

The national montelukast survey

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Background: Randomized controlled trials have demonstrated the efficacy of montelukast for treating asthma; whether this can be extrapolated to clinical effectiveness in routine practice has yet to be established.

Objective: To examine the use, effectiveness, and tolerability of montelukast in clinical practice for treating asthma and to explore prognostic factors that could predict a favorable response to the drug.

Methods: This was a retrospective, cross-sectional, observational study of clinical outcomes seen in patients prescribed montelukast for asthma that used routinely collected clinical information. Data were collected on all consenting patients who had been prescribed montelukast for asthma irrespective of the continuation or duration of treatment. Independent observers, treating physicians, and patients assessed certain outcomes after the initiation of montelukast, including the general asthma response and changes in activity-related symptoms.

Results: Fifty-six centers in the United Kingdom (20 primary care and 36 secondary care) participated. The analysis was based on 1351 eligible patients for whom essential data were available. Eight hundred thirty patients (66.4%; 95% CI, 63.8% to 69.0%) were recorded as having shown an improvement in their asthma control, and 103 (8.2%; 95% CI, 6.8% to 9.9%) experienced a dramatic improvement. The greatest proportion of patients responding was seen in those

with mild to moderate asthma. Montelukast was well tolerated; no new adverse events were recorded.

Conclusions: Montelukast is an effective, well-tolerated treatment for asthma in routine practice. The overall response rate and tolerability seen in this survey are similar to those reported in randomized clinical trials. (*J Allergy Clin Immunol* 2005;115:47-54.)

Key words: Montelukast, survey, retrospective

The roles of cysteinyl leukotrienes in the pathogenesis of asthma are well established.^{1,2} Randomized controlled trials (RCTs) have confirmed the efficacy of leukotriene receptor antagonists (LTRAs) when used as monotherapy³⁻⁵ or added to inhaled corticosteroids (ICSs)⁶⁻⁸ in improving asthma outcomes, including lung function, symptoms, asthma exacerbations, and health-related quality of life. Although current guidelines place LTRAs as a therapeutic option at a range of levels of asthma severity, there is still uncertainty among clinicians about their role in relation to other therapies. RCTs have shown benefits when this group of drugs is used in patients with asthma, but there is a paucity of data examining their use in everyday practice, which could complement the findings of RCTs, which by necessity limit the patient population studied.⁹

Interest is growing in using observational studies to support clinical interventions,^{10,11} with their acknowledged drawbacks and advantages. The drawbacks include a lack of randomization, a lack of placebo control, and a “regression to the mean” effect in symptomatic patients. In addition, the quality of clinical record keeping may fall below that required for clinical trials, and the availability of specific outcomes and reliable data extraction may be difficult. Such studies have consequently been viewed as inferior to RCTs. The positive aspects of observational studies include the large numbers of patients that may be studied with comparative ease, thus allowing clinicians to better understand the range of responses seen in clinical practice. Similar outcomes observed over a range of settings can reassure clinicians that RCT findings should apply to the patients they see and treat, whereas discrepancies may point to the need for further investigation. Observational study findings are more easily generalized and representative of real-world practice.

Increased interest in observational data has prompted the use of quality markers for such studies.¹⁰ It is important that data be accurately and reproducibly extracted. When

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Abbreviations used

GP: General practice (practitioner)
ICS: Inhaled corticosteroid
LABA: Long-acting β agonist
LTRA: Leukotriene receptor antagonist
RCT: Randomized controlled trials

a pharmaceutical company involved in marketing a product sponsors such studies, an independent steering committee should be involved in the study design, execution, analysis, and presentation of results, with a commitment to disseminate the findings.¹⁰

We now report such a retrospective, observational, cross-sectional survey performed in the United Kingdom to assess the use, effectiveness, and tolerability of montelukast when prescribed in routine clinical practice for the treatment of asthma.

METHODS

General

The detailed methodology underlying this study, which included 3 pilot trials, is described elsewhere.¹² The pilot studies explored methods for data extraction and questionnaire development until an acceptable level of reproducibility was achieved.¹² Briefly, an independent steering committee was commissioned whose members included hospital respiratory physicians, primary care physicians, and nurses with experience of observational studies and clinical audit. This committee devised the study protocol, oversaw development and piloting of data-collection methods and questionnaires, reviewed the results, and wrote the publications.

A large number of centers, comprising both primary and secondary care, that had experience with using montelukast (at least 5 patients having received treatment) were approached to provide a reasonable pool of patients from which data could be collected. Attempts were made to gain wide geographic coverage and to include both pediatric and adult patients.

The appropriate ethics committees approved the methods of this study and all pilot studies.

Patient selection

Participating physicians identified all patients who had asthma documented (ie, physician-diagnosed asthma) in their notes and who had been prescribed montelukast at any time between February 1998 and June 2000. Any patients prescribed montelukast as part of a clinical trial were excluded. All eligible patients were contacted by post, and written informed consent was sought to review their medical notes.

Outcomes measured

Data were collected with 3 different questionnaires completed by an independent observer, the prescribing physician, and the patient. To minimize bias, the data collected by the experienced National Respiratory Training Centre nurse trainers (independent observers) were regarded as the primary data for the study. These independent observers had no connection with the centers or prior knowledge of the patients. To maintain objectivity, they collected information by using only the patient medical records (no contact with the patient or

physician). Accompanying guidance notes had been developed to increase the consistency and quality of the data collected.¹² Data collected by the independent observer included the demographic information, the duration of asthma, the documented presence of concomitant conditions, and the condition recorded in the notes at the time montelukast was initiated (assumed to be the reason for initiating treatment). The independent observer assessed the response to montelukast by reference to the medical records in a number of asthma-related areas, including general asthma response, lung function, activity-related asthma symptoms, and asthma-related sleep disturbances. Details of the presence of concomitant rhinitis and any changes in this condition after montelukast were captured if recorded.

A 7-point Likert scale was used that graded the response on all assessed parameters from very much worse (−3) to dramatically improved (+3); no change was coded as 0. Physicians completed a short questionnaire on the response to treatment only. Both the independent observer and physician were asked to report any recorded adverse events thought to be related to montelukast.

All patients older than 18 years who had been prescribed montelukast within 6 months of the start of the survey, irrespective of whether they were continuing with montelukast treatment, were identified and sent a short questionnaire. This was designed and validated by the Mapi Research Institute (Lyons, France) with the aim of capturing the patients' perception of response and feelings about the drug. A 6-month cutoff was used to reduce recall bias, which would cover the typical general practice (GP) review within 3 months of prescribing.

Because most of the important data, including the basic demographics, were collected from the independent-observer questionnaire, patients were excluded from the main analyses if they did not have an independent observer form completed and returned. Medication lists are reliable because GPs in the United Kingdom do the preponderance of prescribing. Pilot studies highlighted the difficulties in reliably estimating from the records the intended doses of ICSs taken by patients in the hospital centers, so therapy at the time of montelukast initiation was classified as follows:

1. Short-acting β_2 agonist only
2. ICS only
3. ICS + long-acting β agonist (LABA) only
4. ICS and LABA and other (other medication, excluding oral steroids)
5. ICS and oral (regular oral corticosteroids with or without other concomitant medication)

Statistical analysis

Descriptive statistics were used to present results. Logistic regression analysis was used to explore the relationship between baseline asthma treatment categories and demographic variables and response to montelukast, defined as any level of positive outcome for general asthma response. The survey was powered by consideration of the precision of the estimates. One thousand two hundred patients were required to ensure that the 95% CIs of the percentages estimated were <3 percentage points in either direction. Analysis was performed with SAS version 8 (SAS Institute, Cary, NC).

RESULTS

General

A total of 56 centers from throughout the United Kingdom agreed to participate in the survey (20 GP centers and 36 hospitals). The physicians contacted

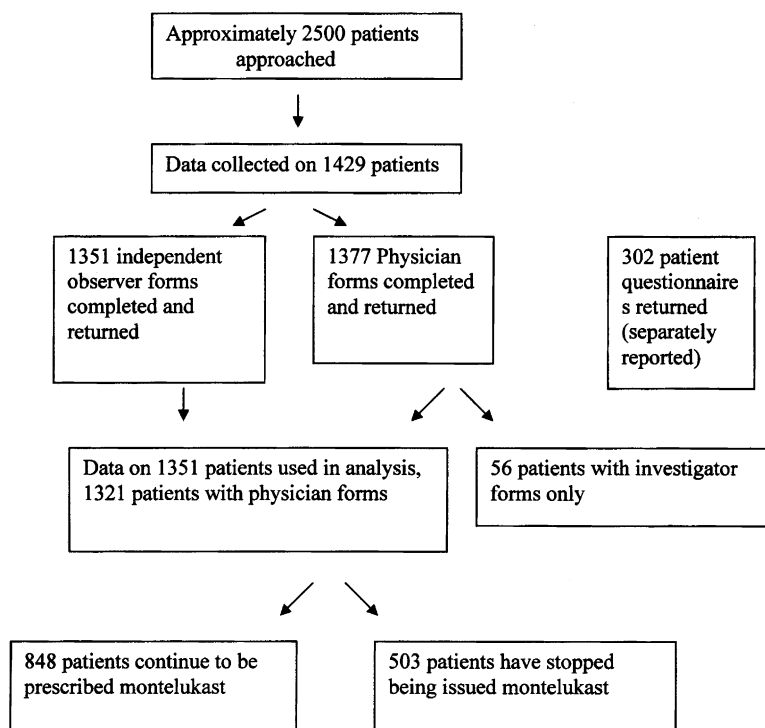


FIG 1. Patient data.

approximately 2500 patients, and more than half (56%) consented for their notes to be reviewed.

Independent observer and physician questionnaires were completed and returned for 1429 patients. Fig 1 shows the various sources of the data and the number of patients included in this analysis. The demographics for the 1351 patients included are presented in Table I. More than half of the patients (55%) were female, but this was similar for both center types. Larger proportions of the patients seen in the hospital centers were younger (reflecting the inclusion of a large number of pediatric centers), required more treatment, and had had asthma longer. This is true of real-world practice, in which secondary-care centers predominantly treat patients with more severe and resistant asthma. The large number of pediatric centers meant that 507 participants (37.5%) were younger than 16 years of age. The age range was 6 months to 75 years, with bimodal peaks at ages 6 to 15 years and across the span 36 to 65 years. The duration of montelukast treatment at the time of the survey ranged from <1 month to 38 months (median, 15 months) for patients still taking montelukast and from <1 month to 36 months (median, 3 months) in patients who had discontinued treatment. A Kaplan-Meier plot of time for the duration of treatment for all patients is shown in Fig 2.

Responses to treatment

Table II summarizes the general asthma response by center type and age and gives a comparison between the independent observers' assessment and that of the treating

physician. According to the independent observers' assessments, >66% (66.4%; 95% CI, 63.8% to 69.0%; n = 830) of patients over all centers were reported as experiencing an improvement in their asthma, and 8.2% (95% CI, 6.8% to 9.9%; n = 103) were assessed as having a dramatic or very good improvement in their asthma. The proportion of patients with improvement in asthma was similar in the 2 types of treatment centers; however, a greater proportion of children were recorded as having their asthma "much" or "dramatically" improved after treatment with montelukast compared with adults (41.3% [95% CI, 36.8% to 45.6%] and 33.5% [95% CI, 30.2% to 37.0%], respectively). The overall response was similar for the independent observers and the physicians.

Other asthma outcomes measured—the reductions in asthma-related sleep disturbances and the improvement in asthma-related activity symptoms—showed patterns of response similar to those seen in overall asthma response, with 64.3% (95% CI, 60.0% to 68.5%) and 63.9% (95% CI, 60.3% to 67.5%) of patients experiencing an overall improvement, respectively.

Fig 3 shows the distribution of responses for general asthma by treatment group and indicates that a slightly greater proportion of patients improved when taking lower medication doses at the time montelukast was initiated. Approximately 40% (40.4%; 95% CI, 37.8% to 43.1%; n = 546) of all patients were recorded as having coexisting rhinitis in their medical notes; of these, 211 (39%) had a recorded response, and 54.5% (95% CI, 47.5% to 61.4%; n = 115) were recorded as showing an improvement in rhinitis.

TABLE I. Demography

Variable	GP centers	Hospital centers	All centers
Sex, n (%)			
Male	190 (42)	407 (46)	597 (44.2)
Female	263 (58)	480 (54)	743 (55.0)
Age, y, mean (range)	41 (4-88)	32 (1-88)	35 (1-88)
Duration of asthma, n (%)			
<1 y	4 (1)	7 (1)	11 (0.8)
1-10 y	193 (42)	405 (45)	598 (44)
>10 y	214 (47)	380 (42)	594 (44)
Reason for initiation, n (%)*			
Acute exacerbation	186 (42.2)	339 (37.9)	525 (39.3)
Activity-induced asthma	102 (23.1)	246 (27.5)	348 (26.1)
Desire to reduce ICS dose/avoid increasing dose	99 (22.4)	278 (31.1)	377 (28.2)
Sleep disturbance	53 (12.0)	262 (29.3)	315 (23.6)
Comorbidity†	74 (16.8)	209 (23.4)	283 (21.2)
Additional	66 (15.0)	102 (11.4)	168 (12.6)
Not known	29 (6.6)	24 (2.7)	53 (4.0)
Therapy group when montelukast was initiated, n (%)			
SABA only	27 (6.1)	43 (4.8)	70 (5.2)
ICS only	199 (45.1)	153 (17.1)	352 (26.4)
ICS and LABA only	106 (24.0)	408 (45.6)	514 (38.5)
ICS and LABA and other treatment	33 (7.5)	111 (12.4)	144 (10.8)
ICS and oral corticosteroids	30 (6.8)	121 (13.5)	151 (11.3)
Other	46 (10.4)	58 (6.5)	104 (7.8)
Concomitant conditions recorded, n (%)			
Rhinitis	205 (45)	341 (38)	546 (40)
Eczema	122 (27)	231 (26)	353 (26)
Smoking status, n (%)‡			
Smoker	49 (11)	49 (5)	98 (7)
Nonsmoker/ex-smoker/unknown	407 (89)	846 (95)	1253 (93)

GP, General practice; ICS, inhaled corticosteroid; LABA, long-acting β agonist; SABA, short-acting β agonist.

*Patients could have had more than 1 condition present when montelukast was initiated.

†Comorbidity that was hoped to be treated alongside asthma with montelukast.

‡Children 12 years of age and younger were assumed to be nonsmokers.

Objective lung function measurements (peak flowmeter or spirometry) were poorly recorded in both GP and hospital centers and were noted in only approximately 35% of patient records; they have therefore not been reported here.

Patient assessment

Three hundred two patient questionnaires were completed and returned. From the 292 patients who answered the question on overall asthma response, a pattern of response to montelukast treatment was seen that was similar to both the physicians' and independent observers' assessments (Fig 4). Most patients experienced an improvement in their asthma after treatment and were happy to continue taking montelukast. Approximately two thirds of the patients ($n = 199$) were continuing to take montelukast; of these, 69.8% (95% CI, 35.7% to 63.9%; $n = 99$) believed that their asthma was much better, and 69.8% (95% CI, 66.8% to 79.7%, $n = 139$) reported reductions in their use of reliever medication.

Exploratory analyses were performed with logistic regression to investigate associations between demographic and baseline characteristics and the probability of having a positive response of general asthma to the

drug. The existing associations between these factors themselves necessarily led to a degree of arbitrariness in the interpretation of these results. Factors considered were as follows:

1. Age (adult or child)
2. Sex
3. Center type (hospital or GP)
4. Duration of asthma (<1 year, 1-10 years, or >10 years)
5. Treatment subgroup (short-acting β_2 agonist only, ICS only, ICS + LABA, ICS + LABA + other, or ICS + oral steroids)
6. Other atopy (yes or no)
7. Acute exacerbation at initiation (yes or no)
8. Activity-induced asthma at initiation (yes or no)
9. Desire to reduce ICS or avoid increase at initiation (yes or no)
10. Sleep disturbance at initiation (yes or no)
11. Comorbidity at initiation (yes or no)

Each factor was modeled individually, and then stepwise forward modeling was undertaken. This included the most important significant factor in the model in the first round and in subsequent rounds added in the next most

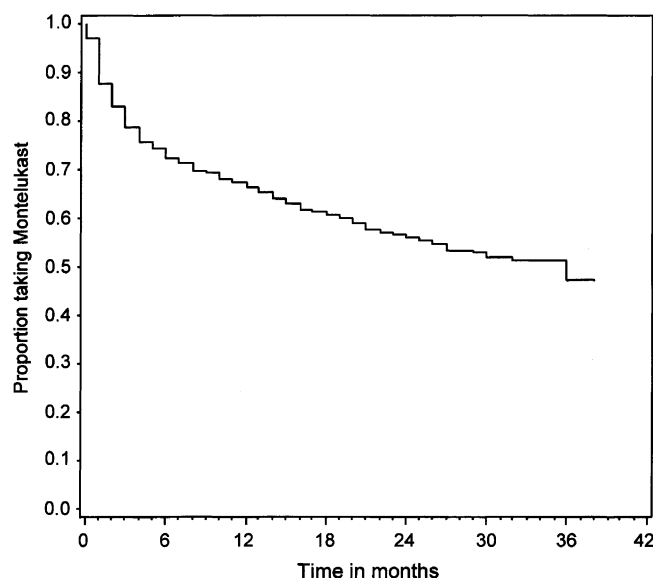


FIG 2. Duration of montelukast treatment—all patients.

TABLE II. Response to montelukast by center, age, group, and observer

Characteristic	n	Response score percentage						
		Deterioration			Improvement			
		−3	−2	−1	0	1	2	3
General practice center	418	0	1	1	33	35	24	6
Hospital center	832	0	0	1	31	27	30	9
Adults	751	0	1	1	34	30	26	7
Pediatric	480	0	0	2	27	30	32	10
Independent observer	1250	0	1	1	32	30	28	8
Physician	1245	0	0	1	32	27	30	10

important factor if it met the significance level set ($P < .1$). The results of the individual factor analyses are shown in Table III. Individual factors showing a significant association ($P < .05$) were age group (a child was more likely to be a responder), sex (males were more likely to respond), treatment group (those treated with ICS + LABA only were the most likely to respond, with a slight trailing off of the response rate as the therapy group indicated more severe or less severe asthma; Fig 3), activity-induced asthma (those with this condition were more likely to respond), and sleep disturbance (those with this condition were more likely to respond). A forward inclusion model resulted in the factor activity-induced asthma only being included in the model (at $P = .002$). Noted associations between covariates were age with sex (more males among the patients <16 years old) and more children with activity-induced asthma and sleep disturbance. Therefore, the inclusion in the multiple regression approach of activity-induced asthma only could encapsulate the effects of age, sex, and sleep disturbance.

Tolerability and continuation of therapy

Montelukast seemed to be well tolerated. Adverse events attributed to montelukast were noted in 137

patients' records (9.3%; 95% CI, 7.8% to 11.1%). A single serious adverse event (diarrhea) was recorded that the physician believed to be possibly drug related. Eleven other serious adverse events were seen that were not considered to be drug related, either by the physician or independent observer, including abdominal pain, headache, asthma, myocardial infarction, and hypoglycemic reaction. Most patients ($n = 843$, 62.4%; 95% CI, 59.8% to 65.0%) continued to take montelukast. The most common reasons for stopping treatment were "montelukast was ineffective" (19.1%; 95% CI, 17.0% to 21.3%; $n = 258$) and "montelukast caused side effects" (6.6%; 95% CI, 5.3% to 8.0%; $n = 89$). The reason for stopping treatment had not been recorded for 7.2% (95% CI, 5.9% to 8.7%; $n = 97$) of the patients.

DISCUSSION

There are a number of reasons why additional sources of information may be useful to augment RCT data and to investigate the extent to which findings from such studies may be generalized to routine practice. The entry criteria for RCTs comparing asthma therapies are generally

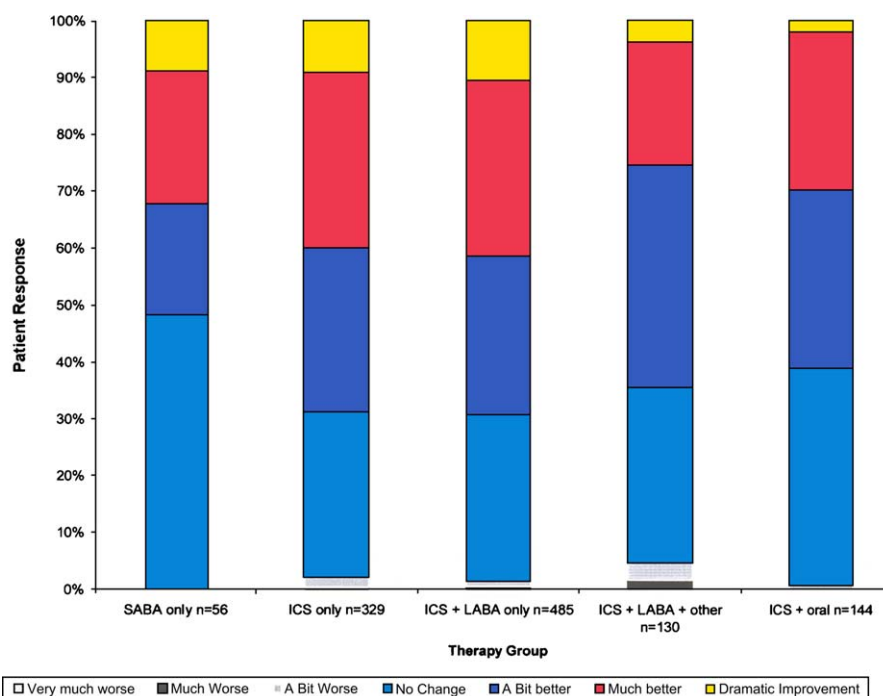


FIG 3. General asthma response according to therapy group before initiation.

rigorous, and such RCTs include frequent medical assessments and monitoring of lung function, symptoms, and health status. As a consequence, many of the patients treated in everyday practice are underrepresented in RCTs, and the findings from such studies cannot automatically be extrapolated to them. There is evidence showing that compliance with inhaled therapy is often poor¹³ and that deficiencies in inhaler technique may occur.¹⁴ These and other real-life constraints may affect the translation of pharmacologic efficacy into clinical effectiveness. There is also some evidence that in more real-life (pragmatic trials) settings, the comparative clinical effectiveness of LTRAs may be greater than suggested by tightly controlled RCTs.¹⁵

The aims of this study were to assess the effectiveness and tolerability of montelukast in the treatment of asthma in everyday clinical practice in representative patient groups, by using a retrospective cross-sectional survey of routinely collected clinical information. Pilot studies allowed refinement of the questionnaires and confirmed the accuracy and reproducibility of the data collected from the patient records. By using the 3 questionnaires (independent observer, physician, and patient) it was possible to compare assessments of the clinical effectiveness and tolerability of montelukast from 3 perspectives. To our knowledge, no comparable multiperspective comparisons of asthma therapies have been performed. It is interesting to note that very similar overall assessments of effectiveness and tolerability outcomes emerged from all 3 data sources, and patterns of response and side effects were similar to those found in published RCTs of montelukast.^{7,8} Overall, the level of response was rated

slightly higher by the physicians than by the independent observers and was rated highest by the patients themselves (this is reassuring, although self-selection bias cannot be excluded). The magnitudes of the differences in assessments were small and did not greatly affect the overall pattern of response observed.

Although it is possible to present only the main outcome data (ie, general asthma response) in this report because of space constraints, a similar pattern of outcome responses was seen from all the assessed asthma outcome parameters (activity symptoms, quality of life, cough, and sleep disturbance) for all patient groups. Most patients showed improvements in asthma control in all outcomes measured. The overall pattern of asthma response documented for all patient groups and asthma outcome categories indicated approximately one third of patients showing no improvement or deterioration, one third having better asthma control, and one third having much or dramatically improved asthma control recorded.

The degree of response to clinical parameters was assessed in relationship to asthma treatment at the time of montelukast initiation. Although there was a tendency for higher positive assessments of response in patients receiving lower treatment levels, most patients at all treatment levels, including those receiving maintenance oral corticosteroid therapy, were assessed as showing clinical improvements. This is of interest because there is a paucity of information of the effectiveness on LTRAs in more severe asthma; 1 short trial of patients with moderate and severe asthma at a tertiary care center failed to show benefits.¹⁶ From 5% to 10% of patients were recorded as showing dramatic responses

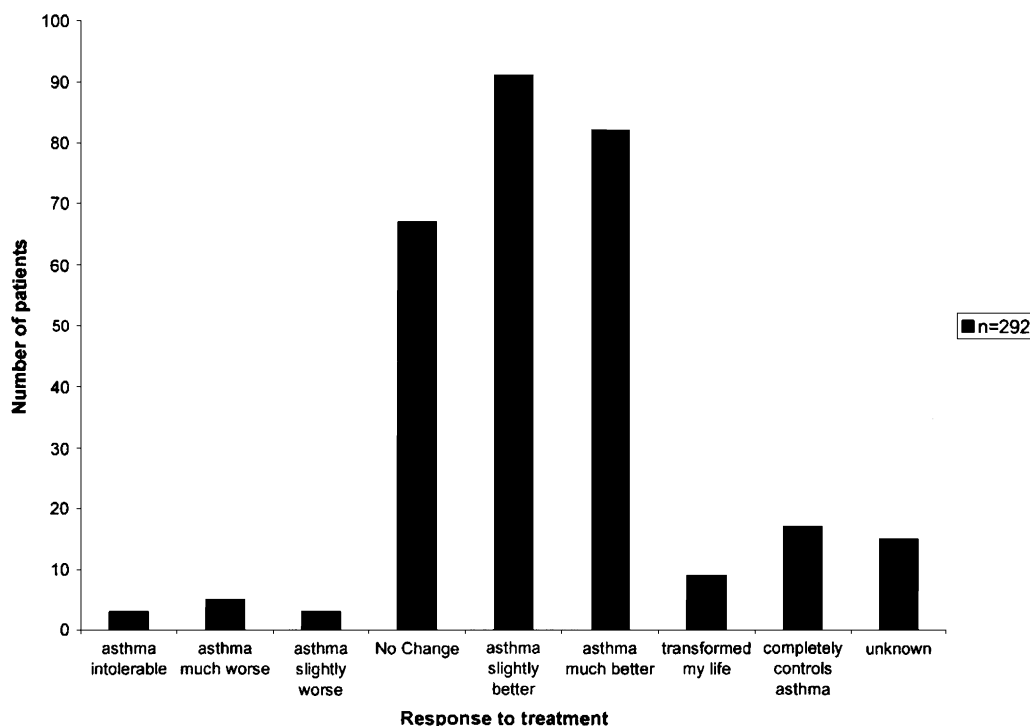


FIG 4. Patient questionnaire "Overall effect of Montelukast."

TABLE III. Individual logistic regression results

Factor	Odds ratio (95% CI)	P value
Child compared with adult	1.31 (1.02-1.68)	.034
Male compared with female	1.27 (1.00-1.62)	.046
Hospital compared with GP center	1.08 (0.84-1.38)	.56
Duration of asthma (3 groups)		.11
Treatment subgroup (5 groups)	See text	.048
Other atopy (yes compared with no)	1.17 (0.93-1.48)	.18
Acute exacerbation at initiation (yes compared with no)	0.97 (0.76-1.23)	.81
Activity-induced asthma at initiation (yes compared with no)	1.56 (1.18-2.06)	.002
Reduction of ICS at initiation (yes compared with no)	1.05 (0.81-1.36)	.73
Sleep disturbance at initiation (yes compared with no)	1.35 (1.02-1.80)	.038
Comorbidity at initiation (yes compared with no)	1.24 (0.92-1.66)	.17

ICS, Inhaled corticosteroid.

to montelukast. This was irrespective of age, premontelukast treatment group, or duration of asthma, with a pattern of slightly higher levels of dramatic response seen in patients receiving lower levels of asthma treatment. It would seem that montelukast is an effective asthma treatment for most patients.

The survey deliberately included several pediatric respiratory centers to gain information on the response of children with asthma, and this is reflected in the high proportion of patients aged <16 years in the analysis; this mirrors overall asthma prevalence figures.¹⁷ Primary and secondary care centers were included to allow assessment of representative patient groups and to enable review of the responses seen for a variety of subgroups. Information

collected from the clinical records included demographic data, information on comorbidity with rhinitis, and reasons for the addition of montelukast. The most common reason for initiating treatment with montelukast was worsening asthma or an acute exacerbation. However, activity-induced asthma symptoms, sleep disturbance, desire of the prescriber to limit the dose of ICS, and the presence of comorbid atopic conditions that the prescriber hoped would also be improved by montelukast were also relatively common. It seems from this survey that prescribers are initiating montelukast in line with the published RCT data on efficacy, as add-on therapy for poorly controlled asthma, for activity-induced asthma, and in the aspiration to treat other comorbid conditions that

may be mediated by leukotrienes. Logistic regression analysis was performed in an attempt to identify baseline characteristics that may predict a response to LTRAs. The single most important factor was activity-induced asthma at initiation. This was associated with age, sex, and sleep disturbance; the utility of these findings is disappointing. We lack clinical or biological predictors of likely responsiveness to LTRAs; therefore, a therapeutic trial remains the only realistic strategy for assessing clinical responsiveness. Of the patients with documented comorbid rhinitis, improvements in rhinitis were seen in approximately 55% of those with a recorded response.

Adverse events possibly related to montelukast occurred in a proportion similar to those seen in the montelukast and placebo groups in RCTs.^{6,18,19} Montelukast was discontinued in one third of patients for a variety of reasons, principally noneffectiveness. It is encouraging to see evidence of appropriate clinical behavior emerging from this survey on the part of physicians such as the discontinuation of treatment in those in whom the drug proved ineffective. The long median duration of treatment (>15 months) for those continuing treatment reassures us that “regression to the mean” effects are unlikely to play a major confounding role in the assessments.

The results of this survey should reassure the clinician that montelukast seems to produce results in everyday clinical practice—as assessed by prescribing physicians, independent assessors of clinical records, and the patients themselves—similar to those reported in controlled clinical trials.

APPENDIX 1. MEMBERS OF THE MONTELUKAST STEERING COMMITTEE

Greta Barnes, founder and past chief executive, National Respiratory Training Centre, Warwick; Professor Neil Barnes, Consultant Respiratory Physician, The London Chest Hospital, London; Dr. John Costello, Consultant Physician, King's College School of Medicine & Dentistry, London; Dr. Mark Everard, Consultant Pediatrician, Sheffield Children's Hospital, Sheffield; Dr. Siobhán O'Sullivan, Lecturer, Department of Clinical Immunology, Royal Free and University College, London School of Medicine; Dr. Mike Pearson, Consultant Physician, Aintree Chest Hospital, University of Aintree, Liverpool, and Director, Clinical Effectiveness and Evaluation Unit, Royal College of Physicians, London; Dr. Gavin Petrie, Consultant Physician, Victoria Hospital, Kirkcaldy, Fife; Professor David Price, General Practice Airways Group, Professor of Primary Care, University of Aberdeen, Aberdeen; Dr. Glennis Scadding, Consultant Physician, Royal National Throat, Nose & Ear Hospital, London; Dr. Mike Thomas, GPIAG Clinical Research Fellow, Department of General Practice and Primary Care, University of Aberdeen,

Aberdeen; Stephanie Wolfe, Respiratory Specialist Nurse, Primary Research Ltd, Thorpe End, Norwich; and David Thompson, Applied Statistics, Romsey, Hampshire.

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