

Clinical safety and tolerability of montelukast, a leukotriene receptor antagonist, in controlled clinical trials in patients aged ≥ 6 years

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Summary

Objective Montelukast is a leukotriene receptor antagonist administered orally once daily for treatment of chronic asthma in adults and children. A comprehensive analysis of safety data from double-blind, randomized, placebo-controlled trials with montelukast has not been previously reported.

Patients and methods A pooled analysis of safety data from 11 multicentre, randomized, controlled montelukast Phase IIb and III trials and five long-term extension studies was performed. A total of 3386 adult patients (aged 15–85 years) and 336 paediatric patients (aged 6–14 years) were enrolled in the trials; 2031 adults received montelukast for up to 4.1 years, and 257 children received montelukast for up to 1.8 years. Summary statistics comparing incidences of adverse events among treatment groups were calculated.

Results The overall incidence of clinical and laboratory adverse events among montelukast-treated patients, both adult and paediatric, was similar to that among patients receiving placebo. There were no clinically relevant differences in individual adverse events, including infectious upper respiratory conditions and transaminase elevations, between montelukast and placebo groups. Discontinuations due to adverse events occurred with similar frequencies during placebo, montelukast and inhaled beclomethasone therapy. No dose-related adverse effects of montelukast were observed in adults treated with dosages as high as 200 mg per day (20 times the recommended dose) for 5 months. This tolerability profile montelukast observed in clinical trials has been generally reflected in the post-marketing safety experience seen to date.

Conclusion These data indicate a tolerability profile for montelukast similar to placebo during both short-term and long-term administration, even at doses substantially higher than the recommended clinical dose of 10 mg once daily for adults and 5 mg once daily for children aged 6–14 years.

Keywords: asthma, cysteinyl leukotriene receptor antagonist, montelukast, safety, tolerability

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Introduction

Asthma is a serious disease characterized by reversible airflow obstruction, airway hyperresponsiveness, and

allergic inflammation. Over 5% of Americans reported having asthma in 1994, a 75% increase since 1980, while asthma in pre-school age children increased 160% [1]. Increasing asthma incidence, mortality and morbidity have fuelled a need for improved therapy, initiating accelerated basic science research in asthma pathophysiology. Much of this effort has focused on the inflammatory component; the

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Table 1 Study design and characteristics

Study number	Study design	Number of patients			Duration of study	Total daily dose of montelukast
		Placebo	Montelukast	Becl.		
1 [8]	Phase IIb; Adult; double-blind	58	285	0	6 weeks	10 mg, 20 mg, 100 mg, or 200 mg
1 extension	Phase IIb; Adult; open label	0	73	0	4.1 years	200 mg for 22 weeks; 100 mg for 12 weeks; 50 mg for 28 weeks, then 10 mg
2 [6]	Phase IIb; Adult; double blind	69	212	0	3 weeks	2 mg, 10 mg, or 50 mg
3	Phase III; Adult; double blind	40	40	0	4 weeks	10 mg
3 extension	Phase III; Adult; double blind for 1 month; then open label	35	65	0	1.5 years	50 or 10 mg for 1 month; then 10 mg
4	Phase III; Adult; double blind	257	387	251	12 weeks	10 mg
4 extension	Phase III; Adult; double blind	0	269	167	10.3 months	10 mg
5	Phase III; Adult; double blind	248	394	0	12 weeks	10 mg
6 [5]	Phase III; Adult; double blind	273	408	0	12 weeks	10 mg
6 extension	Phase III; Adult; open label	0	291	83	2.5 years	10 mg
7 [10]	Phase III; Adult; double blind	56	54	0	12 weeks	10 mg
8	Phase III; Adult; double blind	113	113	0	12 weeks	10 mg
9	Phase III; Adult; double blind	21	19	0	4 weeks	10 mg
10	Phase III; Adult; double blind	45	43	0	6 weeks	10 mg
11 [7]	Phase III; Paediatric; double-blind	135	201	0	8 weeks	5 mg
11 extension	Phase III; Paediatric; open label	0	207	38	1.8 years	5 mg

pro-inflammatory cysteinyl leukotrienes were found to be important mediators of asthma causing pulmonary bronchoconstriction, mucous secretion, increased vascular permeability, and decreased activity of respiratory cilia. Building on this basic research, a new class of anti-asthma therapy, the anti-leukotriene agents, is now available for clinical use.

Montelukast is a selective antagonist of the cysteinyl leukotriene receptor-1 [2], with a pharmacodynamic profile of receptor blockade up to 24 h after administration [3,4]. In controlled clinical trials, montelukast, given once daily at bedtime as a 10-mg film-coated tablet for adults age 15 years and older and as a 5-mg chewable tablet for children aged 6–14 years, causes significant improvement in clinical signs and symptoms of chronic asthma [4–8]. In addition, montelukast provides greater inhibition of exercise-induced bronchoconstriction compared to placebo at the end of a once-daily dosing interval, with no development of tolerance over a 12-week treatment period [9].

Although much of the efficacy data from the montelukast clinical trials is available in the literature [4–8,10], a comprehensive review of safety and tolerability data has not been published. In order to address this need, we have summarized safety data on over 2000 adult and 250 paediatric patients who received montelukast in controlled clinical trials. In this pooled analysis, we describe the data on the tolerability of montelukast derived from the 11 placebo-controlled,

double-blind Phase IIb and III clinical trials in patients with chronic asthma, 10 in adults aged 15–85 years and one in children aged 6–14 years. In addition, we include data from five extension studies; four adult with exposures up to 4.1 years, and one paediatric with exposures up to 1.8 years.

Patients and methods

Study design

A summary of studies in this pooled safety analysis is listed in Table 1. All trials were multicentre, randomized, double-blind and placebo controlled; some protocols also included an active comparator arm of inhaled beclomethasone. Sites in Africa, Australia, Canada, Central/South America, Europe, South-east Asia, and the United States were included. Of the 10 adult studies, the two Phase IIb trials (study #1 and 2) were 6 and 3 weeks duration, respectively; montelukast was administered at dosages of 2–200 mg per day [6,8]. The 8 Phase III trials (study #3 through 10) were 4–16 weeks duration; all patients received a dosage of one 10-mg film-coated tablet of montelukast or matching-image placebo once daily in the evening [5,9,10]. The study that included an inhaled beclomethasone comparison arm also had a matching-image placebo inhaler. In the paediatric Phase III trial (study #11), one 5-mg chewable tablet of

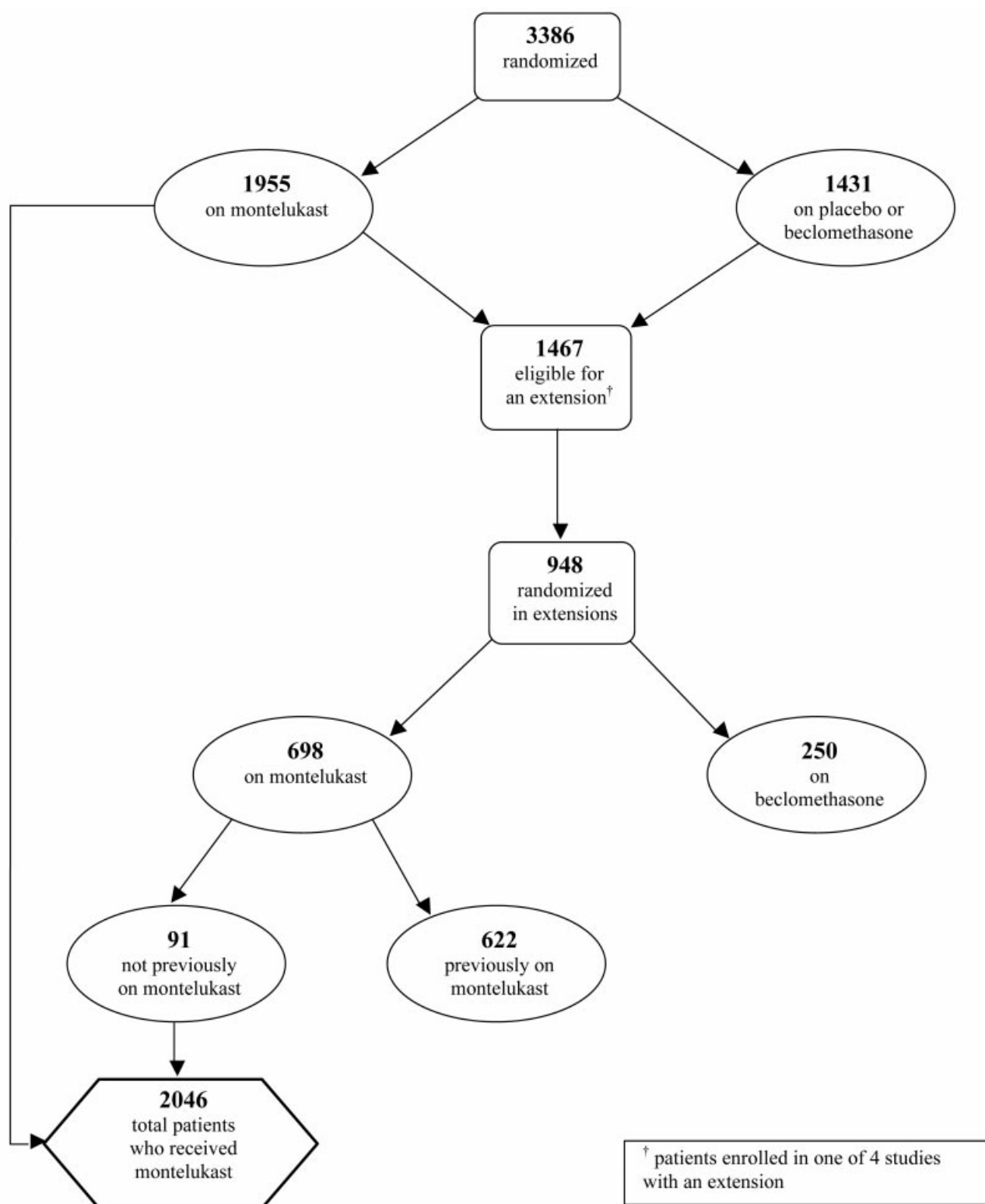


Fig. 1. Adult patients in Phase IIb/III studies. Flow diagram of number of patients randomized by treatment group in 10 adult phase IIb/III studies and 4 adult extension studies.

montelukast or a matching-image placebo was administered once daily in the evening for 8 weeks [7]. Two adult extension studies were open-label and uncontrolled, lasting a total duration of 4.1 and 1.5 years, respectively (study #1 extension and 3 extension). A third extension was double-blind with an active comparator agent, lasting 10.3 months. The remaining two extension studies (one adult and one paediatric) were open-label with an active comparator agent (inhaled beclomethasone) (study # 6 extension and 11 extension), lasting 2.5 and 1.8 years, respectively.

Patients

A total of 3386 adult patients (aged ≥ 15 years) with chronic asthma were enrolled in the Phase IIb and III trials (Fig. 1) [4,5,8–10]. Of these, 1955 adults received montelukast; the remainder of patients received either placebo or an active comparator agent, inhaled beclomethasone. One thousand four hundred and sixty-four patients were enrolled in one of the four adult studies with safety extensions. Of these, 948 continued in an extension study (698 received montelukast and 250 received inhaled beclomethasone). Cumulatively, total continuous exposure to montelukast in these extensions for adults was 698 patients for up to 6 months, 525 patients for at least 1 year, 152 patients for at least 2 years, and 25 patients for at least 3 years, giving an overall exposure of 734 patient-years. Three hundred and thirty-six 6–14-year-old patients were enrolled in the paediatric phase III trial [7], with 201 children receiving montelukast. Two hundred and forty-five of these children continued in an open-label, controlled extension study in which 207 received montelukast and 38 received an inhaled corticosteroid. The paediatric population included a cumulative total of 207 patients with continuous montelukast exposure for up to 6 months, 132 patients for at least 1 year, and 112 patients for at least 1.5 years.

A broad population (asthma severity, age, gender and race) of individuals with chronic asthma were enrolled. Baseline spirometry criteria included patients with FEV₁ of 40–90% of predicted values, placing patients in the mild, moderate and severe persistent categories according to the National Asthma Education and Prevention Program Guidelines [11]. During all trials, patients continued to take inhaled short-acting beta agonists as necessary to control asthma symptoms. The use of oral or long-acting beta agonists, anticholinergic agents and non-sedating antihistamines was not permitted during the trials and for set periods before the start of double-blind therapy. Oral, intramuscular and intravenous corticosteroids were also excluded, although oral corticosteroid rescue for worsening asthma symptoms according to a pre-specified protocol was generally permitted. In some trials, a pre-defined percentage of patients were allowed to receive concomitant asthma therapy with a constant dose of inhaled corticosteroids, oral corticosteroids or oral theophylline.

Reporting of adverse events

Tolerability evaluation included routine clinical and laboratory assessments. Initial and follow-up serum pregnancy tests were required for all females of childbearing potential. The incidence of upper respiratory infections was specifically examined due to the theoretical concern that leukotrienes might be involved in normal defences against infection. Additionally, ALT and AST elevations were examined in detail because of increased transaminase levels with other leukotriene blockers [12]. Using a more inclusive modification of the criteria set forth by Lanham *et al.* for diagnosis of Churg–Strauss syndrome (CSS) [13], records for patients with any single eosinophil count $\geq 1.45 \times 10^9/L$ were reviewed for the possibility of CSS or vasculitis. Records for patients with any single eosinophil count between $1.00 \times 10^9/L$ and $1.44 \times 10^9/L$ and a clinical adverse event that could potentially be related to CSS were also reviewed.

Clinical adverse events were monitored throughout all studies and were defined as any unfavourable or unintended change in the structure, function or chemistry of the body, or worsening of a pre-existing condition. Seriousness, severity, causal relationship to study drug, and action taken, were recorded for each adverse event by the clinician investigator at the study site. A serious adverse event was defined as one which resulted in death, permanent/substantial disability, an inpatient hospitalization, or was immediately life threatening, a congenital abnormality, a cancer, or an overdose. All adverse events were recorded and reported according to international regulatory guidelines [14].

Standardized laboratory tests, including haematology, blood chemistry and urinalysis, were performed for all patients in all studies. Using the criteria outlined above, a laboratory adverse event was a clinically important change based on the investigator's judgement. A separate analysis of serum transaminase levels was performed to identify the percentage of patients with any single value elevation above the upper limit of normal. Normal laboratory ranges based on the patient's age at pre-randomization were used for analyses.

Statistical analyses

Summary statistics of incidence rates were calculated; between group differences were assessed using the corresponding 95% confidence interval. Any adverse event in which the 95% confidence interval for the between group difference did not cover zero is significant at a level of 0.05 and is highlighted in the text. In these studies, there were no *a priori* tolerability hypotheses; therefore, no formal significance testing was applied. Data from patients with different lengths of follow-up and those receiving differing montelukast

Table 2. Baseline characteristics of adult patients enrolled in Phase IIb and III studies

	Placebo (n = 1180)	Montelukast (n = 1955)	Beclomethasone (n = 251)
Gender, n (%)			
Female	610 (52%)	959 (49%)	164 (65%)
Male	570 (48%)	996 (51%)	87 (35%)
Mean age (SD)	37 (14)	37 (14)	37 (15)
Age range	15–85	15–78	15–74
Race, n (%)			
Caucasian	947 (80%)	1600 (82%)	119 (47%)
Hispanic	116 (10%)	189 (10%)	86 (34%)
Black	43 (4%)	86 (4%)	7 (3%)
Other†	74 (6%)	80 (4%)	39 (16%)
Allergic rhinitis history, n (%)	924 (78%)	1541 (79%)	154 (61%)

†Including Asian, Indian and Native American.

dosages were pooled in the presented tables. All patients randomly allocated to each study were included, as was each patient entering extension protocols. Adverse events were summarized as the number of patients reporting at least one adverse event occurrence. Multiple occurrences of the same adverse event affecting an individual patient were included as a single event in calculations of adverse event incidence.

Results

Patients

Baseline patient characteristics for the adult and paediatric Phase IIb and III clinical trials are summarized in Tables 2 and 3 for adult and paediatric patients, respectively. Similar percentages of each demographic group entered into the extensions.

Discontinuations due to clinical adverse events

The percentages of patients discontinuing from a study because of a clinical adverse event are presented in Table 4. The percentage of patients discontinuing adult Phase IIb/III studies because of a clinical adverse event was highest in the placebo group, largely because of asthma-related events, which caused discontinuation in 4.0% of placebo-, 2.3% of montelukast- and 0.4% of beclomethasone-treated patients. Likewise, the most common clinical adverse event resulting in study discontinuation in the adult extensions was asthma, occurring in 2.9% of montelukast- and 2.4% of beclomethasone-treated patients. For paediatric patients enrolled in the Phase III study, 1.5% of placebo- and 2.5% of montelukast-treated patients discontinued due to asthma-related events, again the most common clinical adverse event causing discontinuation. In the paediatric extension study, adverse

clinical events from a variety of different organ systems caused discontinuation.

Clinical adverse events

In the 10 adult Phase IIb/III trials, the overall incidence of clinical adverse events was largely comparable among placebo-, montelukast- and beclomethasone-treated patients, although the percentage of patients on placebo who had at least one clinical adverse event was greater than that for montelukast or beclomethasone (Table 5a). The difference (95% confidence interval) between placebo and montelukast was 4.8% (1.3%–8.3%); the difference between placebo and beclomethasone was 7.6% (1.0%–14.7%).

Table 3. Baseline characteristics of paediatric patients enrolled in the Phase III study

	Placebo (n = 135)	Montelukast 5 mg (n = 201)
Gender, n (%)		
Female	52 (39%)	67 (33%)
Male	83 (62%)	134 (67%)
Mean age (SD)	11 (2)	11 (2)
Age range	6–15	6–15
Race, n (%)		
Caucasian	108 (80%)	161 (80%)
Hispanic	5 (4%)	10 (5%)
Black	19 (14%)	24 (12%)
Other†	3 (2%)	6 (3%)
Allergic rhinitis history, n (%)	124 (92%)	191 (95%)

†Including Asian and Indian.

Table 4. Patients discontinued due to clinical adverse experiences

	Placebo		Montelukast		Beclomethasone†	
	<i>n</i>	(%)	<i>n</i>	(%)	<i>n</i>	(%)
Adult Phase IIb/III studies						
Discontinuations	61/1180	(5.2)	73/1955	(3.7)	5/251	(2.0)
Adult extension studies						
Discontinuations	–	–	40/698	(5.7)	10/250	(4.0)
Paediatric Phase III study						
Discontinuations	3/135	(2.2)	8/201	(4.0)	–	–
Paediatric extension study						
Discontinuations	–	–	9/207	(4.3)	0/38	0

†Patients in the paediatric extension study were not limited to beclomethasone and could receive any inhaled corticosteroid.

The most common clinical adverse events were upper respiratory infection, asthma and headache (Table 5a). Individual adverse events occurred with similar frequencies in the three treatment groups, except for asthma, upper respiratory infection and rhinitis. Asthma occurred more frequently in the placebo group than in the montelukast group; the difference between placebo and montelukast was 5.6% (2.8%–8.8%). Infectious upper respiratory conditions were recorded with similar frequencies in the montelukast and placebo groups, both cumulatively (36.9% in the placebo group and 31.6% in the montelukast group) and individually (including upper respiratory infection, pharyngitis and influenza; Table 5a).

Cumulative incidence of upper respiratory infection (combination of upper respiratory events noted above) occurred less frequently in the beclomethasone group (29.9%); the difference between placebo and beclomethasone was 11.5% (5.8%–17.4%), and the difference between montelukast and beclomethasone was 8.4% (3.0%–14.0%). Additionally, patients receiving beclomethasone reported slightly more adverse events of rhinitis than patients on placebo or montelukast; the difference between beclomethasone and placebo was 2.6% (0.1%–6.7%), and the difference between beclomethasone and montelukast was 3.2% (1.0%–7.0%). There were no apparent differences in the incidence of clinical adverse events among montelukast-treated patients as related to age, gender or race of patients (data not shown).

The percentage of patients in the adult extension studies reporting one or more clinical adverse events during the extension studies was 80.1% in the montelukast group and 74.4% in the beclomethasone group. The incidence of individual adverse events, including upper respiratory system infections, was generally similar in the montelukast and beclomethasone groups (Table 5b), despite the larger number of patients exposed to montelukast.

At least one clinical adverse event was reported by 75.6%

and 75.1% of paediatric patients receiving placebo and montelukast, respectively, in the Phase III trial. Individual adverse events occurred with similar frequency between treatment groups (Table 6a). Specifically, infectious upper respiratory-related conditions were reported by similar percentages of patients in the two treatment groups, namely, 66 (48.9%) in the placebo group and 98 (48.8%) in the montelukast group. Frequencies of individual upper respiratory conditions, including upper respiratory infection, pharyngitis and influenza, were also similar in the two groups.

Clinical adverse events were reported by 95.2% of montelukast-treated patients and 86.8% of patients receiving inhaled corticosteroids during the paediatric extension study. The incidence of individual adverse events was similar between the two treatment groups (Table 6b) except for rhinorrhea, which was reported by fewer patients on montelukast than beclomethasone; the difference between beclomethasone and montelukast was 11.8% (1.5%–29.9%).

Laboratory adverse events

The incidences of laboratory adverse events in the adult Phase IIb/III trials were similar among treatment groups — 6.7%, 6.3% and 6.0% in the placebo, montelukast and beclomethasone groups, respectively. There were no clinically important differences among treatment groups in the incidence of any specific laboratory adverse event or discontinuations due to adverse events. Four montelukast-treated patients withdrew because of positive pregnancy tests.

During the adult extension studies, similar percentages of patients in the montelukast and beclomethasone groups experienced laboratory adverse events (9.8% vs. 8.6%), and 1.6% of patients in both treatment groups (11 in the montelukast group and four in the beclomethasone group) were discontinued from therapy because of laboratory adverse events. In the montelukast group, one patient discontinued because of an elevated AST value (40 U/L;

Table 5a. Most common clinical adverse events†, regardless of causality, among adults enrolled in 10 Phase IIb/III studies

	Placebo (<i>n</i> = 1180)		Montelukast (<i>n</i> = 1955)		Beclomethasone (<i>n</i> = 251)	
	<i>n</i>	(%)	<i>n</i>	(%)	<i>n</i>	(%)
Total patients with 1 or more clinical adverse events*	841	(71.3)	1300	(66.5)	160	(63.7)
Upper respiratory infection*	290	(24.6)	420	(21.5)	33	(13.1)
Headache	214	(18.1)	360	(18.4)	47	(18.7)
Asthma*	233	(19.7)	275	(14.1)	48	(19.1)
Pharyngitis	83	(7.0)	106	(5.4)	16	(6.4)
Influenza	46	(3.9)	82	(4.2)	17	(6.8)
Sinusitis	51	(4.3)	79	(4.0)	6	(2.4)
Diarrhoea	36	(3.1)	61	(3.1)	5	(2.0)
Bronchitis	42	(3.6)	47	(2.4)	7	(2.8)
Abdominal pain	29	(2.5)	56	(2.9)	8	(3.2)
Nausea	35	(3.0)	50	(2.6)	5	(2.0)
Rhinitis*	16	(1.4)	15	(0.8)	10	(4.0)

†Adverse events occurring in 3% or more of enrolled patients in any treatment group.

*Significant between group differences.

Table 5b. Most common clinical adverse events†, regardless of causality, among adults enrolled in 4 extension studies

	Montelukast (<i>n</i> = 698)		Beclomethasone (<i>n</i> = 250)	
	<i>n</i>	(%)	<i>n</i>	(%)
Total patients with 1 or more clinical adverse events	559	(80.1)	186	(74.4)
Upper respiratory infection	245	(35.1)	74	(29.6)
Asthma	224	(32.1)	64	(25.6)
Headache	139	(19.9)	55	(22.0)
Pharyngitis	88	(12.6)	31	(12.4)
Sinusitis	59	(8.5)	16	(6.4)
Influenza	52	(7.4)	21	(8.4)
Bronchitis	52	(7.4)	15	(6.0)
Back pain	47	(6.7)	11	(4.4)
Rhinitis	31	(4.4)	15	(6.0)
Abdominal pain	35	(5.0)	10	(4.0)

†Adverse events occurring in 5% or more of enrolled patients in either treatment group.

normal range, 11–36 U/L); in the beclomethasone group, one patient discontinued because of an elevated ALT value (58 U/L; normal range, 6–43 U/L). The remaining patients discontinued due to positive pregnancy tests.

Thirteen patients in the paediatric Phase III trial had one or more laboratory adverse events, two (1.5%) in the placebo group and 11 (5.5%) in the montelukast group. There were no significant differences between treatment groups in the incidence of any individual laboratory adverse event. Two montelukast-treated patients discontinued from therapy

because of laboratory adverse events (elevated ALT value and decreased neutrophil count, respectively); both of these abnormalities had been present at pre-randomization testing.

During the paediatric extension study, 25 patients (12.1%) in the montelukast group and three patients (8.1%) in the inhaled corticosteroid group had laboratory adverse events. Four patients in the montelukast group (1.9%) were discontinued from therapy because of a laboratory adverse event. The laboratory abnormalities in

Table 6a. Most common clinical adverse events†, regardless of causality, among paediatric patients enrolled in the Phase III study‡

	Placebo (n = 135)		Montelukast 5 mg (n = 201)	
	n	(%)	n	(%)
Total patients with 1 or more clinical adverse events	102	(75.6)	151	(75.1)
Upper respiratory infection	40	(29.6)	48	(23.9)
Headache	29	(21.5)	38	(18.9)
Asthma	31	(23.0)	33	(16.4)
Pharyngitis	17	(12.6)	28	(13.9)
Abdominal pain	14	(10.4)	10	(5.0)
Influenza	6	(4.4)	17	(8.5)
Cough	10	(7.4)	12	(6.0)
Fever	5	(3.7)	15	(7.5)
Nausea	5	(3.7)	8	(4.0)
Nasal congestion	7	(5.2)	7	(3.5)
Sinusitis	2	(1.5)	10	(5.0)
Infectious gastroenteritis	6	(4.4)	4	(2.0)
Vomiting	6	(4.4)	3	(1.5)

†Adverse events occurring in 4% or more of enrolled patients in either treatment group.

‡Knorr B, Matz J, Bernstein JA *et al.* Montelukast for chronic asthma in 6–14-year-old children: a randomized, double-blind trial. *JAMA*. 1998; 279:1181–1186. 'Copyright 1998, American Medical Association'.

Table 6b. Most common clinical adverse events†, regardless of causality, among paediatric patients enrolled in the extension study

	Montelukast 5 mg (n = 207)		Inhaled corticosteroid (n = 38)	
	n	(%)	n	(%)
Total patients with 1 or more clinical adverse events	197	(95.2)	33	(86.8)
Upper respiratory infection	117	(56.5)	19	(50.0)
Asthma	87	(42.0)	13	(34.2)
Headache	68	(32.9)	9	(23.7)
Pharyngitis	54	(26.1)	10	(26.3)
Sinusitis	42	(20.3)	6	(15.8)
Cough	40	(19.3)	5	(13.2)
Fever	31	(15.0)	2	(5.3)
Abdominal pain	23	(11.1)	4	(10.5)
Rash	22	(10.6)	3	(7.9)
Nasal congestion	23	(11.1)	1	(2.6)
Infectious gastroenteritis	21	(10.1)	2	(5.3)
Dizziness	6	(2.9)	4	(10.5)
Rhinorrhea*	3	(1.4)	5	(13.2)

†Adverse events occurring in 10% or more of enrolled patients in either treatment group.

*Significant between group difference.

two discontinued patients, one with an elevated ALT and one with decreased neutrophils, had resolved by the time of study discontinuation. The third discontinued patient had an elevated bilirubin value (2.4 mg/dL; normal range,

0.2–1.2 mg/dL) that had decreased to 1.6 mg/dL at the time of discontinuation. The fourth patient was discontinued for decreased neutrophils but had a history of cyclic neutropenia.

Table 7. Patients with serum transaminase values above the upper limit of normal

	Placebo		Montelukast		Beclomethasone†	
	<i>n</i>	(%)	<i>n</i>	(%)	<i>n</i>	(%)
Adult Phase IIb/III studies						
Alanine transaminase	135/1169	(11.5)	249/1934	(12.9)	29/249	(11.6)
Aspartate transaminase	66/1169	(5.6)	127/1934	(6.6)	15/249	(6.0)
Adult extension studies						
Alanine transaminase	—	—	119/686	(17.3)	36/241	(14.9)
Aspartate transaminase	—	—	62/686	(9.0)	17/241	(7.1)
Paediatric Phase III study						
Alanine transaminase	3/135	(2.2)	6/200	(3.0)	—	—
Aspartate transaminase	4/135	(3.0)	12/200	(6.0)	—	—
Paediatric extension study						
Alanine transaminase	—	—	14/207	(6.8)	5/37	(13.5)
Aspartate transaminase	—	—	25/207	(12.1)	5/37	(13.5)

†Patients in the paediatric extension study were not limited to beclomethasone and could receive any inhaled corticosteroid.

The percentages of patients with increases in ALT or AST above the upper limit of normal are presented in Table 7. Most of these increases were > 1 but ≤ 2 times the upper limit of normal. Elevations were usually transient and self-limited. Clinically significant transaminase elevations of > 3 times the upper limit of normal were rare, occurring in 1% or less of patients receiving montelukast in all 11 studies and five extensions, and were similar in frequency in all treatment groups.

High doses of montelukast

No increase in treatment discontinuations or frequency of clinical or laboratory adverse events were seen for patients in study #1 and 2, who received montelukast at substantially higher than the marketed dose of 10 mg. Moreover, in extension study #1 included in this summary, adult patients received montelukast at 200 mg for 22 weeks, 100 mg for 12 weeks and then 50 mg for 28 weeks with no change in the tolerability profile. Therefore, results from these studies are not summarized separately but are included as part of the overall analysis.

Churg–Strauss syndrome

None of the adult and paediatric patients from all three treatment groups in these 11 montelukast clinical trials and extensions had vasculitis or CSS listed as a clinical adverse experience. Fifty-four (1.5%) had one or more peripheral blood eosinophil counts $\geq 1.45 \times 10^9/L$. Additionally, 128 (3.4%) patients had one or more peripheral blood eosinophil counts of $1.00 \times 10^9/L$ to $1.44 \times 10^9/L$ and an associated clinical adverse event. These included fever,

weight loss, rash, asthma exacerbation, pulmonary infiltrate, joint pain, and sinus, gastrointestinal, cardiac or renal disorders. Overall, the percentage of patients with any single eosinophil count elevation described above was numerically similar in all three treatment groups both for adult and paediatric patients. None of the 182 patients met the clinical criteria for CSS. All of the associated clinical adverse experiences found were unrelated to CSS and were self-limited and/or resolved on continued treatment.

Pregnancy

Thirty randomized patients (six placebo, 20 montelukast, four beclomethasone) became pregnant during one of these 11 clinical studies. One of the 30 pregnancies occurred in a 16-year-old patient participating in the paediatric extension study. A cumulative total of 13 healthy infants were born (three placebo, nine montelukast, one beclomethasone), 16 pregnancies were aborted (three placebo, 10 montelukast, three beclomethasone), and one pregnancy (montelukast) was lost to follow-up. Of the 10 aborted montelukast pregnancies, six were elective, three were spontaneous, and one was not specified.

Post-marketing experience

Approximately 2 million patients have received montelukast world-wide, with a total of 493.9 million montelukast tablets distributed as of 30 January 2000. Overall, the post-marketing surveillance data for montelukast are consistent with the favourable tolerability profile seen in clinical trials. A voluntary, physician-reported pregnancy registry

has been set up to follow all patients who become pregnant while taking montelukast.

CSS, or allergic granulomatous vasculitis, is a rare disorder characterized by asthma, hypereosinophilia and systemic vasculitis. Post-marketing experience has identified rare case reports of eosinophilic conditions consistent with CSS in patients taking montelukast [15]. Post-marketing data show a reporting incidence of 0.0037 cases per 100 000, consistent with the incidence of CSS in the general asthmatic population. Cases are characterized by adult patients with significant asthma histories who received multiple asthma medications, often including systemic corticosteroids. No cases have been reported in children. Clinical features associated with CSS usually occurred or worsened during or following corticosteroid reduction. In many cases, features consistent with CSS were present prior to initiation of montelukast therapy. A causal relationship between the leukotriene receptor antagonists and eosinophilic conditions has not been established.

Discussion

This meta-analysis demonstrates a favourable tolerability profile of montelukast in both randomized controlled trials as well as in long-term, comparative extension studies up to 4 years in duration in patients from 6 to 85 years of age. The overall incidence of clinical and laboratory adverse events among montelukast-treated patients, both adult and paediatric, was similar to that among patients receiving placebo in the Phase IIb and III trials. The incidence of individual adverse events was also similar for the two treatment groups, with the exception of asthma, which occurred more frequently and resulted in more frequent treatment discontinuation in the placebo groups. The most common clinical adverse events recorded for both adults and children were upper respiratory infection, asthma and headache. Although headache is reported in the USA product label for both montelukast [16] and zafirlukast [17], no excess incidence of headache occurred in either adult or paediatric patients in these trials. Montelukast had a similar safety profile across demographic subgroups, suggesting that pharmacogenetic influences may play a minimal role in the tolerability of this drug. There were no age-, gender- or race-related differences in the incidence of adverse events in the Phase IIb and III trials.

Montelukast was well tolerated during long-term treatment. In the adult extension studies, the incidence of clinical and laboratory adverse events was slightly higher in the montelukast group than that in the inhaled beclomethasone group (80.1% vs. 74.4% for clinical adverse events and 9.8% vs. 8.6% for laboratory adverse events). However, the cumulative exposure to montelukast in extension studies was almost four times that to beclomethasone (734 vs. 214 patient-years); thus, somewhat higher adverse event rates

would be expected in the montelukast group. In the paediatric extension study, the inhaled corticosteroid group was small (38 patients), limiting the ability to make comparisons; however, the frequency of adverse events was similar in the two treatment groups.

No dose-related adverse effects of montelukast have been observed even in subjects or patients treated with doses substantially greater than the clinical dose for long periods of time. In Phase I and IIa studies, subjects received 300 mg montelukast three times daily (900 mg/day) for 7.3 days [15]. These results were confirmed and extended in the Phase IIb studies and extensions reported here, indicating a large safety margin for the compound.

The incidence of upper respiratory infections was specifically examined because of concern that leukotriene receptor antagonism could interfere with normal host defences. Leukotrienes are thought to play a role in haemopoietic stem cell proliferation, a process required for generation of an inflammatory cell response to infection [18]. Direct involvement of leukotrienes with host defence against bacteria has been suggested [19], although from available evidence it seems that leukotriene B₄ and not the cysteinyl leukotrienes are involved (leukotriene-receptor antagonists do not affect leukotriene B₄) [20]. We found no differences between montelukast- and placebo-treated patients, adults or children, in the overall incidence of infectious upper respiratory adverse events or in the incidence of individual infectious upper respiratory conditions.

Any possible association of montelukast therapy with ALT and AST elevations was closely examined. In all studies, including the extension studies, there were no important differences among treatment groups in the frequency of patients with ALT or AST values greater than the upper limit of normal. Most outlier values during montelukast treatment were transient, self-limited, and had other clinical explanations (e.g. mononucleosis). In contrast, clinically important elevations in serum transaminase values have been reported in approximately 3% of patients treated with a 5-lipoxygenase inhibitor for 13 weeks [12]. Additionally, reports of elevated liver enzymes have occurred in patients receiving high dosages of zafirlukast, another leukotriene receptor antagonist [21].

No association between montelukast and eosinophilia or eosinophilic conditions was seen in the Phase IIb/III clinical trials, even after a specific analysis was conducted evaluating peripheral blood eosinophil counts and all terminology that could potentially be associated with a vasculitic syndrome. CSS, or allergic granulomatous vasculitis, has been reported in association with zafirlukast treatment in at least 11 patients [22–24]. CSS has also been reported in at least one patient following the introduction of fluticasone [25], as well as in montelukast post-marketing surveillance [15]. Post-marketing reports of CSS with multiple different

anti-asthma therapies makes any mechanism-based association with a single drug or class of drugs less likely [15].

Despite the relatively large number of patients included in these montelukast trials, it is possible that rare case reports of adverse events may be reported in post-marketing experience, when the drug is used in very large populations, that were not seen in the randomized studies. This is a general limitation of safety data from clinical trials. Since post-marketing reporting remains uncontrolled and selective, reporting of safety data from clinical trials still offers the best opportunity to evaluate the safety profile of the drug [26]. The tolerability profile of montelukast observed in clinical trials has been generally reflected in the post-marketing safety experience reported to date.

Conclusion

These data indicate an excellent safety and tolerability profile in all age groups for montelukast during both short-term and long-term administration, even at doses substantially higher than the recommended clinical dose of 10 mg once daily for adult patients and 5 mg once daily for paediatric patients (aged 6–14 years) with chronic asthma.

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