmatic responses (LAR) in patients with mild asthma (FEV_1 = 79 to 109% predicted) after allergen challenge in a double-blind, placebo-controlled, crossover study.

Montelukast reduced the deterioration in lung function after a standard exercise challenge (6-minute treadmill test) in patients with persistent asthma and exercise-induced bronchoconstriction treated for 8 or 12 weeks in well-designed trials. There was no evidence of tolerance to the protective effects of montelukast 10 mg/day, which were apparent within 3 days, in patients with exercise-induced bronchoconstriction. However, in patients treated with inhaled salmeterol 42μg twice daily, tolerance became apparent after an initial favourable response.

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The frequency of as-needed β_2-agonist usage after exercise challenge was significantly lower among patients treated with montelukast than placebo or salmeterol.

In children aged 6 to 14 years with exercise-induced bronchoconstriction, montelukast 5 mg/day for 2 days had similar protective effects to those achieved to those achieved in adults with 10 mg/day.

Pharmacokinetic Properties

After oral administration, approximately 64% of a 10mg dose of montelukast is absorbed, and maximum plasma concentrations are achieved within 3 to 4 hours. Steady state plasma concentrations are achieved on the second day of administration in volunteers. Montelukast is eliminated primarily by biliary excretion and hepatic oxidative metabolism. Oxidative metabolism of montelukast was attributed to cytochrome P450 isozymes (CYP3A4 and CYP2C9).

The pharmacokinetics of oral montelukast 10mg were generally similar in elderly volunteers (aged ≥65 years) and younger adults (aged 20 to 45 years).

In children aged 6 to 14 years, a 5mg dose administered as a chewable tablet provided similar systemic exposure to that obtained in adults after a 10mg dose.

Montelukast appears to have a low potential for drug-drug interactions. No pharmacokinetic drug-drug interactions were evident in patients receiving clinically significant doses of montelukast (10 mg/day) and warfarin, digoxin, terfenadine, fexofenadine, combined oral contraceptives, theophylline, prednisone or prednisolone.

Phenobarbital appeared to increase the metabolism of montelukast; however, dosage adjustments are not warranted in patients receiving this combination.

Therapeutic Potential in Patients With Persistent Asthma

Montelukast has been evaluated in randomised, placebo-controlled studies in adults, adolescents and children with persistent asthma. The drug was administered in the evening in all clinical trials.

In multicentre randomised, double-blind, placebo-controlled trials of 8 or 12 weeks' duration in adults (aged ≥15 years) or children (aged 5 to 14 years) montelukast had a rapid onset of action (i.e. within 1 day).

In Adults

Adult patients with persistent asthma (FEV_1 = 50 to 85% predicted) received montelukast 10 mg/day or placebo (n = 681) in 1 study, and montelukast 10 mg/day, inhaled beclomethasone 400 μg/day or placebo in another trial (n = 895). After 12 weeks of treatment in both studies, significant improvements in all outcome variables (FEV_1, daytime symptom scores, morning and evening peak expiratory flow rate (PEF), frequency of as-needed β_2-agonist usage, frequency of nocturnal awakenings, health-related quality of life scores and peripheral eosinophil counts) were obtained in montelukast- or inhaled beclomethasone-treated patients, but not in recipients of placebo. Improvements with inhaled beclomethasone were significantly greater than with montelukast. Recipients of montelukast or inhaled beclomethasone experienced significantly more asthma control days and significantly fewer asthma exacerbation days than placebo recipients in these trials.

The combination of montelukast 10 mg/day plus inhaled beclomethasone 200μg twice daily provided significantly better asthma control than inhaled beclomethasone 200μg twice daily in patients with poorly controlled asthma (mean FEV_1 = 72% predicted, n = 642) despite 4 weeks treatment with inhaled beclomethasone. Patients were randomised to 1 of 4 double-blind treatments (montelukast 10mg daily plus inhaled placebo, inhaled beclomethasone 200μg

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twice daily plus oral placebo, montelukast plus beclomethasone, or oral and inhaled placebos) in the study. When compared with patients continuing on inhaled beclomethasone alone, patients receiving the combination experienced significant improvements in FEV_1 and morning PEF, significant reductions in daytime symptom scores, as-needed β_2 agonist usage and night-time awakenings with asthma, and had significantly lower peripheral blood eosinophil counts after 16 weeks. Asthma control generally deteriorated in patients assigned to placebo and the frequency of discontinuation from the study because of worsening asthma was 15, 11.4, 4 and 1%, respectively, among patients who received placebo, montelukast, inhaled beclomethasone or the 2 drugs combined. These findings indicate that montelukast is not suitable for monotherapy in patients with moderate or severe persistent asthma.

Montelukast 10 mg/day allowed for significant reductions in inhaled corticosteroid dosages in patients with persistent asthma receiving ongoing treatment with inhaled corticosteroids. Between the start of treatment and the end of a randomised, double-blind, 12-week study, the mean daily dosage of inhaled corticosteroid was decreased by 47 and 30% in patients treated with montelukast or placebo, respectively. A higher proportion of montelukast (40%) than placebo recipients (29%) were successfully tapered off of inhaled corticosteroids and significantly fewer patients discontinued montelukast than placebo because of failed corticosteroid rescues (16 *vs* 30%).

Montelukast 10 mg/day plus loratadine 20 mg/day produced significantly greater improvements in FEV_1, symptom scores and β_2-agonist use than montelukast plus placebo in a 2-week, randomised, crossover study in patients with mild to severe persistent asthma.

Meta-analysis of data from 4 multicentre, placebo-controlled trials demonstrated that there was no apparent differences in the magnitude of improvement in clinical end-points between patients with or without a history of allergic rhinitis after treatment with montelukast 10 mg/day.

In aspirin-sensitive adults with persistent asthma, 4 weeks' treatment with montelukast 10 mg/day produced significant improvements in most outcome measures (i.e. FEV_1, morning PEF, β_2-agonist usage and nocturnal, but not daytime symptom scores) compared with placebo.

In Children

In paediatric patients aged 6 to 14 years, montelukast 5 mg/day for 8 weeks produced significant improvements in FEV_1, the primary outcome variable, in a multicentre, randomised, double-blind study. Significant improvement was also obtained in many (frequency of as-needed β_2-agonist use, clinic PEF, Paediatric AQLQ scores and peripheral eosinophil counts) but not all secondary outcome variables (daytime symptom scores, morning and evening PEF in patient diaries, nocturnal awakenings). Montelukast significantly reduced the frequency of days with asthma exacerbations and the proportion of patients with asthma exacerbations compared with placebo.

Among children randomised to further treatment with montelukast or inhaled beclomethasone at the end of this study the mean change from baseline in FEV_1 was similar (6.47 and 6.39%) after 1.4 years of follow-up.

Four weeks of treatment with montelukast 5 mg/day was compared with inhaled sodium cromoglycate 1.6 mg four times daily in 2 randomised, crossover studies in children aged 6 to 11 years with persistent asthma. Withdrawal rates

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were greater during treatment with sodium cromoglycate than montelukast. ≥86% of parents and ≥79% of patients expressed a preference for montelukast. In 1 of these studies, in which adherence with inhaled sodium cromoglycate was poor compared with montelukast (45 *vs* 82%, respectively), as-needed β_2-agonist usage was significantly lower during treatment with montelukast.

Tolerability

During clinical trials in adults or children with persistent asthma the frequency of adverse events in montelukast-treated patients was similar to that in placebo recipients. Headache was the most frequent adverse event, reported by 18.4 and 18.1% of adult recipients of montelukast and placebo, respectively.

In paediatric patients treated for 8 weeks, diarrhoea, laryngitis, pharyngitis, nausea, otitis, sinusitis and viral infections occurred in more than 2% of patients treated with montelukast and were more prevalent in recipients of montelukast 5 mg/day than placebo.

Churg-Strauss syndrome has been reported rarely in adult patients during treatment with montelukast; however, it is unlikely that there is a causal relationship between the drug and the emergence of this condition.

Dosage and Administration

Montelukast is indicated for the treatment of persistent asthma in patients aged ≥6 years. The recommended dosage of montelukast is 10 mg/day in adults and adolescents aged ≥15 years and 5 mg/day in children aged 6 to 14 years. The drug is administered in the evening with or without food. Dosage adjustments are not required in elderly patients or in those with renal or mild to moderate hepatic dysfunction.

1. Therapy for Persistent Asthma

Current guidelines for asthma advocate the use of anti-inflammatory therapy in all patients with chronic or persistent asthma.[1-3] According to guidelines issued by the Global Initiative for Asthma (GINA) and US authorities,[1,2] persistent asthma is present when a patient's lung function, symptom frequency or the characteristics of exacerbations exceed a defined threshold (table I). Patients with mild persistent asthma should receive preventive therapy consisting of inhaled corticosteroids (the preferred treatment), inhaled sodium cromoglycate or nedocromil, oral antileukotrienes (e.g. montelukast, zafirlukast, zileuton) or oral sustained-release theophylline.[2] The British guidelines include a similar array of preventive therapies, with the exception of antileukotrienes (which were not available when the guidelines were developed), in patients with chronic asthma who require inhaled β_2-agonist bronchodilators more than once daily.[3]

Much of the clinical data pertaining to antileukotrienes in general, and montelukast in particular, has been published since the dissemination of these guidelines. Hence, the full potential of antileukotrienes in the treatment of persistent asthma is not reflected in these documents. Montelukast is a specific cysteinyl leukotriene type 1 receptor ($cysLT_1$) antagonist, which has been studied in patients with asthma, seasonal allergic rhinitis and

Table I. Classification of persistent asthma according to the Global Initiative for Asthma[1]a

	Mild	Moderate	Severe
PEF or FEV_1b	≥80%	>60 but <80%	≤60%
PEF variability[c]	20-30%	>30%	>30%
Symptom frequency	>2/week but <1/day	Daily	Continual
Nocturnal symptoms	>2/month	>1/week	>1/week
Exacerbations	May affect activity	Affect activity	Frequent

a The presence of 1 or more features characteristic of a particular category are sufficient to place a patient in that category.

b Predicted values based on age, gender and height.

c Variability between morning and evening.

FEV_1 = forced expiratory volume in 1 second; **PEF** = peak expiratory flow rate.

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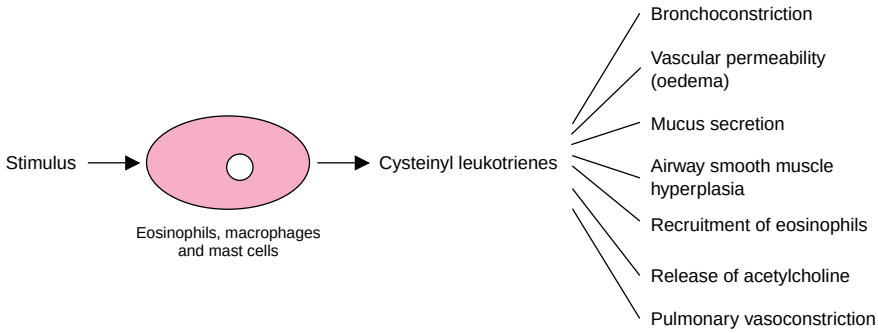

Fig. 1. Physiological effects of cysteinyl leukotrienes in patients with asthma.[7,12-25]

conjunctivitis,[4] and migraine.[5] A brief overview of the properties of montelukast was previously published in *Drugs*.[6] In this article the clinical potential of montelukast in patients with persistent asthma is comprehensively reviewed.

1.1 The Role of Leukotrienes in Asthma

Leukotrienes are important pro-inflammatory mediators in asthma. These eicosanoids are derived from the metabolism of membrane phospholipids within alveolar macrophages, eosinophils, mast cells and neutrophils; these cells are involved in the pathophysiology of this disease.[7]

Leukotriene A_4 (LTA_4) is produced by the action of 5-lipoxygenase on arachidonic acid in membrane phospholipids. LTA_4 is converted to leukotriene B_4, which mediates chemotaxis,[7,8] or leukotriene C_4 (LTC_4) by the addition of glutathione (glu-cys-gly).[9] LTC_4 is exported from the cell via a specific transmembrane transport protein. Cleavage of the glutamic acid moiety from LTC_4 yields leukotriene D_4 (LTD_4) and further modification by extracellular dipeptidases yields leukotriene E_4 (LTE_4). Because LTC_4, LTD_4 and LTE_4 each retain the cysteine residue originally donated by glutathione, they are known as the cysteinyl leukotrienes. These eicosanoids were formerly referred to collectively as the slow-reacting substance of anaphylaxis.[7,10]

Specific receptors, $cysLT_1$ and $cysLT_2$, are involved in the transduction of the physiological signals expressed by cysteinyl leukotrienes.[7,11] Activation of $cysLT_1$ receptors results in contraction of smooth muscle in the airways, increased vascular permeability and chemotaxis.[11]

The role of cysteinyl leukotrienes in asthma has been extensively reviewed elsewhere.[7,12-25] Briefly, these compounds have important bronchoconstrictive and pro-inflammatory effects in patients with asthma, including those with exercise-induced bronchoconstriction and/or aspirin sensitivity. Concentrations of cysteinyl leukotrienes are elevated in bronchoalveolar lavage (BAL) fluid obtained after antigen challenge,[26] induced sputum[27] and urine[28-32] in patients with asthma. The physiological effects of leukotrienes in asthma are illustrated in figure 1.

Cysteinyl leukotrienes mediate bronchoconstriction in humans. These substances are much more potent bronchoconstrictors than either histamine or methacholine,[33] appear to exert their effects in both large and small calibre airways[34] and are important in maintaining the baseline resting tone in human airways.[35,36] Cysteinyl leukotrienes are important mediators of exercise-induced bronchoconstriction in patients with asthma.[37]

Leukotrienes appear to contribute to the recruitment of inflammatory cells in the airways of patients with asthma, although the exact mechanism has yet to be elucidated.[24,37-43]

There is a well-documented increase in urinary LTE_4 excretion during the early asthmatic response

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(EAR) which is associated with a rapid onset of bronchoconstriction after allergen challenge.[28,30] The EAR reaches a maximum within approximately 30 minutes and thereafter wanes within 1 to 3 hours. The late asthmatic response (LAR) is a second more protracted response (with an onset several hours after the EAR) during which the narrowing of the airways may persist for ≥12 hours.[44]

Although early studies provided limited evidence for a role of leukotrienes in the LAR, recent studies suggest that leukotrienes may play an integral role in this phase.[29,30,37] The finding that antileukotrienes (including montelukast, see section 2.3.3) attenuate both the EAR (by 48 to 75%) and the LAR (by 31 to 57%) further substantiates the role of cysteinyl leukotrienes in the pathophysiology of these responses.[45-47]

Cysteinyl leukotrienes are pivotal mediators in aspirin-induced asthma.[7,48] This condition results from an increased expression of LTC_4 synthase in bronchial tissue,[49] the result of a mutation in the promoter region of the gene for this enzyme.[50-52] Patients with aspirin-induced asthma have elevated levels of LTE_4 in urine[53-55] which correspond to the severity of respiratory reactions during aspirin challenge.[54] Importantly, these individuals may experience persistent symptoms even if nonsteroidal anti-inflammatory drugs (NSAIDs) are strictly avoided.[48,56] Antileukotrienes, including montelukast (section 4.1.1), appear to improve clinical parameters in patients with aspirin-sensitive asthma,[55] including those receiving inhaled corticosteroids.[57,58]

2. Pharmacodynamic Properties

2.1 Receptor Binding Studies

Montelukast is a competitive antagonist at $cysLT_1$ receptors. This glycosylated G-protein-coupled receptor comprises 337 amino acids (molecular weight 38 549D) and signals through elevation of intracellular calcium.[59-62] The gene for the receptor has been mapped to the human X chromosome and its expression in normal human tissue, as indicated by the presence of mRNA, was greatest in spleen and peripheral blood leucocytes. mRNA for the receptor was present in peribronchial and peribronchiolar smooth muscle cells and tissue macrophages in lung tissue.[59]

The affinity of montelukast [50% inhibitory concentration (IC_{50}) ≥ 2.3 nmol/L] for the cloned human $cysLT_1$ receptor was 2.5 to 5-fold lower than that of LTD_4 (which, among the natural ligands, has the greatest affinity for this receptor; IC_{50} = 0.9 nmol/L) and was generally similar to that of other commercially available $cysLT_1$ receptor antagonists (pranlukast, zafirlukast). Unlike pranlukast, receptor binding of montelukast was not affected by the presence of human serum albumin 0.05%.[59] The receptor binding properties of montelukast have also been demonstrated in guinea-pig and sheep tissue preparations and in membrane preparations from human cell (dU937, THP-1) lines.[63-66]

2.2 Studies In Experimental Models

In animals, montelukast inhibited the acute bronchoconstrictive properties of inhaled or intravenous LTD_4 or inhaled antigen.[63] The drug also inhibited the early[63] and late[63,67] bronchoconstrictor response to inhaled allergen in sensitised animals. In contrast, montelukast did not inhibit bronchoconstriction elicited by histamine, serotonin, acetylcholine or arachidonic acid in guinea pigs.[63] The results of *in vivo* pharmacological studies of montelukast are presented in table II.

There is evidence that montelukast has anti-inflammatory effects. Montelukast blocked expression of mRNA for interleukin-5 (IL-5) in antigen-stimulated cells obtained from patients with asthma.[68] After allergen challenge the drug reduced eosinophil levels and suppressed IL-5 expression by inflammatory cells in both BAL fluid and lung tissue in rats (table II).[67]

2.3 Studies In Patients With Asthma

2.3.1 Effects on Nitric Oxide Levels in Exhaled Air

Montelukast reduced nitric oxide (NO) levels in exhaled air, a marker of inflammation that correlates with asthma severity, sputum eosinophil levels, bronchial hyperresponsiveness and peak

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Table II. Summary of *in vitro* and *in vivo* pharmacological studies with montelukast

Study (no. of patients or volunteers)	Montelukast dosage (study design)	Effect of montelukast
***In vitro* study**		
Ag-stimulated PBMC[68]a	5-50 μmol/L	Inhibited IL-5 MRNA expression (10 μmol/L) and inhibited cysLT release (≥5 μmol/L) in cells from some, but not all patients with asthma
***In vivo* studies in animals**		
Anaesthetised guinea pigs[63]	10 μg/kg IV[b]	≥70-fold shift in the dose response curve of LTD_4 (EC_{50} = 0.001 μg/kg)
	≤3 mg/kg IV[b]	Did not inhibit bronchoconstriction elicited by IV histamine, serotonin, acetylcholine or arachidonic acid
Squirrel monkeys allergic to *Ascaris suum* Ag[63]	0.1 mg/kg PO[b]	Inhibited *A. suum*-induced early and late phase bronchoconstriction (as measured by sRaw) by 69 and 64%, respectively ($p < 0.05$ *vs* control)
	0.01-0.03 mg/kg PO[b]	Attenuated the increase in R_L (by 52 to 86%; $p < 0.02$ *vs* control) and the decrease in C_{dyn} (by 42 to 100%; $p \leq 0.05$ *vs* control) induced by *A. suum* Ag
Sheep allergic to *A. suum* Ag[63]	8 μg/kg/min CI[c]	Inhibited *A. suum* Ag-induced early and late phase bronchoconstriction (as measured by sRaw) by 70 and 75%, respectively ($p < 0.05$ *vs* control)
Inbred hyperreactive rats[63]	0.015-0.5 mg/kg PO[b]	Inhibited ovalbumin-induced bronchoconstriction in a dose-dependent manner (range = 46 to 63%; $p < 0.05$ *vs* control; EC_{50} = 0.032 mg/kg)
Brown Norway rats sensitised to ovalbumin[67]	3 mg/kg IV[d]	Inhibited ovalbumin-induced bronchoconstriction (AUC_{0-8h}) by 59% ($p < 0.01$ *vs* control)
		Suppressed influx of eosinophils into BAL fluid and lung tissue by 60 and 44%, respectively, after ovalbumin challenge ($p < 0.05$ *vs* control)
		Suppressed expression of IL-5 mRNA by inflammatory cells (including eosinophils and CD3+ T cells) in BAL fluid and lung tissue by 55 and 53%, respectively, after ovalbumin challenge ($p < 0.01$ *vs* control)
Studies in children aged ≥6y or adults with persistent asthma		
Children (17)[69]	5 mg/d PO x 4wk[e] (co)	LTC_4 concentrations in nasal fluid washes were reduced 2.6-fold (1.58 *vs* 4.09 μg/L after inhaled sodium cromoglycate, $p = 0.02$)
Children (26)[70]	5 mg/d PO x 2wk (r,db,pc,co)	NO levels in exhaled air decreased by 20% (29.1 *vs* 36.3 ppb after PL, $p = 0.02$)
Children (12)[71]	5 mg/d PO x 4wk (nc)	NO levels in exhaled air decreased by 30% (from 83 ppb at baseline to 58 ppb after 4wk, $p < 0.01$) and increased to 69 ppb 2wk after withdrawal
Adults (77)[72]	10 mg/d PO x 6wk (r,db,pc,pg)	Decreased chromotrope 2R+ cells in bronchial biopsy specimens [from 3.8 to 1.1 cells/mm RBC after 6wk of montelukast, $p < 0.05$ *vs* baseline, but not PL (with which cell numbers decreased from 2.7 to 2.1/mm RBC)]
Adults (40)[73]	10 mg/d PO x 4wk (r,db,pc,pg)	Decreased the proportion of eosinophils in induced sputum (3.9 *vs* 17.9%, $p < 0.05$ *vs* PL) and eosinophil counts in peripheral blood (25 *vs* 2%; $p = 0.009$ *vs* PL)
Studies in healthy volunteers		
Elite athletes (12)[74]	10mg PO sd 4h before exercise (db,co)	No ergogenic effects (i.e. no effects on lung function, ventilation, work economy or maximum work capacity)

a PBMCs from 14 patients were incubated for 24h with ragweed or mite Ag in the presence or absence of montelukast 5-50 μmol/L.

b Montelukast was administered ≥5 min prior to challenge with IV LTD_4 or 4h prior to challenge with aerosolised LTD_4, *A. suum* Ag or ovalbumin.

c Following a 1 mg/kg IV loading dose montelukast was administered by CI for 2h prior to and 8h after Ag challenge.

d Montelukast was administered 30 min prior to challenge with aerosolised ovalbumin.

e Children received montelukast and inhaled sodium cromoglycate 1mg qid separated by a 2wk washout period.

Ag = antigen; **AUC_{0-8h}** = area under the R_L *vs* time curve from 0-8h after ovalbumin challenge; **BAL** = bronchoalveolar lavage fluid; **C_{dyn}** = dynamic compliance; **CI** = continuous infusion; **co** = crossover; **cysLT** = cysteinyl leukotriene; **db** = double-blind; **EC_{50}** = concentration of montelukast that inhibited LTD_4- or ovalbumin-induced bronchoconstriction by 50%; **IL-5** = interleukin-5; **IV** = intravenous; **LTC_4** = leukotriene C_4; **LTD_4** = leukotriene D_4; **nc =** noncomparative; **NO** = nitric oxide; **PBMC** = peripheral blood mononuclear cells; **pc** = placebo-controlled; **pg** = parallel-group; **PL** = placebo; **PO** = by mouth; **ppb** = parts per billion; **qid** = 4 times daily; **r** = randomised; **RBC** = reticular basement membrane; **R_L** = pulmonary airflow resistance; **sd** = single dose; **sRaw** = specific airway resistance.

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flow variability.[75,76] NO levels in exhaled air were 20% lower after 2 weeks' treatment with montelukast 5 mg/day in children with mild asthma ($p = 0.02$ *vs* placebo, $n = 26$; table II).[70] Importantly, NO levels in exhaled air decreased by 22% during treatment with montelukast in children receiving inhaled corticosteroids (mean dosage 273 μg/day; $n = 11$); the corresponding decrease in inhaled corticosteroid-naive children was 18%.[70]

In a further study in 12 inhaled-corticosteroid-naive children with mild asthma aged 6 to 11 years, exhaled NO levels decreased 30% during treatment with montelukast 5 mg/day (table II).Two weeks after withdrawal of the drug, NO levels in exhaled air had increased, but did not exceed baseline values.[71]

2.3.2 Effects on Eosinophils

In clinical studies, eosinophil counts were consistently reduced by treatment with montelukast. Significant ($p < 0.05$) reductions in peripheral blood eosinophil levels were documented between baseline and end-point in adult and paediatric patients treated with clinically relevant dosages of montelukast for ≥4 weeks (section 4).[73,77-80] Reductions in eosinophil counts were similar in patients assigned to montelukast 10 mg/day or inhaled beclomethasone 400 μg/day (section 4.1.1)[78] and were significantly ($p < 0.05$) greater in patients receiving montelukast 10 mg/day plus inhaled beclomethasone 400 μg/day than in those receiving inhaled beclomethasone alone (section 4.1.2).[80] These findings are clinically relevant because peripheral eosinophil counts are elevated in patients with asthma[81-83] and are inversely correlated with the forced expiratory volume in 1 second (FEV_1).[81]

The proportion of eosinophils in induced sputum, a more accurate marker of asthmatic airway inflammation than measurements in peripheral blood,[82] was significantly ($p < 0.05$) lower after 4 weeks' treatment with montelukast 10 mg/day than placebo in adult patients with mild to moderate asthma (FEV_1 = 65 to 85% predicted; table II).[73]

The proportion of chromotrope 2R+ cells in bronchial biopsy specimens, a marker for eosinophils, decreased significantly during 6 weeks of treatment with montelukast 10 mg/day ($p < 0.05$ *vs* baseline, table II), but not placebo in adult patients with asthma. However, there was a large degree of intra- and interpatient variability and the difference between treatments was not statistically significant.[72]

2.3.3 Effects on Leukotriene-Induced Bronchoconstriction

The ability of montelukast to prevent bronchoconstriction was established in a series of double-blind, randomised, crossover experiments in which patients with mild to moderate asthma (FEV_1 ≥70% predicted) were challenged with aerosolised LTD_4.[84] Over a broad dose range (5 to 250mg), montelukast was highly effective in inhibiting acute LTD_4-induced bronchoconstriction [specific airway conductance (sGaw) was measured by constant volume body plethysmography]. Moreover, the onset of the antagonist effect of montelukast was readily apparent after absorption of a single dose.

In single dose studies it was not possible to determine the concentration of LTD_4 required to produce a 50% decrease (PC_{50}) in sGaw after treatment with montelukast 5 to 250mg (a ≥50% decrease in sGaw was not observed in any of the 8 patients[1]).[84] Estimates of the PC_{50} for LTD_4 during montelukast treatment ranged from >21- to >1225-fold greater than placebo.[84]

In a further experiment, patients received montelukast 40 or 200 mg/day for 2 days. sGaw was measured 20 to 24 hours after administration of the second dose, a period which corresponds with steady-state trough concentrations of the drug in plasma (section 3.1). Similar to the results of single dose studies, the PC_{50} could not be determined in any of the 6 patients during treatment with montelukast 200 mg/day or in 4 of the 6 patients during treatment with montelukast 40 mg/day. The PC_{50} in the 2 remaining patients was 18- and 45-

1 The maximum LTD4 concentration tested was approximately 100-fold greater than the mean of 2 baseline PC^{50} values.

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fold greater during montelukast than placebo treatment.[84]

2.3.4 Effects on Bronchial Hyperresponsiveness

Bronchial hyperresponsiveness is a characteristic feature in patients with asthma. The ability of montelukast to attenuate bronchial hyperresponsiveness to inhaled substances including methacholine and AMP has been investigated in patients with asthma.

The concentration of inhaled AMP required to provoke a 20% decrease in FEV_1 (PC_{20}) increased 2.5-fold after oral montelukast (from 41.8 g/L after placebo to 105.5 g/L 24 hours after a single 10mg dose, $p < 0.05$) in a nonblind, randomised, crossover study in 12 patients with mild to moderate asthma inadequately controlled by inhaled corticosteroids. Inhaled salmeterol 50μg produced a similar (2.8-fold, $p < 0.05$ *vs* placebo) increase in PC_{20} in the same patients. The bronchoprotective effects of these 2 agents were additive; PC_{20} increased 4.4-fold after treatment with montelukast 10mg plus salmeterol 50μg ($p < 0.05$ *vs* placebo). Lung function also improved significantly after administration of the combination (mean FEV_1 increased from 2.59L after placebo to 2.92L, $p < 0.05$), but not after a single dose of montelukast 10 mg (2.66L) or salmeterol 50μg (2.79L).[85]

In adults with exercise-induced bronchoconstriction, the PC_{20} for methacholine increased somewhat during treatment with montelukast 10 mg/day in a 12-week double-blind, placebo-controlled study. However, the increase was not statistically different from placebo (after 12 weeks the PC_{20} was equivalent to 0.45 and 0.14 doubling doses of methacholine in patients treated with montelukast or placebo, respectively).[86]

2.3.5 Effects on Lung Function

Single doses of montelukast produced rapid increases in FEV_1 and reduced the magnitude of the EAR and LAR in patients with asthma.

Oral montelukast 100 or 250mg produced significant improvements in FEV_1 in 22 patients with moderate to severe persistent asthma (FEV_1 = 55 to 79% predicted) in a randomised, double-blind, placebo-controlled, crossover study.[87] FEV_1 values in montelukast recipients exceeded those in placebo recipients within 1 hour of drug administration and remained greater throughout the 6-hour study interval (mean increases in FEV_1 values were 8.9, 16.3 and 20.9% 6 hours after administration of placebo or montelukast 100 or 250mg, respectively). Effects were similar in patients receiving ongoing inhaled corticosteroids (n = 10) and did not preclude a considerable (≈20%) bronchodilator response to inhaled salbutamol (albuterol) 180μg.[87]

Montelukast produced rapid improvement in FEV_1 in 51 patients with mild to severe persistent asthma in a randomised, double-blind crossover study. The mean FEV_1 increased by 18.4, 12.9 and 7.3% one hour after administration of single doses of montelukast 7mg intravenously, 10mg orally and placebo, respectively ($p < 0.001$ for intravenous *vs* oral montelukast); significant improvements in FEV_1 were noted within 15 minutes of administration of intravenous montelukast. Importantly, improvements in FEV_1 were maintained throughout a 24 hour period.[88] These findings have prompted some authors to recommend investigation of leukotriene receptor antagonists in the treatment of acute asthma.[88,89]

The effects of approved oral dosages of montelukast on lung function after longer-term treatment are discussed in section 4.

Montelukast, at a clinically relevant dosage (10mg/day), protected against the EAR and the LAR after allergen challenge in 12 patients with mild asthma (FEV_1 = 79 to 109% predicted). In this double-blind, placebo-controlled, crossover study the EAR and LAR were defined as the area under the time versus response curve between 0 and 3 hours ($AUC_{0\text{-}3h}$), and between 3 and 8 hours ($AUC_{3\text{-}8h}$), after challenge with inhaled house dust mite extract. After treatment with montelukast 10 mg/day for 2 days, the EAR and LAR were reduced by 75.4% ($p < 0.001$ *vs* placebo) and 56.9% ($p = 0.003$ *vs* placebo), respectively. Montelukast also inhibited the maximum decline in the FEV_1 during the EAR (by 53.6%; $p = 0.002$ *vs* placebo) and LAR (by 36.4%; $p = 0.008$ *vs* placebo). Allergen

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challenges were done during steady state (i.e. 12 hours after the second dose of montelukast; see section 3).[45] The ability of montelukast to ameliorate both the EAR and the LAR corroborates the finding that LTE_4 is elevated during both of these phases in patients with asthma (see section 1.1).[29,30]

In contrast to the rapid onset of a significant bronchoprotective response in these patients, there was no difference in the eosinophil counts or eosinophilic cationic protein levels in induced sputum after 2 days' treatment with montelukast.[45] These findings suggest that treatment with montelukast rapidly ameliorates the EAR and LAR in patients with asthma, but prolonged administration may be necessary to effect changes in inflammatory cell counts (see sections 2.3.2, 4.1 and 4.2).

2.4 Studies in Patients with Exercise-Induced Bronchoconstriction

Cysteinyl leukotrienes are important mediators of exercise-induced bronchoconstriction and the effects of montelukast have been evaluated in patients with this condition.[37]

In preliminary studies conducted in adults with exercise-induced bronchoconstriction, montelukast 0.4 to 100 mg/day for 2 days provided dose-related protection in a standardised exercise test (see below).[90,91] Dosages ≥10 mg/day produced maximal clinical effects and the drug remained effective 20 to 24 hours after administration.[90] A further 12-week study was then undertaken to determine the long term efficacy of the marketed dosage of montelukast (10 mg/day) in 110 adult patients with exercise-induced bronchoconstriction.[86] Subsequently, montelukast has been compared with inhaled salmeterol in 2 randomised, studies.[92,93]

Among those enrolled in these studies, the minimum degree of exercise-induced bronchoconstriction at baseline was defined as a ≥18[92] or ≥20% decrease[86,93] in FEV_1 following a standardised exercise challenge (a 6-minute treadmill test conducted at a workload that increased the patient's heart rate to between 80 and 90% of the recommended maximum). A ≥20% decrease in FEV_1 after inhaling aerosolised methacholine (≤4 g/L) was required in 2 studies (section 2.4.1).[86,92]

At the end of 12 weeks, the area under the percent change in FEV_1 versus time curve calculated for the 1 hour after exercise ($AUC_{0\text{-}60}$ FEV_1, the primary efficacy variable) was 47.4% smaller in montelukast than placebo recipients (table III; $p = 0.002$).[86] The maximum decrease in FEV_1 after exercise ($p = 0.003$ *vs* placebo) and the time required for the FEV_1 to return from the nadir to within 5% of the baseline value ($p = 0.04$ *vs* placebo) were both significantly smaller in montelukast- than placebo-treated patients (table III).[86] These data agree with that obtained in other placebo-controlled studies with antileukotrienes in patients with exercise-induced bronchoconstriction.[95,96]

After 12 weeks' treatment, 12 montelukast-treated patients (23 *vs* 6% of placebo recipients) had a maximal decrease in FEV_1 of ≤10%. In contrast, 13 montelukast recipients (25 *vs* 57% in the placebo group) had a maximal decrease in FEV_1 of ≥30%. Although montelukast was significantly more effective than placebo in this study, these results suggest that some patients with exercise-induced bronchoconstriction are 'nonresponders' to montelukast.[97]

In addition to improvement in pharmacodynamic end-points, control of asthma, as reflected in patients' global ratings, improved with montelukast treatment. The proportion of patients describing their asthma control as being better, unchanged, or worse was 73.1, 21.2 and 5.8%, respectively, in montelukast-treated patients, and 44.4, 46.3 and 9.3% among placebo recipients ($p = 0.009$).[86] Furthermore, the frequency of as-needed β_2-agonist usage after exercise challenge was significantly lower among patients treated with montelukast than placebo (fig. 2; $p < 0.05$ at weeks 4, 8 and 12).[86]

2.4.1 Montelukast versus Salmeterol

In patients with moderate persistent asthma (FEV_1 ≥65% predicted) substantial reductions in $AUC_{0\text{-}60}$ FEV_1, the maximum decrease in FEV_1 and recovery time were evident within 3 days of treat-

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Table III. Summary of randomised, double-blind, parallel-group trials comparing oral montelukast 10 mg/day (MK) with placebo (PL) or inhaled salmeterol 42μg twice daily (SLM) in patients aged 14 to 45 years with asthma and exercise-induced bronchoconstriction

Reference	Treatment (no. of patients)	Pre-exercise FEV_1 at baseline (mean % predicted ± SD)	Time of evaluation	Results[ab]		
				$AUC_{0\text{-}60}$ FEV_1 (% change • min)	maximum decrease in FEV_1 (%)	recovery time[c] (min)
MK versus PL						
Leff et al.[86]	MK (54)	83.2 ± 10.9	baseline	1407	36.5	64.6
			week 12	758***	22.2**	44.3*
	PL (56)	83.5 ± 11	baseline	1593	38.9	66.5
			week 12	1441	32.4	60.6
MK versus SLM						
Edelman et al.[93,94]d	MK (97)	87.14 ± 11.24	baseline	1396.3	37.0	62.2
			day 1-3	562.8 [↓71%]	21.7 [↓49%]	[↓64%]
			week 4	575.7 [↓71%†††]	19.6 [↓56%†]	[↓70%††]
			week 8	637.6 [↓67%†††]	20.1 [↓57%††]	[↓75%†††]
	SLM (94)	87.95 ± 13.48	baseline	1311.6	36.6	57.2
			day 1-3	742.3 [↓53%]	23.8 [↓40%]	[↓53%]
			week 4	1088 [↓30%]	27 [↓29%]	[↓15%]
			week 8	1004.4 [↓32%]	27.3 [↓33%]	[↓13%]
Villaran et al.[92]d	MK (102)	86.6 ± 13.7	baseline	1051	33.3	47.5
			day 3	441	17.7	22.4
			week 4	474†††	17.3†††	24.2††
			week 8	447††	15.9†††	23.8††
	SLM (95)	87.2 ± 14	baseline	951	30.5	45.6
			day 3	531	18	24.4
			week 4	820	23.6	36.2
			week 8	674	20.2	33.6

a After a 6-minute treadmill test at a workload which increased the patient's heart rate to 80-90% of the recommended maximum (calculated as 220 minus age) while inhaling compressed dry air. FEV_1 was measured 20 and 5 minutes prior to exercise and 0, 5, 10, 15, 30, 45 and 60 minutes after completion of the treadmill phase. If a value was missing at week 12 then the last measurement for that patient was carried forward. The use of inhaled β_2 agonists was not allowed within 6 hours of clinic assessments, but was provided during or after exercise challenge if deemed necessary by the investigator (the last FEV_1 measurement prior to β_2-agonist administration was carried forward in such cases).

b Mean values are presented. Values in square brackets are median changes from baseline which were estimated from graphs in Edelman et al.[93]

c Time required for the FEV_1 to return to within 5% of baseline after completion of the exercise test.

d Use of inhaled corticosteroids, theophylline, sodium cromoglycate and/or nedocromil was prohibited in the study by Edelman et al.[93] In the study by Villaran et al.[92] 10% of participants (14 MK and 6 SLM recipients) were receiving inhaled corticosteroids (200-500 μg/day) as per the study protocol.

$AUC_{0\text{-}60}$ FEV_1 = area under the FEV_1 (expressed as the % change from baseline) *vs* time curve from 0 to 60 minutes after exercise challenge; **FEV_1** = forced expiratory volume in 1 second; **SD** = standard deviation; ↓ indicates a decrease; *p = 0.04 *vs* PL; **p = 0.003 *vs* PL; ***p = 0.002 *vs* PL; †p = 0.0015 *vs* SLM; ††p ≤ 0.01 *vs* SLM; †††p ≤ 0.001 *vs* SLM.

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ment with montelukast 10 mg/day or inhaled salmeterol 42µg[2] twice daily (table III). The efficacy of montelukast did not wane during 8 weeks of treatment. In contrast, $AUC_{0\text{-}60}$ FEV_1, the maximum decrease in FEV_1 and recovery time were greater in salmeterol recipients after 4 and 8 weeks of continuous treatment compared with days 1 to 3, and were significantly ($p \leq 0.015$ at weeks 4 and 8) greater than in montelukast-treated patients.[92,93]

These results suggest that montelukast may provide superior long term prophylaxis of exercise-induced bronchoconstriction than inhaled salmeterol. Tolerance, clearly evident in patients treated with salmeterol, but not montelukast, in these 2 studies, has been reported with prolonged use of salmeterol in other studies of exercise-induced bronchoconstriction.[98-100]

Similar to the findings in the placebo-controlled study described above,[86] montelukast-treated patients could be described as 'responders' and 'non-responders'. Approximately two-thirds of the patients assigned to montelukast in these 2 studies experienced a ≤20% decline in FEV_1 after 8 weeks[93,101] (the corresponding proportion was 45.6% among salmeterol recipients in 1 trial[93]). Among patients randomised to montelukast or salmeterol in 1 study,[92] 24 and 14% of patients, respectively, had a maximum decrease in FEV_1 of ≤5% at week 8.[92]

The proportion of patients requiring supplemental β_2 agonists after exercise was reported in 1 study.[93] Significantly fewer montelukast than salmeterol recipients required supplemental salbutamol (26 *vs* 40%, respectively; $p = 0.044$).[93]

2.4.2 In Children

In children aged 6 to 14 years with exercise-induced bronchoconstriction, montelukast administered at a dosage of 5 mg/day had similar protective effects to those achieved in adults with 10 mg/day. Paediatric patients (n = 27) eligible for this multi-centre, randomised, double-blind, crossover study were required to have a pre-exercise FEV_1 of ≥70% (mean: 87%) and a decrease of ≥20% in FEV_1 following a standardised exercise challenge (described above). Children received montelukast 5 mg/day for 2 days and exercise testing was done 20 to 24 hours after the second dose.[102]

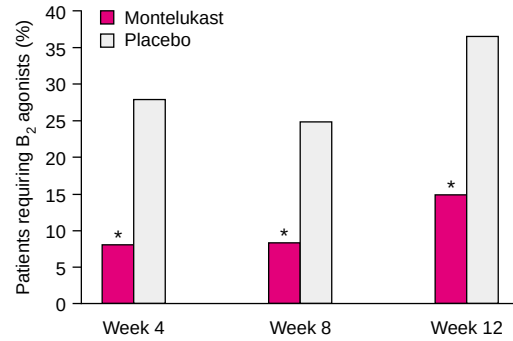

Fig. 2. As-needed β_2-agonist usage after exercise in patients with exercise-induced bronchoconstriction during treatment with montelukast. Percentage of patients that used as-needed β_2-agonist bronchodilators after a standard exercise challenge during treatment with montelukast 10 mg/day (n = 54) or placebo (n = 56) in a 12-week, multicentre, randomised, double-blind, parallel group trial.[86] At baseline patients had mild persistent asthma (mean FEV_1 = 83.4%) and experienced a decrease of ≥20% in FEV_1 after exercise challenge. The exercise challenge consisted of 6 minutes on a treadmill at a rate that increased the patient's heart rate to 80 to 90% of the recommended maximum (calculated as 220 minus age). The FEV_1 was monitored at intervals for 1 hour after the challenge. **FEV_1** = forced expiratory volume in 1 second; *p < 0.05 *vs* placebo.

Relative to placebo treatment, montelukast decreased the AUC FEV_1 by 55% (590 *vs* 265% · min; $p \leq 0.05$), reduced the maximum decrease in FEV_1 by 31% (-26 *vs* -18%; $p \leq 0.05$) and reduced the recovery time (i.e. from nadir to within 5% of the baseline FEV_1) by 36% (28 *vs* 18 minutes; not significant).[102] These and other results[103] confirm that antileukotrienes, including montelukast, significantly attenuate exercise-induced bronchoconstriction in children.

3. Pharmacokinetics

The pharmacokinetics of montelukast 10mg administered as a tablet have been studied in healthy volunteers, including healthy elderly volunteers.

2 In accord with US labelling requirements, the dose of salmeterol was reported as the amount delivered through the mouthpiece (42µg) rather than the amount delivered per actuation (50µg).

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Steady state pharmacokinetic parameters for montelukast 10 mg/day in healthy volunteers are presented in table IV.

3.1 Absorption and Distribution

Approximately two-thirds of a 10mg oral dose of montelukast is absorbed from the gastrointestinal tract, after which it is highly bound to plasma proteins. Food does not impair absorption of montelukast to a clinically significant extent, hence the drug may be administered with or without meals.[104] Steady state plasma concentrations were achieved on the second day of administration in volunteers.[105] The accumulation ratio [calculated as the ratio of the area under the plasma concentration versus time curve from 0 to 24 hours after administration (AUC_{24}) on day 7 to day 1] was 1.14 in a multidose study in 12 volunteers, suggesting that there was a small, but statistically significant ($p = 0.034$) accumulation of montelukast after multiple doses.[105]

Studies in animals suggest that penetration of the blood brain barrier by montelukast is minimal.[104] Montelukast crosses the placenta in rats and rabbits and is excreted in the milk of rats.[104]

3.2 Metabolism and Excretion

Montelukast is eliminated primarily by biliary excretion and hepatic oxidative metabolism. Montelukast has 1 major metabolite and 5 minor metabolites which were recovered in bile samples.[106] Hydroxylation and sulfoxidation of the drug are catalysed by cytochrome P450 (CYP) 3A4, and methylhydroxylation is attributable to CYP2C9.[106,107] *In vitro* studies with hepatic microsomes obtained from adults aged 50 to 65 years and children aged 6 to 11 years demonstrate that the metabolic profiles for acyl glucuronidation and oxidative metabolism are similar in these 2 age groups.[107] Moreover, all oxidative metabolic transformation was attributable to CYP isozymes.[107]

In 6 healthy volunteers 86.3% of a single 102mg radiolabelled oral dose of montelukast was recovered in faeces within 5 days of administration; <0.2% was recovered in urine.[104,106] In these individuals, the ratio of the AUC_{∞} for montelukast to that for total radioactivity in serum was 0.8, indicating that the systemic exposure to montelukast metabolites was low.[106] Indeed, <2% of the recovered radioactivity was associated with the diastereomers of 2 minor metabolites.[106]

Montelukast is the pure R-enantiomer of a racemic molecule and there is no evidence of bioconversion of montelukast to its S-enantiomer in humans. The S-enantiomer was not detected [limit of detection = 9.6 μg/L] in plasma in 6 volunteers who received montelukast 10 mg/day for 7 days.[108]

3.3 In Elderly Volunteers

The pharmacokinetic profile of oral montelukast 10mg in 12 elderly volunteers aged ≥65 years (range 65 to 73 years) was generally similar to that in 12 healthy younger adults aged 20 to 48 years. Single dose values for oral bioavailability, maximum plasma concentration (C_{max}), the time required to achieve C_{max} (t_{max}) and AUC_{∞} differed little between the 2 groups.[105] However, the clearance of montelukast was significantly lower in elderly versus younger adults (1.85 *vs* 2.81 L/h; $p < 0.001$) and the terminal elimination half-life ($t_{½\beta}$) was significantly longer (6.6 *vs* 5.3 hours; $p <$

Table IV. Steady state pharmacokinetic parameters of montelukast 10 mg/day in healthy fasted adults[104,105]

F (%)		64
C_{max} (mg/L)		0.6
C_{min} (mg/L)		0.02
t_{max} (h)		3-4
V_d (L)		8-11
AUC_{24} (mg/L • h)		3.98
Plasma protein binding (%)		>99%
Major metabolic pathways		CYP3A4, CYP2C9
Excretion (%)	faecal	86%
	urinary	<0.2%
Cl (L/h)		2.7
$t_{½\beta}$ (h)		2.7-5.5

AUC_{24} = area under the plasma concentration *vs* time curve from 0 to 24 hours after administration; **Cl** = systemic clearance **C_{max}** = peak plasma concentration; **C_{min}** = trough plasma concentration; **CYP** = cytochrome P450; **F** = mean oral bioavailability; **$t_{½\beta}$** = terminal elimination half-life; **t_{max}** = time to reach C_{max}; **V_d** = apparent volume of distribution at steady state.

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0.001). In spite of these differences, the montelukast dosage need not be adjusted in otherwise healthy elderly patients with asthma (section 6).[105]

3.4 In Children

In children aged 6 to 14 years, montelukast 5mg administered as a chewable tablet provided an AUC similar to that obtained in adults after a 10mg dose administered as a film-coated tablet.[109] Using similar population pharmacokinetic techniques in children aged 2 to 5 years the AUC was 2.72 mg/L · h in 15 children aged 2 to 5 years after a single 4mg dose. This compares well with historical data obtained in adults given the 10mg film-coated tablet (AUC = 2.56 mg/L · h).[110]

3.5 Potential for Pharmacokinetic Drug-Drug Interactions

3.5.1 In Vitro *Studies*

Selective inhibitors of CYP2A6 (coumarin), CYP2C19 (S-mephenytoin), CYP1A2 (furafylline), CYP2D6 (quinidine), and CYP2E1 (diethyldithiocarbamate) did not alter the metabolism of montelukast in human liver microsomes.[107] In contrast, selective inhibitors of CYP3A4 (troleandomycin, ketoconazole and L-754,394) and CYP2C9 (sulfaphenazole), substantially reduced the oxidative metabolism of the drug. These results suggest that inhibitors of CYP3A4 (e.g. ketoconazole, erythromycin) and/or CYP2C9 (e.g. fluconazole) may have the potential to inhibit the metabolism of montelukast.[104,107] Drug interaction studies with these inhibitors have not been done in patients or volunteers.

Montelukast was a competitive inhibitor of methyl hydroxylation of tolbutamide in human microsomes and, to a lesser extent, 6β-hydroxylation of testosterone and 4'-hydroxylation of S-mephenytoin, but had minimal effects on O-deethylation of phenacetin, 7-hydroxylation of coumarin or 4-hydroxylation of debrisoquine.[107] Further *in vitro* studies demonstrate that the drug does not inhibit CYP1A2, CYP2A6, CYP3A4, CYP2C9, CYP2C19 or CYP2D6.[104]

3.5.2 Studies in Humans

No clinically significant drug-drug interactions involving montelukast have been reported in patients with asthma. Placebo-controlled drug interaction studies have been conducted in volunteers. In 10 healthy volunteers aged 23 to 56 years, the AUC_{∞} and C_{max} of a single 10mg oral dose of montelukast were reduced by 37.5 (from 2.47 to 1.54 mg/L · h) and 21% (from 0.38 to 0.3 mg/L), respectively, after receiving phenobarbital 100 mg/day for 14 days.[111] Despite the apparent induction of montelukast metabolism, the authors of this study concluded that no dosage adjustments were warranted in patients receiving concurrent montelukast and phenobarbital. Pharmacokinetic values for phenobarbital were not reported in the abstract.[111]

Montelukast 10 mg/day did not alter the pharmacokinetics of theophylline, a substrate of CYP1A2 and, to a lesser extent, CYP3A4, to a clinically significant extent. The mean AUC_{∞} of a single intravenous dose (4.65 mg/kg) of theophylline decreased by 8% and the clearance increased by 9% when administered to 15 volunteers who had been receiving montelukast 10 mg/day for 10 days in a placebo-controlled, crossover study.[112] The geometric mean ratios for the AUC and C_{max} of theophylline remained within the predefined values for bioequivalence during the study. Hence, the recommended dosage of montelukast may be administered concomitantly with theophylline without the need for dosage adjustment or additional serum concentration monitoring of the latter.

In volunteers receiving montelukast 10 mg/day at steady state there was no change in the international normalised ratio or pharmacokinetic profile (AUC or C_{max}) of either the R or S enantiomer of warfarin after a single 30mg dose (substrates of CYP2A6 and CYP2C9).[113] There was no change in the pharmacokinetic profile or urinary excretion of immunoreactive digoxin in another study.[104,114]

Montelukast 10 mg/day for 7 days had no discernable effect on the AUC_{12} and C_{max} of terfenadine, or the QTc interval in 9 volunteers aged 19 to 37 years who had received terfenadine 60mg twice

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daily for 14 days.[115] Furthermore, montelukast did not change the pharmacokinetic profile of fexofenadine.[104]

Concentrations of ethinyl estradiol, norethindrone and sex hormone binding globulin were unaffected by montelukast 100 mg/day for 8 days in 23 women receiving ongoing treatment with a combined oral contraceptive pill (ethinyl estradiol 35μg plus norethindrone 1mg).[116]

No significant change in the single dose plasma profiles of oral prednisone or intravenous prednisolone were detected in volunteers receiving montelukast ≥100 mg/day at steady state.[104]

4. Therapeutic Potential in Patients with Persistent Asthma

In dose-finding studies of 3[117] or 6 weeks'[118] duration in patients with persistent asthma, the magnitude of the treatment effect was similar with all dosages of montelukast ≥10 mg/day (2 to 200 mg/day were evaluated); hence, 10 mg/day was the dosage selected for use in subsequent clinical trials in adults.[119] A dosage of 5 mg/day was selected for use in children aged 6 to 14 years, because this dosage provides an AUC similar to that achieved with a 10 mg/day dosage in adults (see section 3.4).[109] Montelukast was administered in the evening in all trials so that peak plasma concentrations occurred during the early morning hours, a time at which asthma patients are prone to bronchoconstriction because of natural circadian variation in airway obstruction.[119]

The clinical efficacy of montelukast in adults and children with persistent asthma,[77-80,120-122] including patients sensitive to aspirin,[123] has been evaluated in randomised, double-blind trials. In adult patients, montelukast 10mg has been compared with placebo[77,78,120] and inhaled beclomethasone;[78,120,122] the therapeutic effects of the drug have also been studied in patients receiving concomitant inhaled beclomethasone 400 μg/day[80] or loratadine 20 mg/day.[124] The inhaled corticosteroid-sparing potential of the drug has been assessed in a randomised, double-blind, dosage reduction study.[121] In children, montelukast 5mg has been compared with placebo[79] and inhaled sodium cromoglycate.[125,126] Several studies are available only as abstracts.[120,122-127]

In published comparative trials, patients received placebo during a 2- or 4-week run-in phase.[77-80] Patients eligible for these trials were nonsmokers who displayed the following during the run-in phase:

- a baseline FEV_1 of 50 to 85% of the predicted value for the patient's age, gender and height,
- an increase in FEV_1 of ≥15% 20 to 30 minutes after inhalation of a short-acting β_2-agonist bronchodilator,
- use of ≥1 puff of as-needed salbutamol per day
- and a total daytime asthma score of ≥64 out of 336 in adults, or a minimum score of 21 in the biweekly assessment of daytime asthma symptoms in children.[77-80]

A 3-week double-blind washout period was included in 2 studies to assess patients after withdrawal of montelukast.[77,78]

Patients were generally receiving few medications prior to enrolment. Patients were excluded if they had received: oral or injectable corticosteroids or inhaled sodium cromoglycate or nedocromil within the previous month; methylxanthines (e.g. theophylline), oral or long acting inhaled β_2-agonist bronchodilators or anticholinergic agents within the previous 2 weeks.[77-80] Recent use of terfenadine,[77-80] loratadine[77-79] (within 2 weeks) or astemizole (within the previous 3 months) were also exclusion criteria.[77-80]

Recent use of inhaled corticosteroids was an exclusion criteria in several studies.[77-79] Notwithstanding this, a subset of patients (not to exceed 25% in 1 study[77]) who were receiving ongoing treatment with stable dosages of inhaled corticosteroids for ≥4 weeks prior to enrolment were allowed to continue the regimen during 2 trials.[77,79] In a further study, participants were allowed to continue use of theophylline if they had been receiving the drug for >2 weeks.[78]

In 1 study, in which montelukast was administered with inhaled beclomethasone, eligible patients had a ≥1 year history of intermittent or per-

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Table V. Composite measures of asthma control used in clinical trials of montelukast[77,78,120]

Asthma exacerbation days (≥1 of the following occurred):
PEF <180 L/min
>20% decrease in morning PEF compared with baseline
>70% increase in as-needed use of a short acting β_2-agonist compared with baseline (minimum increase of 2 puffs)
>50% increase in symptom score compared with baseline
Awake all night with asthma
Worsening asthma requiring oral corticosteroids, a visit to a physician or hospitalisation
Asthma control days (none of the following occurred):
Use of >2 puffs of a short acting β_2-agonists
Nocturnal awakening because of asthma
Worsening asthma requiring oral corticosteroids, a visit to a physician or hospitalisation

PEF = peak expiratory flow rate.

sistent asthma and had received inhaled corticosteroids for the preceding 6 weeks (beclomethasone 400 to 500 μg/day or equivalent). Inhaled beclomethasone 200μg twice daily was administered with placebo tablets during the 4-week run-in phase of the trial.[80]

Patients were allowed to use a short acting inhaled β_2-agonist bronchodilator (e.g. salbutamol) on an as-needed basis during all studies.

In each study the primary outcome measure was the FEV_1;[77-80] daily symptom scores were also used as primary outcome measures in studies in adults.[77,78,80]

Daytime and nocturnal symptom scores were recorded each day. Adults evaluated daytime symptoms using a 7-point scale to answer 4 questions.[77,78,80,128] The daily responses to the 4 questions were averaged to produce a daily symptom score which ranged from 0 (no symptoms) to 24 (severe symptoms). Nocturnal awakenings were evaluated with a 4-point scale. Both the daytime and night-time symptom scores used in these trials have been validated using data from large clinical trials in adults with mild to moderate asthma.[128]

For the paediatric study,[79] the symptom scale was modified and validated – the first such scale to be validated for use in children with asthma.[129]

Composite measures of asthma control were reported in some studies.[77,78,120] These included asthma exacerbation days and asthma control days (table V). In 1 study, in which the asthma control day was the primary outcome measure, sustained asthma control was defined as ≥3 consecutive asthma control days and asthma flare-ups were defined as ≥3 consecutive nonasthma control days (available as an abstract).[120] Composite measures have been shown to be clinically meaningful in patients receiving treatment for asthma.[130] The proportion of patients withdrawn because of loss of efficacy was also reported in some trials.[77,78,80]

Valid disease-specific instruments were used to measure health-related quality of life (QOL). The Asthma Quality of Life Questionnaire (AQLQ) was used in studies in adults[77,78] and the Paediatric AQLQ was used in studies in children.[79] The AQLQ consists of 32 items which evaluate QOL in 4 domains (Activity Limitation, Symptoms, Emotional Function and Environmental Stimuli) over the preceding 2 weeks and is able to detect changes in patients who respond to treatment or experience natural fluctuations in asthma severity.[131,132] The minimum clinically significant change in total AQLQ score or in scores in any of the 4 domains has been estimated to be ≈0.5 units.[133]

The Paediatric AQLQ was derived from the AQLQ and consists of 23 items in 3 domains (Activity Limitation, Symptoms and Emotional Function) that measure impairment during the preceding week.[134] Like the AQLQ, the Paediatric AQLQ is able to detect changes in response to treatment or natural fluctuations in disease severity.[134] The minimum clinically significant change in the total Paediatric AQLQ score has been estimated to be ≈0.4 units.[134]

The average minimal patient perceivable improvement in several outcome measures used in trials with montelukast have been estimated.[135] Threshold values for perceptible improvement for FEV_1 (0.23L), PEF (18.79 L/min) symptom scores (change of -0.31 points on the 7 point scale) and as-needed β_2-agonist use (-0.81 puffs/day) were based on the results of a randomised placebo-controlled trial in 281 adult patients with persistent asthma (FEV_1 = 40 to 80% predicted).[135]

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4.1 Studies in Adults

4.1.1 Montelukast versus Placebo or Inhaled Beclomethasone

Montelukast has a rapid onset of action. Within 1 day of treatment improvements in the mean morning PEF (≈20L),[77,78] daytime asthma scores (mean decrease = 0.31)[77] and the frequency of as-needed β_2-agonist use (mean decrease = 22%)[77] were apparent in montelukast recipients (estimated from graphs).[77] In contrast, the mean morning PEF increased by <10 L/min in beclomethasone recipients (estimated from a graph)[78] and there was no discernible improvement in placebo-treated patients after 1 day.[77,78]

After 12 weeks of treatment, patients randomised to montelukast or inhaled beclomethasone had significantly greater improvements in primary (FEV_1, daytime symptom scores) and secondary end-points ($p < 0.05$ for montelukast or beclomethasone *vs* placebo; table VI) than placebo recipients.[77,78] However, inhaled beclomethasone produced significantly greater improvements in FEV_1, daytime symptom scores, PEF, nocturnal awakenings and AQLQ scores than montelukast. Improvement in FEV_1 was greater in beclomethasone than montelukast recipients in a further trial which is available as an abstract [FEV_1 improved by 0.23, 0.37 and 0.09L, respectively, in patients treated with montelukast (n = 337), beclomethasone (n = 327) and placebo (n = 111) for 6 weeks; $p < 0.05$ for either active treatment *vs* placebo and for montelukast *vs* beclomethasone].[120]

Mean improvements in FEV_1, PEF, symptom scores and as-needed β_2-agonist use generally exceeded the threshold estimate for perceivable improvement (see introduction to section 4)[135] in montelukast and inhaled beclomethasone, but not placebo recipients.[77,78]

Data obtained in 1 trial suggest that the study population comprised responders and nonresponders to both montelukast and beclomethasone.[78] Among beclomethasone-treated patients the median improvement in FEV_1 between baseline and end-point was 11%. The proportion of montelukast recipients who experienced ≥11% improvement in FEV_1 was 42%. 34 and 22% of those patients treated with montelukast or beclomethasone, respectively, experienced no improvement in FEV_1.[78]

The use of concomitant inhaled corticosteroids did not significantly influence the response to montelukast.[77] Ongoing treatment with inhaled corticosteroids was allowed in 22.3 and 23.4% of patients assigned to treatment with montelukast or placebo, respectively, in 1 study.[77] In this stratum, the FEV_1 increased by 10.3 and 1.6% in montelukast and placebo recipients, respectively; among patients who did not use inhaled corticosteroids the corresponding increases in FEV_1 were 13.9 and 5%.[77] These findings suggest that montelukast can improve asthma control in patients who are symptomatic on low dosages of inhaled corticosteroids (see section 4.1.2).[77]

In the subset of patients in whom montelukast was discontinued and placebo administered during a 3-week, double-blind, washout phase,[77,78] the mean FEV_1, daytime symptom score, morning PEF and frequency of as-needed β_2-agonist use approached values obtained in patients who received placebo continuously during the treatment and washout phases. Thus, there was no evidence of rebound worsening of asthma symptoms or a sustained benefit after the withdrawal of montelukast in either study.[77,78]

Improvements in AQLQ scores and in global ratings by physicians and patients were significantly greater in montelukast or beclomethasone recipients ($p < 0.001$ *vs* placebo). The change in AQLQ scores in montelukast- or beclomethasone-treated patients, but not placebo recipients, approximated or exceeded the minimum clinically significant difference (0.5 units) in both studies (table VI).[77,78] Nonetheless, the increase in mean AQLQ scores was significantly ($p < 0.01$) greater in patients treated with inhaled beclomethasone than montelukast.[78]

Asthma control, as indicated by composite measures, was significantly better in recipients of both active treatments than placebo.[77,78,120] Fewer asthma exacerbation days were recorded in pa-

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Table VI. Summary of published, multicentre, randomised, double-blind, placebo-controlled, parallel-group trials involving montelukast 10 mg/day (MK) in patients aged ≥15 years with mild to severe persistent asthma (FEV_1 = 50 to 85% predicted)

Treatment (no. of patients)	Time	Results [mean change from baseline at end-point (95% confidence intervals)][a]						
		FEV_1 (L) [% predicted]	PEF (L/min, am; pm)	daytime symptom score[b]	as-needed β_2-agonist usage (puffs/day)	nights with awakenings (no./week)	AQLQ score	peripheral blood eosinophils ($x10^9$/L)
MK *vs* placebo (PL): Reiss et al.[77][cd]								
MK (408)	BL	2.5 ± 0.7 [68.5]	381 ± 88; 413 ± 90	2.5 ± 0.8	5.4 ± 3.2	4 ± 2.4	3.6 ± 0.9[e]	0.33 ± 0.23
	wk 12	↑13.1%**	↑24**; ↑15.9**	↓0.5**	↓27.5%**	↓1.66*	↑0.45-0.74**[f]	↓0.09**
PL (273)	BL	2.5 ± 0.7 [66.7]	391 ± 90; 421 ± 90	2.5 ± 0.8	5.3 ± 3.2	4 ± 2.6	3.6 ± 0.9[e]	0.31 ± 0.26
	wk 12	↑4.2%	↑4.6; ↑4.2	↓0.34	↓14.5%	↓0.8	↑0.26-0.28[f]	↓0.03
MK *vs* inhaled beclomethasone 200μg twice daily administered by metered dose inhaler with a spacer device (BDP): Malmstrom et al.[78][f]								
MK (387)	BL	2.2 ± 0.6 [65]	339 ± 96; 355 ± 102	2.4 ± 0.9	5.4 ± 3.4	5.5 ± 1.6	3.32 ± 1.10[e]	0.38 ± 0.38
	wk 12	↑7.4% (4.6, 10.1)**†	↑23.8 (16.6, 30.9)**†; ↑20.8 (13.8, 27.8)**†	↓0.41 (-0.53, -0.29)**†	↓23.9% (-31.4, -16.5)**	↓1.7 (-2.07, 1.3)**†	↑0.62 (0.48, 0.77)**†[g]	↓0.08 (-0.12, -0.03)*
BDP (251)	BL	2.1 ± 0.6 [65]	331 ± 97; 348 ± 96	2.4 ± 0.9	5.5 ± 4.2	5.3 ± 1.7	3.16 ± 1.04[e]	0.35 ± 0.34
	wk 12	↑13.1% (10.1, 16.2)**	↑39.1 (31, 47.1)**; ↑32.1 (24.2, 39.9)**	↓0.62 (-0.75, 0.49)**	↓40% (-48.5, -31.5)**	↓2.4 (-2.8, -2)**	↑0.83 (0.67, 0.99)**[g]	↓0.07 (-0.12, -0.02)*
PL (257)	BL	2.2 ± 0.7 [66]	333 ± 99; 354 ± 99	2.4 ± 0.8	5.8 ± 3.9	5.6 ± 1.5	3.15 ± 1.14[e]	0.35 ± 0.32
	wk 12	↑0.7% (-2.3, 3.7)	↑0.8 (-7.1, 8.6); ↑0.3 (-7.3, 8)	↓0.17 (-0.3, -0.05)	0 (-8.3, 8.3)	↓0.5 (-0.9, -0.1)	↑0.25 (0.09, 0.41)[g]	↓0.02 (-0.07, 0.03)
MK combined with BDP: Laviolette et al.[80][h]								
MK (201)	BL	2.6 ± 0.7 [72]	420 ± 92; 433 ± 92	2.1 ± 0.8	3.5 ± 2.3	NR		0.23 ± 0.19
	wk 16	↓5.31	NR	↑0.27	NR	NR		↑0.04
BDP (200)	BL	2.5 ± 0.7 [71]	403 ± 86; 416 ± 82	2.2 ± 0.8	3.5 ± 2.5	NR		0.22 ± 0.18
	wk 16	↑0.72% (-0.89, 2.33)	↑2.65 (-1.31, 6.6); ↑1.81 (-1.92, 5.55)	↓0.02 (-0.10, 0.06)	↑6.04% (-3.78, 15.86)	↓0.45 (-0.85, -0.05)		↑0.04
MK plus BDP (193)	BL	2.6 ± 0.7 [72]	412 ± 91; 431 ± 92	2.2 ± 0.8	3.4 ± 2.2	NR		0.22 ± 0.18
	wk 16	↑5.08% (3.43, 6.74)‡‡‡	↑10.41 (6.36, 14.47)‡‡; ↑5.84 (2, 9.68)	↓0.13 (-0.22, -0.05)‡	↓5.51% (-15.54, 4.52)	↓1.04 (-1.42, -0.67)‡‡		0‡

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tients treated with montelukast or beclomethasone than placebo ($p < 0.001$; fig. 3).[77,78] Moreover, among patients treated with montelukast or inhaled beclomethasone for 6[120] or 12 weeks,[77,78] the proportion of asthma control days was ≥36% and ≥40.1%, respectively, but ≤27.4% in placebo recipients ($p < 0.05$ for montelukast or beclomethasone *vs* placebo; fig. 3.). Sustained asthma control (≥3 consecutive asthma control days) occurred significantly more often in montelukast- (33.4% of days), or beclomethasone- (32.1%) than placebo-treated patients (19.3%) in 1 trial ($p < 0.05$ for montelukast or beclomethasone *vs* placebo; reported in an abstract).[120] Similarly, the proportion of patients who experienced an asthma flare-up (≥3 consecutive nonasthma control days) was lower in patients receiving montelukast (78%), beclomethasone (82.4%) or placebo (91.9%; $p < 0.05$ for montelukast *vs* placebo).[120]

Montelukast and inhaled beclomethasone showed a high degree of concordance in the proportion of asthma control days in 1 study.[122] The overlap in the distribution of asthma control days was 89% [95% confidence interval (CI): 80 to 98%] among 679 patients randomised to 6 weeks' treatment with montelukast or inhaled beclomethasone in the multicentre, double-blind study. Further results were not available in the abstract.[122]

In 1 of the trials which included an inhaled beclomethasone treatment group,[78] beclomethasone recipients experienced a significantly greater proportion of asthma control days than montelukast-treated patients ($p < 0.01$). The frequency of asthma control days was similar in montelukast- and inhaled beclomethasone-treated patients in the other study (40.3 *vs* 40.1%), the results of which are available as an abstract.[120]

Asthma exacerbations and withdrawals from trials because of worsening asthma were less frequent in patients receiving active treatment than placebo.[77,78,120] For example, in 1 study,[78] significantly fewer beclomethasone (10.1%) or montelukast (15.6%) than placebo recipients (27.3%) experienced asthma attacks, defined as worsening asthma requiring oral corticosteroid treatment or

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PL (48)	BL	2.5 ± 0.7 [71]	407 ± 73; 419 ± 71	2.4 ± 0.7	4.2 ± 3	NR	0.23 ± 0.2
	wk 16	↓11.96%	NR	↑0.31	↑59.2%	↑0.44	↑0.09

a Intention to treat analyses were used with the last measurement carried forward for patients with missing values. Baseline measurements are means ± standard deviations.

b The daytime symptom score is the mean of the patient's responses to 4 questions (0 indicates best; 6 indicates worst).

c End of treatment values for daytime symptom scores, β_2-agonist usage, AQLQ scores and peripheral eosinophil counts were estimated from graphs.

d Montelukast and matching placebo were administered in the evening.

e Mean pooled scores for the 4 domains (Activity, Symptoms, Emotions and Environment).

f Range of improvements for the 4 domains.

g Least-squares mean improvements for the 4 domains.

h All patients received inhaled beclomethasone 200μg twice daily plus oral placebo once daily during a 4-week, nonblind run-in phase. In patients randomised to receive inhaled placebo, withdrawal of beclomethasone was done by replacing the morning and evening doses with identical placebo inhalers 2 and 4 weeks after randomisation, respectively.

am = morning; **AQLQ** = asthma quality of life questionnaire; **BL** = baseline; **FEV_1** = forced expiratory volume in 1 second; **NR** = not reported; **PEF** = peak expiratory flow rate; **pm** = evening; **wk** = week; ↓ indicates decrease; ↑ indicates increase; *p < 0.05; **p < 0.001 *vs* PL; † p <0.01 for MK *vs* BDP; ‡p = 0.05; ‡‡p ≤ 0.01; ‡‡‡p < 0.001 for MK plus BDP *vs* BDP.

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an unscheduled visit to a physician, emergency department, or hospital ($p < 0.001$ for either agent *vs* placebo; $p < 0.01$ for montelukast *vs* beclomethasone). Furthermore, 4 montelukast-treated patients (1%), 1 beclomethasone-treated patients (0.4%) and 8 placebo recipients (3.1%) discontinued therapy because of worsening asthma, which was defined *a priori* as more than 2 episodes of worsening asthma requiring supplemental oral corticosteroids.[78] In another published study,[77] a greater proportion of placebo recipients (3.7%) than montelukast-treated patients (1.5%) discontinued therapy because of worsening asthma, although the difference was not statistically significant ($p = 0.07$).

Adherence rates with oral and inhaled therapy, reported in 1 study, were >99% and ≈90%, respectively.[78]

Montelukast provided consistent asthma control during 1 year in an extension of 1 trial described above.[77] 373 patients who had received double-blind treatment with montelukast for 3 months were randomised to nonblind treatment with montelukast 10 mg/day or inhaled beclomethasone 400 μg/day. After 9 months, patients treated with montelukast or beclomethasone experienced increases in FEV_1 [10.92% (CI: 8.69 to 13.14%) and 16.31% (CI: 12.51 to 20.11%), respectively; statistical significance was not reported in the abstract], and decreases in daytime symptom scores [0.59 (CI: -0.72 to -0.46) and 0.67 (CI: -0.89 to -0.45), respectively] and daily β_2-agonist use [35.63% (CI: -42.1 to -29.17%) and 37.2% (CI: -48.38 to -26.12%), respectively] compared with baseline.[136] In a further abstract, the mean FEV_1 was reported to be 12.4 (CI: 9.4 to 15.4%, n = 283) and 14.3% (CI: 8 to 20.7%, n = 81) above baseline after 2.4 years of treatment with montelukast 10 mg/day or inhaled beclomethasone 200μg twice daily.[137]

In Patients with Allergic Rhinitis

Montelukast was effective in patients with asthma and allergic rhinitis. The results of a meta-analysis revealed significant ($p < 0.05$ *vs* placebo) improvements in all outcome measures (i.e. FEV_1, morning PEF, daytime symptom score, frequency of β_2-agonist use and QOL score) in patients with (n = 967) or without (n = 245) allergic rhinitis treated with montelukast 10 mg/day in 4 multicentre, placebo-controlled studies.[138] Moreover, there were no apparent differences in the magnitude of improvement in clinical end-points between patients with and without a history of allergic rhinitis. The effect of montelukast on the signs or symptoms of allergic rhinitis were not included in the abstract.[138]

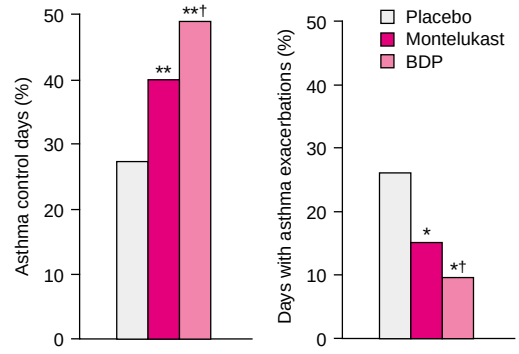

Fig. 3. Asthma control in patients with persistent asthma during 12 weeks of treatment with montelukast, inhaled beclomethasone or placebo. Percentage of asthma control days (left) and days with asthma exacerbations (right) during 12 weeks of treatment with oral montelukast 10 mg/day (n = 387), inhaled beclomethasone (n = 251) or placebo (n 257) in patients with mild to severe (FEV_1 = 50 to 85% predicted; mean = 65%) persistent asthma in a multicentre, randomised, double-blind, double-dummy study.[78] On asthma control days none of the following occurred: worsening asthma requiring oral corticosteroid rescue, visit to a physician's office or hospitalisation, nocturnal awakenings or use of more than 2 puffs of as-needed β_2-agonist. Asthma exacerbation days were defined as a day when any 1 of the following occurred: PEF ≤180 L/min, decrease in morning PEF ≥20% compared with the baseline value, ≥70% increase in use of as-needed β_2-agonist from baseline (minimum increase 2 puffs), ≥50% increase in symptom score over baseline, awake all night with asthma or worsening asthma requiring oral corticosteroids or a visit to a physician or hospitalisation. **FEV_1** = forced expiratory volume in 1 second. *$p < 0.05$; **$p < 0.001$ *vs* placebo; †$p < 0.05$ *vs* montelukast.

Montelukast Plus Loratadine

Montelukast plus loratadine had a greater effect on several outcome measures than montelukast plus placebo in 136 patients with mild to severe persistent asthma (FEV_1 = 50 to 80% predicted).

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After 2 weeks of treatment with montelukast 10 mg/day plus oral loratadine 20 mg/day, the FEV_1 (13.86 *vs* 9.72% increase from baseline; $p \leq 0.001$) was significantly greater and the frequency of as-needed β_2-agonist use (34.56 *vs* 27.41% decrease from baseline; $p < 0.05$) and daytime symptom scores (decreased by 0.7 *vs* 0.48; $p \leq 0.001$ from baseline) were significantly lower than after treatment with montelukast plus placebo in a randomised, crossover study. The magnitude of the treatment effect was apparently similar in patients with or without a history of seasonal allergies, although the supporting data were not presented in the abstract.[124]

Effects in Aspirin-Sensitive Patients

Montelukast 10 mg/day improved clinical parameters in aspirin-sensitive patients with moderate persistent asthma (mean FEV_1 = 69% predicted). After 4 weeks of montelukast treatment, significant increases were documented in FEV_1 (8.55 ± 1.92 *vs* -1.74 ± 1.71L in placebo recipients) and morning PEF (26.26 ± 4.66 *vs* -1.92 ± 4.61 L/min) and significant reductions were seen in β_2-agonist usage (-1.04 ± 1.2 *vs* -0.08 ± 0.3 puffs/day) and nocturnal symptom scores (-0.33 ± 0.09 *vs* 0 ± 0.07), but not daytime symptom scores (-30 ± 0.09 *vs* -0.03 ± 0.09), in a double-blind, randomised study ($p < 0.05$ *vs* placebo for all comparisons; n = 80).[123] These results are consistent with the findings for other antileukotrienes in aspirin-sensitive patients with asthma.[53,57,58,139]

4.1.2 Montelukast Combined with Inhaled Beclomethasone

The complementary effects of montelukast and inhaled beclomethasone were examined in adult patients with persistent, inhaled corticosteroid-dependent asthma.[80] Patients with poorly controlled asthma (mean FEV_1 = 72% predicted, daytime asthma symptom score ≥64, β_2-agonist use ≥1 puff/day) after receiving beclomethasone 200μg twice daily for 4 weeks were randomised to 1 of 4 double-blind treatments (montelukast 10mg daily plus inhaled placebo, inhaled beclomethasone 200μg twice daily plus oral placebo, montelukast plus beclomethasone, or oral and inhaled placebos).

The combination of montelukast 10 mg/day plus inhaled beclomethasone 200μg twice daily provided better asthma control than either agent alone in this study. When compared with patients continuing on inhaled beclomethasone alone, patients receiving the combination experienced significant improvements in FEV_1 and morning PEF, significant reductions in daytime symptom scores, as-needed β_2 agonist usage and night-time awakenings with asthma, and had significantly lower peripheral blood eosinophil counts after 16 weeks ($p < 0.05$ for the combination *vs* inhaled beclomethasone; table VI). As the primary comparison in the study was between these 2 groups, comprehensive results and statistical comparisons were not reported for patients randomised to montelukast monotherapy or placebo.[80]

The addition of montelukast to inhaled beclomethasone produced improvements in composite measures of asthma control. The frequency of asthma exacerbation days decreased significantly among patients receiving the combination (fig. 4; $p = 0.041$ *vs* beclomethasone plus placebo). The proportion of patients experiencing asthma attacks also decreased in patients treated with the 2 drugs; however, the difference was not statistically significant (fig. 4; $p = 0.055$).[80]

Asthma control generally deteriorated in the small number of patients assigned to placebo (table VI), demonstrating that the patients required anti-inflammatory therapy and benefitted from the inhaled corticosteroid.[80]

Consistent with results presented in section 4.1.1,[78] patients receiving inhaled beclomethasone, (alone or combined with montelukast), had better asthma control than patients receiving montelukast monotherapy at the end of the 16-week study. Indeed, the frequency of discontinuation from the study because of worsening asthma was 15, 11.4, 4 and 1%, respectively, among patients treated with placebo, montelukast, inhaled beclomethasone or the 2 drugs combined. These findings indicate that, given the greater benefits of

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a relatively low dosage of inhaled beclomethasone, montelukast is not suitable as monotherapy in patients with moderate or severe persistent asthma. Rather, the data demonstrate that the drug provides significant benefit when added to an inhaled corticosteroid regimen in patients with poor disease control. As the therapeutic effects of inhaled corticosteroids are dose-dependent, it would be of interest in future studies to determine the relative benefits of adding montelukast to an ineffective inhaled corticosteroid regimen, versus increasing the inhaled corticosteroid dosage.

4.1.3 Inhaled Corticosteroid Sparing Properties

There is evidence that montelukast 10 mg/day allows for reductions in inhaled corticosteroid dosages in patients with stable asthma. Inhaled corticosteroid dosages were titrated to the minimum effective level over ≥7 weeks prior to randomisation to montelukast 10 mg/day or placebo for 12 weeks in a multicentre, double-blind study. Eligible patients had moderate persistent asthma (FEV_1 ≥70%) and were receiving ongoing treatment with various inhaled corticosteroids (i.e. ≥3 weeks' treatment with 800 to 3600 μg/day of beclomethasone, budesonide, flunisolide or triamcinolone; 500 to 2000 μg/day of fluticasone). Patients were evaluated at 2-week intervals during the study and, based on an objectively defined composite clinical score (which incorporated the FEV_1, the frequency of as-needed β_2-agonist use and symptoms), the dosage of inhaled corticosteroid was either increased or decreased by approximately 25%, or maintained. Patients were withdrawn from the study if they had worsening asthma requiring treatment with systemic corticosteroids.[121]

Between the start of treatment and end-point, the mean dosage of inhaled corticosteroid was decreased by 47% and 30% in patients treated with montelukast or placebo, respectively (p = 0.046), with no significant differences in FEV_1, asthma symptom scores or β_2-agonist usage.[121] 62% of montelukast-treated patients tolerated corticosteroid reductions of ≥50% (*vs* 50% of placebo recipients; not significant). Conversely, 28 and 36% of montelukast or placebo recipients could not tolerate any reduction in the corticosteroid dosage (p = 0.055). A higher proportion of montelukast-treated patients than placebo recipients (40 *vs* 29%; not significant) were successfully tapered off of inhaled corticosteroids during the study and significantly fewer patients discontinued montelukast than placebo because of failed corticosteroid rescues (16 *vs* 30%, p = 0.01).[121]

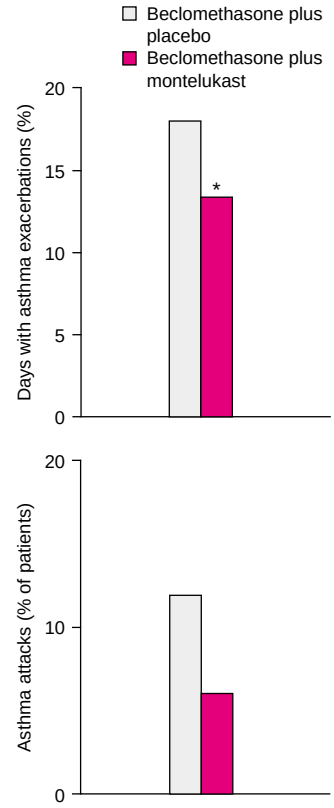

Fig. 4. Asthma control in adult patients with persistent asthma during treatment with inhaled beclomethasone plus montelukast or placebo. Frequency of asthma attacks (bottom; percent of patients) and days with asthma exacerbations (top) during 16 weeks of treatment with inhaled beclomethasone 400 μg/day plus oral placebo (n = 200) or inhaled beclomethasone 400 μg/day plus oral montelukast 10 mg/day (n = 193) in a multicentre, randomised, double-blind, double-dummy study.[80] Patients had mild to severe persistent asthma despite treatment with inhaled beclomethasone 400 μg/day during a 4 week run-in period. Composite measures of asthma control were not reported for patients randomised to montelukast monotherapy or placebo. *p = 0.041 *vs* inhaled beclomethasone plus placebo.

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4.2 Studies in Children Aged ≥6 Years

Montelukast 5 mg/day was evaluated in an 8-week multicentre, randomised, double-blind, placebo-controlled study in children aged 6 to 14 years with persistent asthma (FEV_1 50 to 85% predicted).[79] FEV_1 averaged over the 8 weeks of treatment, the primary efficacy variable in the study, increased by 3.58 (CI: 1.29 to 5.87%) and 8.23% (CI: 6.33 to 10.13%) among children assigned to placebo or montelukast, respectively ($p < 0.001$).[79] The effect of montelukast was consistent across all ages; increasing by 7.7% in those aged 6 to 11 years and by 9.8% in those aged 12 to 14 years.

Significant improvement was obtained in many but not all secondary outcome measures included in the trial (table VII); however, the study was not powered to detect significant differences in these parameters.[79] Among children treated with montelukast, the frequency of days with asthma exacerbations (20.6 *vs* 25.7% with placebo; $p = 0.049$) and the proportion of patients with asthma exacerbations (84.8 *vs* 95.5%; $p = 0.002$) were significantly lower than in placebo-treated children.[79]

Similar to the results of studies in adults (section 4.1), the onset of action of montelukast was rapid. Within 1 day of initiating treatment there was a significant reduction in the frequency of as-needed β_2-agonist use ($p = 0.02$ *vs* placebo).[79] Morning PEF was significantly greater in montelukast than placebo recipients during the first 21 days of treatment ($p = 0.03$). Although daytime symptom scores were reduced to a greater extent in montelukast-treated patients than placebo recipients during the first 3 weeks of the study, the difference was not statistically significant ($p = 0.06$).

The efficacy of montelukast, as measured by FEV_1 or use of as-needed β_2-agonists, was not affected by gender, ethnic group, Tanner developmental stage, history of allergic rhinitis or exercise-induced asthma, or by the use of concomitant inhaled corticosteroids (39 and 33% of montelukast and placebo recipients continued inhaled corticosteroids during the study; the dosage was not specified in the report).[79]

The efficacy of montelukast was maintained for more than 1 year during a nonblind extension of this study. After 1.4 years, the mean change from baseline in the FEV_1 was 6.47% (CI: 4.56 to 8.38, n = 201) and 6.39% (CI: 2.49 to 10.28, n = 38) among patients randomised to montelukast 5 mg/day) or inhaled beclomethasone (mean dosage = 252 μg/day).[137]

4.2.1 Montelukast versus Inhaled Sodium Cromoglycate

Montelukast was preferred over inhaled sodium cromoglycate by children aged 6 to 11 years with asthma and their caregivers. Four weeks' treatment with montelukast 5 mg/day was compared with inhaled sodium cromoglycate 1.6mg 4 times daily[3] in 2 randomised, nonblind, crossover studies (available as abstracts).[125,126] A 2-week washout phase separated the 2 treatment periods. In both studies the frequency of β_2-agonist usage was lower during treatment with montelukast than sodium cromoglycate; the difference was statistically significant in 1 study ($p = 0.001$).[126] A greater proportion of patients withdrew from the study during treatment with sodium cromoglycate than montelukast [10 *vs* 2 patients, not significant (n = 253);[126] and 16 *vs* 3%, $p < 0.05$ (n = 333)[125]]. Furthermore, ≥86% of parents and ≥79% of patients expressed a preference for montelukast over sodium cromoglycate in both studies ($p < 0.001$ for both parents and patients).[125,126] This finding was reflected in the rates of adherence in 1 study;[126] 82% of patients took montelukast as prescribed on ≥95% of days, but only 45% of patients achieved a similar adherence rate during treatment with sodium cromoglycate ($p < 0.001$).[126]

5. Tolerability

In general, few patients experienced adverse events during clinical trials with montelukast. Fur-

3 The dosage of sodium cromoglycate was reported as 1.6[125] and 2mg[126] 4 times daily in these studies. The differences in reported dosages reflect labelling requirements in the US where the proportion of the dose delivered through the mouthpiece (1.6mg) is used and elsewhere, where the amount actuated (2mg) is used.

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Table VII
Landscape table

thermore, in adults and children, the frequency of adverse events in montelukast-treated patients was similar to that in placebo recipients. Adverse events which occurred in ≥1% of patients aged ≥15 years enrolled in placebo-controlled trials and for which the incidence in montelukast recipients exceeded that in placebo recipients are presented in fig. 5.[104] Headache was the most frequent adverse event, reported by 18.4 and 18.1% of adult recipients of montelukast and placebo, respectively. Elevated liver enzyme values (ALT or AST) were detected in ≤2.1% of patients assigned to montelukast or placebo. Importantly, there was no substantial difference in the frequency of transaminase elevations between the 2 groups in adults,[104] or in children.[79]

In paediatric patients treated for 8 weeks, diarrhoea, laryngitis, pharyngitis, nausea, otitis, sinusitis and viral infections occurred in more than 2% of montelukast recipients and were more prevalent in montelukast-treated patients than placebo recipients (regardless of causality assessment).[104]

Adverse events reported in association with montelukast after the drug was launched in the UK that were not identified during clinical trials included oedema, allergic reactions (including urticaria, angioedema and anaphylaxis), agitation, tremor, dry mouth, chest pain, vertigo and arthralgia.[140] Whether these effects are causally related to montelukast cannot be concluded from this report.[140]

Montelukast is well tolerated over a very broad dosage range. In clinical studies in adults, dosages 20- to 90-fold greater than the currently recommended dosage (10 mg/day) were given for ≥1 week without any unexpected adverse events.[104,118,141] Furthermore, no mortality occurred in mice after administration of montelukast 5000 mg/kg; a dosage which is approximately 2000- and 2400-fold greater on a mg/m^2 basis than the recommend dosages in adults and children, respectively.[104] These results indicate that montelukast should have a wide safety margin in acute overdose.

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Table VII. Summary of an 8-week multicentre, randomised, double-blind, parallel-group trial comparing oral montelukast 5 mg/day (MK) with placebo (PL) in children aged 6 to 14 years with persistent asthma[79]a

Treatment [no. of patients]	Time	Results (mean values during the treatment ± standard deviation)b								
		FEV_1 (L) [% predicted]	PEF (L/min)c	Daytime symptom scored	as-needed β_2-agonist usage (puffs/day)	Nocturnal awakenings (no./week)e	Quality of life domainf			Peripheral eosinophils (x 10^9/L)
							activity	emotions	symptoms	
MK [201]	BL	1.85 ± 0.55 [72]	264.2 ± 81.9	1.28 ± 0.58	3.34 ± 1.91	4.21 ± 1.5	4.35 ± 1.11	5.38 ± 1.24	4.7 ± 1.07	0.44 ±0.31
	wk 8	2.01 ± 0.64**	292 ± 89*	1.09 ± 0.66	2.78 ± 1.32*	2.93 ± 2	5.43 ± 1.09***	5.9 ± 1.2**	5.33 ± 1.07**	0.39 ± 0.35*
PL [135]	BL	1.85 ± 0.53 [72]	270.5 ± 78.4	1.26 ± 0.63	3.24 ± 2.02	4.21 ± 1.55	4.53 ± 1.17	5.67 ± 1.26	4.89 ± 1.08	0.47 ± 0.33
	wk 8	1.93 ± 0.0.62	288.3 ± 85	1.14 ± 0.75	3.01 ± 2.12	3.15 ± 2.07	5.17 ± 1.11	5.85 ± 1.2	5.18 ± 1.05	0.47 ± 0.3

a Among montelukast and placebo recipients, 39 and 33% received inhaled corticosteroids, as allowed by the study protocol.

b An intention to treat analysis was used with the last measurement carried forward.

c Morning PEF as measured in a clinic. There was no significant difference in the morning or evening PEF between montelukast and placebo recipients, as recorded in diaries.

d The mean daily response to 3 questions (0 = best; 5 = worst).

e A prespecified group of patients with ≥2 nocturnal wakenings per week were included in this analysis. The overall frequency of nocturnal wakenings per week was 1.4 and 1.6 in patients treated with placebo and montelukast, respectively.

f Scores in each of the 3 domains of the Paediatric Asthma Quality of Life Questionnaire range from 1 (worst) to 7 (best).

BL = baseline; **FEV_1** = forced expiratory volume in 1 second; **PEF** = peak expiratory flow rate; **wk** = week; ↓ indicates decrease; ↑ indicates increase; *p < 0.05; **p < 0.01; ***p < 0.001 *vs* placebo.

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5.1 Churg-Strauss Syndrome

Churg-Strauss syndrome is a rare granulomatous eosinophilic vasculitic condition that involves the upper and lower airways and manifests as rhinitis, sinusitis and asthma. If untreated the syndrome may progress to systemic vasculitis, peripheral neuropathy and potentially fatal cardiac complications.[142]

Eosinophilic reactions in adults, which resemble Churg-Strauss syndrome, have been reported during treatment with montelukast. The condition has emerged in montelukast-treated patients after tapering of systemic corticosteroids,[143,144] and in those with a history of systemic corticosteroid treatment.[145] In each case, patients responded to discontinuation of montelukast and the reintroduction of systemic corticosteroid therapy, suggesting that the condition was 'unmasked' by the withdrawal of corticosteroids.

Churg-Strauss syndrome has been reported during treatment with other commercially available $cysLT_1$ receptor antagonists (i.e. pranlukast[146] and zafirlukast[147-150]), inhaled sodium cromoglycate[151-154] and inhaled corticosteroids[142,155-158] and has been detected during post-marketing surveillance of nedocromil, bambuterol and salmeterol.[159] Although a causative role for these agents cannot be completely ruled out at present, in most cases the condition emerged during withdrawal of oral corticosteroid therapy. This suggests that these reactions were not directly related to the asthma therapies.[140,142,158-164] The incidence of this condition may previously have been underestimated because patients remained on suppressive dosages of systemic corticosteroids and the full clinical manifestations of the syndrome were rarely observed.[165]

6. Dosage and Administration

In the US montelukast is indicated for the prophylaxis and chronic treatment of asthma in adults and paediatric patients ≥6 years of age.[104]

In the UK montelukast is indicated as add-on therapy in patients with mild to moderate persistent asthma who are inadequately controlled on inhaled corticosteroids and in whom 'as-needed' short acting β-agonists provide inadequate clinical control of asthma.[166] In patients at 'step 2' of the British asthma guidelines, the drug is not currently recommended for use as monotherapy or as an alternative to inhaled corticosteroids.[3,167]

The recommended dosage of montelukast in adolescents and adults aged ≥15 years is 10 mg/day. In children aged 6 to 14 years the recommended dosage is 5 mg/day. The manufacturer recommends that montelukast be taken in the evening. The clinical efficacy of morning versus evening administration has not been evaluated. However, administration at bedtime ensures that higher plasma concentrations of montelukast coincide with the time of maximal airway narrowing in early morning.[119] Montelukast may be taken with or without meals.[104] The drug is available as a 10mg film coated tablet and a 5mg chewable tablet.[104,166]

During treatment with montelukast, the dosage of inhaled corticosteroids may be reduced gradually; however, abrupt discontinuation of inhaled corticosteroids with the substitution of montelukast is not recommended.[104] Oral corticosteroid dependent-patients should be carefully monitored during attempts to reduce the dosage or withdraw the oral corticosteroid after the introduction of montelukast therapy.

Montelukast improves pulmonary function in aspirin-sensitive patients (section 4.1.1). Nonetheless, patients should continue to avoid aspirin or NSAIDs while taking montelukast.

Although montelukast is effective in preventing exercise-induced bronchoconstriction, the drug is not approved in the US as monotherapy for this condition.[104] In the UK the drug is licensed as an adjunctive treatment in patients with exercise-induced bronchoconstriction.[166]

Dosage adjustments are not required in elderly patients or in those with renal or mild to moderate hepatic dysfunction. No dosage recommendations are available for patients with severe hepatic impairment or hepatitis.[104]

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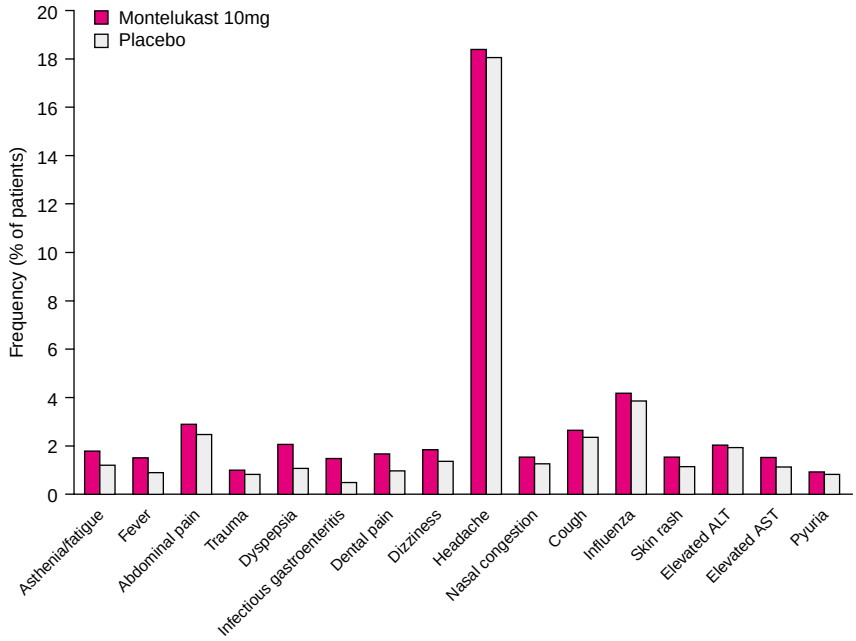

Fig. 5. Adverse events associated with montelukast in clinical trials. Adverse events which occurred in ≥1% of patients for which the incidence in montelukast-treated patients (n = 1955) exceeded that in placebo recipients (n = 1180) during clinical trials.[104] No assessment of causality has been applied to these data.

Caregivers of children with phenylketonuria should be informed that the 5mg chewable tablet contains phenylalanine (0.842mg, present in aspartame).[104]

No data are available on the safety of montelukast during pregnancy or breastfeeding. The drug is included in FDA Class B: no evidence of risk in humans i.e. no adequate studies have been conducted during human pregnancy, or animal trials suggest the drug is not teratogenic.[104]

7. Place of Montelukast in the Management of Persistent Asthma

Available preventive therapies for persistent asthma include inhaled corticosteroids, inhaled sodium cromoglycate or nedocromil, inhaled long-acting β_2-agonists (e.g. salmeterol, formoterol) oral antileukotrienes which comprise the $cysLT_1$ antagonists (montelukast, pranlukast and zafirlukast) and a 5-lipoxygenase inhibitor (zileuton), and oral theophylline. Among these agents, inhaled corticosteroids are widely acknowledged to be the most effective because of their broad spectrum of anti-inflammatory activity, utility across the entire range of asthma severity and evidence of significant benefits with long term use. In spite of this, and specific recommendations for the use of inhaled corticosteroids in asthma management guidelines since 1990,[168] numerous studies have demonstrated that these agents are either underprescribed by physicians and/or underused by patients.[169-177] For example, recent surveys conducted in >5000 patients with persistent asthma enrolled in a California health maintenance organisation (HMO) revealed that approximately half of all patients had obtained any anti-inflammatory agent (i.e. inhaled corticosteroid, sodium cromoglycate or oral corticosteroids) during the previous 6 months.[178] Among those that had a corticosteroid inhaler at home, fewer than half (47.7%) had used the device daily during the preceding month.[179] In spite of the recommendations that anti-inflamma-

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tory medication be used regularly, 23.7% of these patients used bronchodilators without anti-inflammatory medication.[178] Moreover, 11% of those surveyed reported using ≥8 inhalations of β_2-agonist per day in the preceding month.[179]

This suggests that adherence to inhaled preventive therapy is less than optimal. Indeed, even within the confines of controlled, clinical trials, adherence with inhaled preventive therapies may be poor. In a report based on 2 studies in which adherence was measured by an electronic device, inhaled medications were taken as prescribed (1 puff 4 times daily) on approximately 37% of days and were underused on ≤46% of days.[180]

There is limited evidence that patients with asthma prefer oral to inhaled preventive therapies. A review of prescription records in a Minnesota HMO suggested that 79% of patients adhered to therapy with oral theophylline, but only 54 and 44% of patients adhered to therapy with inhaled corticosteroids or sodium cromoglycate, respectively.[181] Adherence with inhaled therapies was poorest in patients aged 12 to 17 years (30 *vs* 73% with oral theophylline).[181] These data suggest that oral agents are preferred by patients with asthma.

In comparative clinical trials, there was a high rate of adherence with oral montelukast treatment. Among patients treated with montelukast or inhaled beclomethasone, adherence rates of >99% and ≈90% were reported.[78] In a paediatric study in which montelukast was compared with inhaled sodium cromoglycate, adherence with montelukast was approximately 80% and was considerably greater than that with inhaled sodium cromoglycate (45%).[126] Moreover, both patients and caregivers expressed a clear preference for oral montelukast therapy in this trial.

Montelukast has a rapid onset of action in patients with asthma, which may promote adherence when treatment is initiated.[182] Consistent with the results of pharmacodynamic studies, the clinical effects of montelukast, including improvements in lung function, symptom scores and reductions in the frequency of as-needed β_2-agonists, were evident within 1 day of initiating therapy in patients enrolled in several studies.[77-79]

The foregoing discussion suggests that patients with asthma prefer oral to inhaled therapies and implies that adherence with oral montelukast is likely to be greater than that with inhaled therapies. Indeed, there appears to be a general consensus that oral administration is an important advantage of the antileukotrienes,[7,182-191] although specific studies designed to assess compliance with antileukotrienes and other asthma therapies have not been published. Nonetheless, the efficacy profile of montelukast is most important in establishing a role for this agent in the treatment of asthma.

The outcome of treatment with a preventive medication in patients with asthma should normalise lung function (i.e. PEF ≥80% and <20% circadian variation in PEF), minimise chronic symptoms, including nocturnal symptoms, usage of as-needed β_2-bronchodilators and exacerbations, and minimise limitations on activities including exercise. Ideally, these outcomes should be achieved with no or minimal medication-related adverse events.[3]

In clinical studies in adults with persistent asthma, montelukast improved lung function and symptoms, reduced the frequency of as-needed β_2-agonist usage and improved QOL, as measured by the AQLQ.[77,78] Moreover the drug increased the proportion of days without asthma and decreased the frequency of days with asthma exacerbations. Although improvements with inhaled corticosteroids were significantly greater, 42% of patients treated with montelukast experienced improvement similar to the median improvement achieved with beclomethasone 400 μg/day.[78] Furthermore, there were nonresponders to both inhaled beclomethasone and montelukast within the study population.

Importantly, montelukast was effective in children aged ≥6 years. The drug improved lung function, reduced the frequency of β_2-agonist usage, improved QOL and reduced the frequency of days with asthma exacerbations.[79]

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These findings support the recommendations in the US guidelines that monotherapy with antileukotrienes is appropriate preventive treatment in patients with mild persistent asthma.[2] In a recent review,[7] the choice of agent for such patients was succinctly described as 'the superior efficacy of inhaled corticosteroids versus the expected superior compliance associated with leukotriene modifiers.' Drazen and Israel[189] have attempted to quantify the outcomes associated with either choice by combining the efficacy data from a comparative trial[78] with the compliance data from the study by Kelloway et al. (described above).[181] They concluded that approximately one-third of patients treated with an inhaled corticosteroid or montelukast would show a 'benefit' after 3 months of treatment.[189] As no well-designed studies have compared compliance rates with montelukast and inhaled corticosteroids in a clinical setting, further study is required to substantiate these estimates and to extend the time frame over which they are valid.

In the US guidelines, which were published before the approval of montelukast, inhaled sodium cromoglycate or nedocromil are listed as being the preferred preventive therapy in children aged <12 years with mild persistent asthma. Preliminary evidence suggests that antileukotrienes are at least as effective as inhaled sodium cromoglycate in patients with mild disease.[125,126,192] Moreover, montelukast is easier to use, which no doubt contributes to the higher rates of adherence and preference for the drug over inhaled sodium cromoglycate (see above).

Does the available evidence suggest a role for montelukast in patients with moderate to severe persistent asthma, in whom inhaled corticosteroids are essential to controlling the disease process? Several studies have shown that oral or inhaled corticosteroids do not alter the production of leukotrienes,[193-195] and *in vitro* data suggest that corticosteroids may increase expression of 5-lipoxygenase activity.[196] Hence, antileukotrienes and inhaled corticosteroids should, in theory at least, be complementary to each other. The finding of significant improvements in lung function and clinical parameters in patients receiving montelukast plus inhaled beclomethasone compared with inhaled beclomethasone alone supports this contention.[80] Nonetheless, further studies are needed to determine the relative merits of adding montelukast to an inhaled corticosteroid regimen or increasing the dosage of the inhaled corticosteroid.

The results of a dose-reduction study in patients aged ≥15 years demonstrate that montelukast has corticosteroid-sparing properties. These results are consistent with the findings in studies that demonstrate corticosteroid-sparing effects for other antileukotrienes in patients with asthma.[197-200]

The corticosteroid-sparing properties of montelukast are important in that many of the long term adverse effects of inhaled corticosteroids are dose-related. Continuous therapy for a period of years may be required to maintain long term control of asthma. For this reason it is important that preventive treatments be well tolerated and effective during long term use.[201] Long term use of inhaled corticosteroids predisposes patients to dose-related adverse events including reduced bone density and osteoporosis, cataracts, ocular hypertension or glaucoma, and skin bruising.[184,202-208] High dosages of these drugs may impair growth in prepubertal children, although other factors may contribute to this effect.[184,207,209-216] The results of a recently published meta-analysis,[203] which included studies conducted in patients and healthy volunteers, suggest that suppression of the hypothalamo-pituitary-adrenal axis, an indicator of systemic absorption, and reductions in bone density are significant with dosages of inhaled corticosteroids ≥1.5 mg/day (≥0.75 mg/day for fluticasone). Hence, the safest dosage of an inhaled corticosteroid is the lowest dosage that provides optimum control of the disease.[184,217] Therapeutic strategies, including the use of antileukotrienes, which minimise the required daily dosage of corticosteroids without compromising asthma control, should be preferred.

Theophylline and long-acting inhaled β_2-agonist bronchodilators also have corticosteroid-sparing effects in patients with persistent

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asthma.[184,218-220] However, there are drawbacks with both of these types of agents. The pharmacokinetics of theophylline are unpredictable and are affected by many drug interactions, which necessitates therapeutic drug monitoring.[182,184,219] Theophylline has a narrow therapeutic index and a well-established profile of frequent adverse events.[184] Moreover, theophylline intoxication is associated with substantial morbidity and mortality.[221] Long acting inhaled β_2-agonists do not have any clinically demonstrable anti-inflammatory effects and pronounced tolerance to the bronchoprotective activity may develop with prolonged use.[184]

Exercise-induced bronchoconstriction can limit the activity of patients with asthma.[2,222] The prevalence of exercise-induced bronchoconstriction was greater in patients with persistent asthma than in those with intermittent asthma in a recent survey.[223] β_2-agonists are important in the management of this condition;[2,222] however, long term control of persistent asthma with anti-inflammatory medication may reduce the frequency and severity of exercise-induced bronchoconstriction.[2]

Montelukast was effective in preventing the characteristic postexertional decline in lung function in patients with exercise-induced bronchoconstriction. The drug significantly reduced the maximum decline in FEV_1 after exercise and reduced the time required for lung function to return to baseline. Approximately 75% of patients with exercise-induced bronchoconstriction derived some degree of benefit from the drug.[97] Importantly, these effects are consistent over 8 to 12 weeks with montelukast,[86,92,93] but were not sustained with continuous use of the long-acting β_2-agonist salmeterol.[92,93,98-100] These data suggest that montelukast may be a useful adjunct in patients with persistent asthma and a history of exercise-induced bronchoconstriction. Nonetheless, the drug is not approved for prophylaxis in patients with exercise-induced bronchoconstriction in the US, and all patients should carry short-acting β_2-agonists.[185]

Aspirin-induced asthma is attributable to cysteinyl leukotrienes; hence, $cysLT_1$ antagonists are uniquely suited for the treatment of individuals with this condition. In aspirin-sensitive patients the addition of montelukast resulted in significant improvements in asthma control. These findings are consistent with the results of other studies in which other antileukotrienes have produced improvements in asthma symptoms in aspirin-sensitive patients in the absence of aspirin challenge.[57,58,139] Despite the theoretical and demonstrated benefits of the drug in such patients, these individuals should be counselled to avoid NSAIDs, as acute bronchocospasm may still occur after ingestion of NSAIDs despite treatment with antileukotrienes.[224]

Montelukast was well tolerated in clinical trials and the frequency of adverse events was no greater in montelukast than placebo recipients. Churg-Strauss syndrome has infrequently occurred in patients during treatment with antileukotrienes, including montelukast (and other anti-asthma medications) and, although unlikely, it is not known with certainty whether a causal relationship exists between anti-asthma therapies and the condition. Nonetheless, montelukast-treated patients should be closely monitored during the tapering or withdrawal of systemic corticosteroids.

Similar to findings with montelukast, other antileukotriene agents improve lung function, and reduce the severity of symptoms and the frequency of exacerbations in patients with persistent asthma.[197,225-233] Zileuton and sustained release theophylline provided similar benefits in patients with moderate persistent asthma in a 13-week study.[234] Zafirlukast was as effective as inhaled sodium cromoglycate in patients with mild persistent asthma in a 13-week study,[192] but was generally less effective than inhaled salmeterol during 4 weeks' treatment in patients receiving inhaled corticosteroids.[235] Studies comparing antileukotrienes have not been published. Montelukast is administered once daily with or without food and it is not necessary to titrate the dosage. Pranlukast and zafirlukast, which must be given on an empty stomach, are administered twice daily[236] Zileuton requires 4 times daily administration.[237] Zileuton

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has been associated with hepatic transaminase elevations and frequent laboratory monitoring is required during therapy with this agent which increases the costs associated with treatment.[237] Importantly, and in contrast to zafirlukast and zileuton,[236,237] montelukast is not associated with any clinically significant drug interactions. Pranlukast is available in Japan only and limited data are available regarding its use.[7,183]

Further studies are required to fully establish the clinical benefits of montelukast. In patients with mild persistent asthma it will be important to demonstrate firstly that compliance is improved with oral montelukast versus inhaled therapies and secondly that this results in better outcomes. In patients with moderate or severe asthma receiving inhaled corticosteroids it remains to be determined whether the combination of these 2 anti-inflammatory agents can prevent serious exacerbations and/or hospitalisation and whether reductions in the dosage of inhaled corticosteroid can reduce the frequency or severity of corticosteroid-related adverse events. Although montelukast was effective and well tolerated in controlled clinical trials of ≤16 weeks' duration, the long term efficacy and tolerability of the drug must also be confirmed in clinical practice. As antileukotrienes are relatively costly agents,[167] pharmacoeconomic analyses are required to determine the net economic benefits of the use of montelukast on health care systems.

In conclusion, montelukast is a well tolerated and effective preventive treatment in adults and children aged ≥6 years with persistent asthma including those with exercise-induced bronchoconstriction and/or aspirin sensitivity. Furthermore, montelukast has glucocorticoid-sparing properties. Hence, montelukast, as monotherapy in patients with mild persistent asthma or as an adjunct to inhaled corticosteroids in patients with more severe disease, is useful across a broad spectrum of patients with persistent asthma.

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