

Asthma and allergy medication use and costs among pediatric primary care patients on asthma controller therapy

Sazonov-Kocevar V, Laforest L, Travier N, Yin DD, Van Ganse E.
Asthma and allergy medication use and costs among pediatric primary care patients on asthma controller therapy.

Pediatr Allergy Immunol 2006.

© 2006 The Authors

Journal compilation © 2006 Blackwell Munksgaard

As observational studies in children initiating GINA-Step 3 therapies are scarce, we evaluated outcomes and costs in a primary care cohort. Two-yr retrospective cohort study included French children (age: 6–14) continuously followed in BKL-Thalès database who received ≥ 2 consecutive prescriptions for GINA-Step 3 therapy (=addition of montelukast or other controllers ('other'), such as increasing inhaled-corticosteroid dose (hICS), adding long-acting β agonist (LABA), or ICS + LABA). After matching on gender and propensity score, medication use [rescue (short-acting β agonists), acute (antibiotics (AB), oral corticosteroids (OCS)), allergy (antihistamines, nasal steroids) and other respiratory] was estimated via mean number of prescriptions and mean cost (per child/per month), and cost trends. During 12-month follow-up, children adding montelukast ($n = 71$) vs. 'other' ($n = 213$) had similar asthma rescue/acute and allergy medication use. Subgroup with asthma and allergic rhinitis (A + AR) adding montelukast used less OCS and AB ($p = 0.014$). Two-yr cost trends suggest stable asthma/allergy medication use in montelukast group (€0.83) compared with increase in 'other' (€5.39), which was driven by nasal steroid use [€0.32 ('other') vs. €–0.04 (montelukast), $p = 0.0013$]. In subgroup with A + AR decline in asthma/allergy medication use in montelukast group (€–0.47) vs. increase in 'other' (€11.05), $p = 0.015$, was driven by differences in AB and OCS ($p = 0.04$) and nasal steroid use ($p = 0.001$). Concomitant asthma/allergy medication use was similar in children adding montelukast or 'other' controllers (hICS, LABA, ICS + LABA), while children with allergic rhinitis on montelukast used less AB. Concomitant medication costs after addition of montelukast remained stable, while 'other' group experienced increase, especially in children with concomitant allergic rhinitis.

Vasilisa Sazonov-Kocevar¹, Laurent Laforest², Noemie Travier², Donald D. Yin¹ and Eric Van Ganse²

¹Merck & Co. Inc., Whitehouse Station, NJ, USA,

²Unité de Pharmacopépidémiologie, Hôpital Lyon Sud, Pierre Benite, France

Key words: asthma; children; control; costs; medication use

Eric Van Ganse, Unité de Pharmacopépidémiologie
EA3091, Hôpital Lyon Sud, 165 Chemin du Grand
Revoyet, Oullins 69921, France
Tel.: +33 472 66 64 38
Fax: +33 472 66 64 44
E-mail: eric.vanganse@recherche.univ_ly.n1.fr

Accepted 13 July 2006

Asthma is the most important chronic childhood respiratory disease, and is frequently confounded by the presence of comorbid allergic rhinitis. There is wide consensus that asthma and allergies are increasing in the pediatric population throughout the western world, with substantial variations between countries (1, 2). While the prevalence of asthma has risen, the severity of asthma attacks and sleep disturbances seems to

be increasing in parallel (3) suggesting increased morbidity. Consequently, the economic burden of asthma and associated diseases is high, particularly among children (4).

Resource utilization related to asthma reflects how well the disease is managed. The use of rescue medications to control asthma exacerbations suggests a poor level of control and subsequently increased utilization and cost of

medications. In adults, asthma-related costs increase significantly with increasing asthma severity and decreasing control (5). A recent evaluation of asthma-related health care costs demonstrated that total resource costs were significantly higher in children with severe asthma when control of asthma was poor (6). Children with asthma also use more health-related services than non-asthmatics (7), while children with asthma and comorbid allergic rhinitis use more resources than children with asthma alone. It is therefore important to study interventions that could improve asthma, which may result in decreased resource use, especially in more vulnerable subgroups as for example asthmatic children with allergic rhinitis.

Current asthma guidelines recommend the use of controller therapy to reduce inflammation and control asthma symptoms in patients with mild to severe asthma (GINA). Treatment with inhaled corticosteroids (ICS) is the preferred first choice, and is recommended for GINA-Step 2 therapy. If Step 2 therapy is not adequate, therapeutic options for GINA-Step 3 therapy include increasing ICS dose to a high dose (hICS; i.e., beyond the low dose appropriate for Step 2), addition of a long-acting β agonist (LABA), or addition of a leukotriene receptor antagonist (LTRA). These recommendations are based on clinical trial evidence, which is abundant for all treatment alternatives. However, efficacy in children has been more thoroughly demonstrated for montelukast (Singulair package insert), which is one of the most widely studied medications for use in children in general. In addition, observational data suggest benefits of these treatment alternatives in real-world clinical practice.

Several observational studies in children have evaluated montelukast vs. ICS in clinical practice and have generally found that asthma-related health care resource use in children treated with montelukast did not differ from ICS in a real-world setting. In children aged 2–5 yr, montelukast use was associated with significantly lower rate of emergency visits for asthma than fluticasone use (9). The use of specific controller agents and the need for asthma-related resources was examined in a group of asthmatic children with allergic rhinitis as well; these results showed that initiating montelukast resulted in lower costs of asthma-rescue and allergy medications compared with initiating ICS (11). The only available observational study comparing addition of montelukast to ICS vs. increased dose of ICS or ICS + LABA combinations was conducted in Italy. It showed similar reduction in asthma attacks, hospitalizations and asthma

rescue/acute medication use in all three groups (12).

An analysis of the relationship between the use of specific controller agents and the need for asthma-related resource utilization in children may further establish the value of therapies that provide better asthma control. The purpose of this study was to evaluate asthma-rescue/acute and allergy medication use and cost among asthmatic children receiving either montelukast (added to ICS) or hICS, LABA or a combination of ICS and LABA for their asthma treated by general practitioners (GPs) across France.

Methods

Study design

This study was a 2-yr retrospective, observational, cohort study with data collection period from 1/1/2000 to 12/31/2002. The study consisted of a 12-month period prior to the initiation of an asthma controller medication, introduction of GINA-Step 3 controller agent (index date) extending for 1 yr during 2001, and a 12-month period post-initiation of controller medication. Every child had a complete 2-yr observation period.

Data source

The data were obtained from the BKL Thalès medical records database that contains longitudinal patient information from 1010 GPs throughout France. This database has been validated and previously used in health services research (5). Data from over one million patients are recorded including patient age, gender, professional status, medical diagnosis and history, visits to GPs, and prescription information (name of drug, dose, and duration of treatment). Patients were assigned unique identifier numbers to preserve anonymity. The costs of current medications were obtained from records of the official drug cost of France (Vidal).

Study cohort

Patients with an asthma diagnosis aged 6–14 yr old, who started GINA-Step 3 therapy (GINA), and having a continuous enrollment in the database were identified using the records from French GPs (Fig. 1). Patients with at least one visit to GP 10 months or more before the index date and at least one visit 10 months after the index date were selected. Exclusion criteria included cystic fibrosis, bronchopulmonary

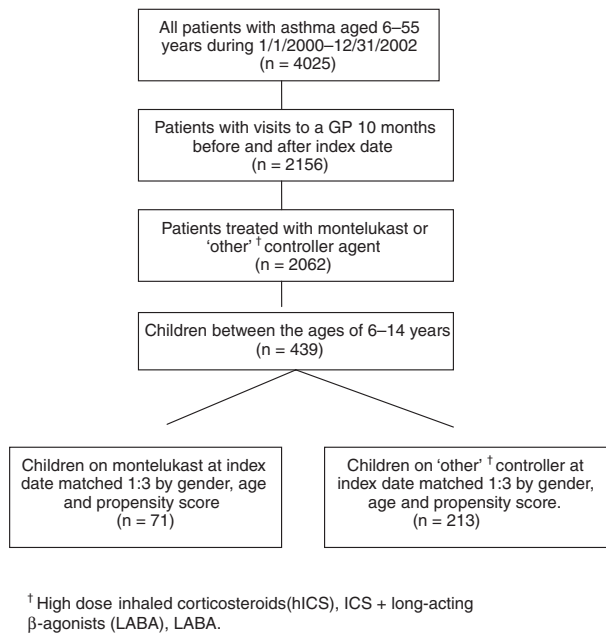


Fig. 1. Flow chart of patient selection.

hyperplasia or chronic obstructive pulmonary disease (COPD).

Patients were divided into two exposure groups: Group 1 ('montelukast') received at least one (index) prescription for montelukast and Group 2 ('other') received at least one (index) prescription for hICS, LABA, or ICS + LABA, between 1/1/2001 and 12/31/2001. In each group, patients had to receive at least one prescription for the same Step 3 controller as the index prescription in the 12-month follow-up period. High-dose ICS was defined using GINA guidelines (GINA). In the montelukast group, 40% of patients were also on stable doses of ICS in accordance with Step 2 of the GINA guidelines (GINA) while some may have dropped ICS therapy upon introduction of montelukast.

In order to minimize differences between exposure groups observed at baseline, patients were matched 1:3 (montelukast:'other') based on gender, and propensity score. The propensity score was used as a control to address the possibility of selection bias leading to choice of a particular controller agent for a particular patient (13), hence to minimize the 'channeling' effect and account for differences in unobservable characteristics. Multiple logistic regression analysis was used to develop propensity scores predicting the probability of being assigned to one treatment group vs. another based on known baseline characteristics including sex, age, number of non-respiratory comorbidities, presence of rhinitis and/or sinusitis, other respiratory disease,

3-month prior use of short-acting β -agonists (SABA) and/or other asthma medications, 12-month prior use of oral corticosteroids (OCS), antibiotics (AB), allergy medications, ICS, and asthma severity score. ICS use was further defined using a 4-category variable (no use, use divided into tertiles). Comorbidities were included that had one or more diagnoses in the 12-month period prior to the index date. The asthma severity score is a 4-category variable calculated using an algorithm based on SABA use and OCS prescriptions for the 12 months preceding the index date (14). This algorithm has been validated for use in administrative databases studying resource utilization for asthma-related outcomes (14) and has been used in previous analyses (11, 15). A subgroup of patients with a history of concomitant allergic rhinitis in the montelukast group and the 'other' group was identified based on prescription history. In the matching process, subjects in the 'other' group were eliminated after three subjects were found for every montelukast subject.

Outcomes

Study outcomes were: observed use of asthma rescue medications (SABA), acute medications used to control exacerbations (AB and OCS), other asthma agents (mast cell stabilizers, xanthines, other LTRAs than montelukast), allergy medications (antihistamines and nasal steroids), and all of the agents combined. Although not recommended by guidelines, the use of AB to alleviate asthma exacerbations has been previously observed in clinical practice (Bukstein 2003) and was therefore included as an outcome. Medication use was measured as the mean number of prescriptions per patient per month and the mean costs per patient per month during the 12 months after introduction of a controller agent (index date), and also as the cost difference between the 12 months after the index date (post) and the 12 months prior to the index date (pre).

Statistical analysis

All statistical analyses were performed using SAS Statistical Software, version 8 (Cary, NC, USA). Descriptive assessment of baseline treatment patterns led to development of the basic study cohort (all new to GINA-Step 3 controller patients) and two exposure groups, montelukast and 'other'. Baseline characteristics were evaluated using chi-square, Kruskal–Wallis or *t*-tests, depending on the type of variable. Analysis required to select a balanced cohort included in

the two groups (montelukast vs. ‘other’) is described above (see *Study Cohort*), where controls were selected in a 1:3 matching process and differences in baseline characteristics were tested to ensure comparability between the two groups.

The number of prescriptions the patients had for asthma rescue, acute asthma and allergy medications during the 12-month follow-up period, and the post-pre-difference and the mean cost of rescue/acute and allergy medications between the 12-month pre- and 12-month post-controller introduction were evaluated using the Kruskal–Wallis tests. A subgroup analysis of the same outcomes (prescriptions and pre-post-trend in costs) in patients with asthma and allergic rhinitis was also performed using the Kruskal–Wallis tests.

Results

Patients

The process used to extract the cohort for this analysis from patients in the Thalés database is described in Fig. 1. There were 439 patients between the ages of 6 and 14 yr old prior to 1:3 matching. The proportion of patients taking montelukast was 16.2% of the total. Patients on ‘other’ controller medications included 24.4% of patients on fixed combination (ICS + LABA) and 2.5% of patients on customized combinations of ICS plus LABA, 37.4% on high-dose ICS, and 19.6% on LABA (Table 1). The baseline characteristics before matching are presented in Table 2. After 1:3 matching, there were 284 patients included in the analysis (71 patients in the montelukast group and 213 patients in the

‘other’ group) (Table 1). The mean age was 9.6 yr for both groups and 65% of patients were males. The majority of patients had mild intermittent asthma as determined based on prior SABA and OCS use (14). From these patients, 46.5% in the montelukast group and 50% in the ‘other’ group had comorbid allergic rhinitis. Baseline characteristics after matching were not significantly different for any parameters between the montelukast and ‘other’ group (Table 2, notes).

Outcomes – medication use

During 12-month follow-up post-introduction of GINA-Step 3 therapy, there was no difference in asthma/allergy medication use in patients adding montelukast to ICS as well as in those who took montelukast as monotherapy, compared with patients using other controllers (High-dose ICS, ICS + LABA, LABA) (Table 3). Numerical trend suggested slightly lower use of OCS (0.54 Rx/patient/yr montelukast vs. 0.70 Rx/patient/yr ‘other’, $p = 0.061$) in the montelukast group. *Post hoc* analyses comparing ICS + montelukast vs. ICS + LABA, and ICS + montelukast vs. high-dose ICS, which would be the comparisons in accordance with the guideline recommendations, also showed no difference between asthma and allergy medication use (data not shown).

In the subgroup of children with asthma and allergic rhinitis, significantly lower use of AB (1.27 Rx/patient/yr montelukast vs. 1.94 Rx/patient/yr ‘other’, $p = 0.012$), other asthma medications (0.00 Rx/patient/yr montelukast vs. 0.22 Rx/patient/yr ‘other’, $p = 0.029$) and all rescue/acute/allergy medications combined

Table 1. Children (6–14 yr) on asthma controller treatment at index date prior and post-matching

	Patients n (% of total)				
	Prior to matching (baseline)	Post-matching (primary analysis, all children: montelukast vs. ‘other’*)	Post-matching (primary analysis, children with concomitant allergic rhinitis: montelukast vs. ‘other’*)	Post-matching (<i>post hoc</i> analyses, all children: ICS + montelukast vs. ICS + LABA† and ICS + montelukast vs. high-dose ICS‡)	
Total cohort	439	284	132	78	117
Montelukast	71 (16.2)	71 (25)	33 (25)	14§ (18)	14§ (12)
Other controllers	368 (83.8)	213 (75)	99 (75)		
ICS + LABA	118 (26.9)			64 (82)	
High-dose ICS	164 (37.4)				103 (88)
LABA	86 (19.6)				

ICS, inhaled corticosteroids; LABA, long-acting β -agonist.

*Primary analysis comparing montelukast (40% of children also received ICS at baseline) vs. other controllers (including ICS + LABA fixed or not, high-dose ICS as per GINA guidelines, LABA) as prescribed by physicians in primary care setting in France.

†*Post hoc* analysis comparing ICS + Montelukast vs. ICS + LABA (fixed or not).

‡*Post hoc* analysis comparing ICS + Montelukast vs. high-dose ICS.

§All patients received Montelukast added to ICS during the first 3 months after the index date.

Outcomes and costs among children on asthma controller therapy

Table 2. Key baseline characteristics for all children before matching and after matching*

	Before matching		p-value§
	Montelukast† n = 71	Other controllers‡ n = 368	
Age, mean (s.d.)	9.56 (2.33)	10.05 (2.48)	0.11
Boys, n (%)	47 (66.2)	234 (63.6)	0.67
Girls, n (%)	24 (33.8)	134 (36.4)	
Asthma severity¶, n (%)			
Mild intermittent	42 (59.2)	234 (63.6)	0.64
Mild persistent	19 (26.8)	94 (25.5)	
Moderate persistent	7 (9.9)	33 (9.0)	
Severe persistent	3 (4.2)	7 (1.9)	
Allergic rhinitis, n (%)	33 (46.5)	184 (50)	0.59
Sinusitis, n (%)	16 (22.5)	100 (27.2)	0.42
Respiratory disease**, n (%)	60 (84.5)	320 (87)	0.58
12-month prior rescue β -agonists (short-acting), n (%)	28 (39.4)	113 (30.7)	0.15
12-month prior inhaled corticosteroids (ICS), n (%)	28 (39.4)	58 (15.8)	0.0002
12-month prior oral corticosteroid prescriptions, mean (s.d.)	0.51 (1.03)	0.38 (0.73)	0.46
12-month prior antibiotics prescriptions, mean (s.d.)	1.65 (1.94)	1.61 (1.72)	0.63

*Baseline characteristics for children with asthma and allergic rhinitis were evaluated before and after matching (data not shown). The two groups did not differ in any observable characteristic after matching 1:3 on gender and propensity score.

†~40% of children also received inhaled corticosteroids (ICS) at baseline.

‡Other: high-dose inhaled corticosteroids (hICS), long-acting β -agonists (LABA) or LABA plus ICS.

§Chi-square test for homogeneity of variance, Kruskal–Wallis test and *t*-test for continuous variables.

¶Asthma severity defined by asthma severity algorithm (14) based on prescription history.

**Respiratory disease included tonsillitis, rhinorrhea, acute upper respiratory conditions, non-atopic conjunctivitis, chronic otitis media, nasal polyposis, eustachian tube disorders.

Table 3. Asthma rescue/acute and allergy medication use among all children with asthma on controller therapy during the 12-month follow-up period (primary analysis†)

	Mean number of prescriptions per patient per yr (s.d.)		
	Montelukast‡ n = 71	Other controllers§ n = 213	p-value¶
Total**	6.20 (4.35)	6.92 (4.42)	0.204
Rescue β -agonists (short-acting)	1.32 (1.40)	1.34 (1.42)	0.878
Acute	2.18 (2.73)	2.60 (2.49)	0.056*
Antibiotics	1.65 (2.14)	1.90 (1.93)	0.109
Oral corticosteroids	0.54 (0.98)	0.70 (0.93)	0.061*
Other asthma medications††	0.07 (0.31)	0.25 (0.92)	0.154
Allergy	2.62 (2.37)	2.73 (2.50)	0.804
Antihistamines	1.70 (1.58)	1.73 (1.95)	0.749
Nasal steroids	0.92 (1.28)	1.00 (1.28)	0.490

MON, montelukast.

* $p < 0.1$.

†Two *post hoc* analyses (ICS + MON vs. ICS + LABA and ICS + MON vs. hICS) described in the text found no difference in outcomes studied between treatment groups.

‡40% of children also received inhaled corticosteroids (ICS) at baseline.

§Other controllers: high-dose inhaled corticosteroids (hICS), long-acting β -agonists (LABA) or LABA plus ICS.

¶Kruskal–Wallis test.

**Total includes rescue β -agonists (short-acting), acute medications (antibiotics, oral corticosteroids), other asthma medications and allergy medications (antihistamines and nasal steroids).

††Xanthines, mast cell stabilizers, anti-leukotrienes other than montelukast.

(5.30 Rx/patient/yr montelukast vs. 7.62 Rx/patient/yr ‘other’, $p = 0.013$) was observed in children treated with montelukast (42% also

used ICS) compared with children using either high-dose ICS, LABA or ICS + LABA combinations (Table 4).

Table 4. Asthma rescue/acute and allergy medication use among children with asthma and allergic rhinitis† on controller therapy during the 12-month follow-up period

	Mean number of prescriptions per patient per yr (s.d.)		
	Montelukast‡ n = 33	Other controllers§ n = 99	p-value¶
Total††	5.30 (3.76)	7.62 (4.52)	0.013**
Rescue β -agonists (short-acting)	0.91 (1.26)	1.35 (1.57)	0.151
Acute	1.61 (2.47)	2.43 (2.36)	0.014**
Antibiotics	1.27 (1.99)	1.94 (1.89)	0.012**
Oral corticosteroids	0.33 (0.65)	0.49 (0.86)	0.375
Other asthma medications‡‡	0.00 (0.00)	0.22 (0.71)	0.029**
Allergy	2.79 (2.46)	3.61 (2.39)	0.071*
Antihistamines	1.79 (1.75)	2.26 (1.83)	0.189
Nasal Steroids	1.00 (1.30)	1.34 (1.29)	0.103

* $p < 0.1$.

** $p < 0.05$.

†Baseline characteristics between the two groups of patients with asthma and allergic rhinitis (defined via diagnosis) were similar after 1:3 matching on gender and propensity score.

‡42% of children also received inhaled corticosteroids (ICS) at baseline.

§Other controllers: high-dose inhaled corticosteroids (hICS), long-acting β -agonists (LABA) or LABA plus ICS.

¶Kruskal–Wallis test.

††Total includes rescue β -agonists (short-acting), acute medications (antibiotics, oral corticosteroids), other asthma medications and allergy medications (antihistamines and nasal steroids).

‡‡Xanthines, mast cell stabilizers, anti-leukotrienes other than montelukast.

Outcomes – medication costs

The mean cost calculated as the number of prescriptions per patients multiplied by the published drug cost (Vidal) showed that patients treated with montelukast had a mean cost for all rescue and acute asthma and allergy-related medications of €9.34 compared with €13.88 for ‘other’ treatments, $p = 0.218$, a difference of €4.54 per patient per month. The mean cost for acute medications (combined AB and OCS) was significantly lower for patients on montelukast compared with patients on ‘other’ controller agents (€2.70 montelukast vs. €3.87 ‘other’, $p = 0.045$). Mean costs for SABA, AB, OCS, other asthma medications (mast cell stabilizers, xanthines, LTRAs), and allergy medications (antihistamines, nasal steroids) were similar among groups.

Analysis of trends in costs between 12-month period prior to GINA-Step 3 controller introduction compared with the 12-month period post-treatment escalation suggests the following. The overall cost increase for asthma and allergy medications for patients taking montelukast was €0.83 compared with €5.39 for patients taking ‘other’ controllers, $p = 0.076$. The costs for SABA (€0.71 vs. €0.74), AB (€0.35 vs. €0.73), and OCS (€0.09 vs. €0.44) for montelukast vs. ‘other’ respectively numerically favored montelukast but were not statistically different. There was a decrease in costs in the montelukast group and an increase in costs for ‘other’ controllers for other respiratory medications (€−0.19 vs. €1.06) and for antihistamines (€−0.11 vs. €2.10). A significant decrease in nasal steroid costs was observed among montelukast patients compared with ‘other’ treatment groups (€−0.04 vs. €0.32, $p = 0.0013$).

For the subgroup of patients with comorbid allergic rhinitis, the overall cost of asthma-rescue/acute medications and allergy medications decreased in the montelukast group (€−0.47) compared with significant increase in ‘other’ controller group (€11.05) ($p = 0.015$) (Fig. 2). The costs of AB (€−0.36 montelukast vs. €2.20 ‘other’, $p = 0.042$) and nasal steroids (€−0.14 montelukast vs. €0.55 ‘other’, $p = 0.001$), and acute medications (€−0.31 montelukast vs. €2.49 ‘other’, $p = 0.038$) were also significantly lower in the montelukast group compared with ‘other’ controllers in the post-period compared with the pre-period. Trends in costs for SABA (€0.24 montelukast vs. €0.76 ‘other’, $p = 0.065$), OCS (€0.09 montelukast vs. €0.44 ‘other’, $p = 0.690$), other asthma medications (€0.09 montelukast vs. €0.44 ‘other’, $p = 0.690$), allergy medications

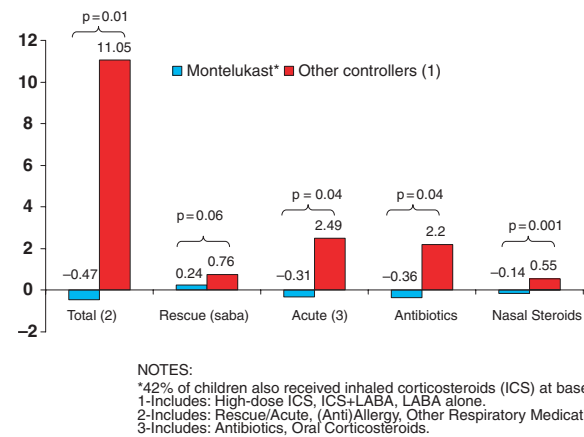


Fig. 2. Trend in asthma rescue/acute and allergy medication cost (Euro per patient per month) 1-yr prior to and 1-yr post-initiation of controller medication among children with asthma and allergic rhinitis.

(€−0.39 montelukast vs. €6.35 ‘other’, $p = 0.150$), and antihistamines (€−0.25 montelukast vs. €5.80 ‘other’, $p = 0.534$), suggest stable use in the montelukast group and numerical but not statistically different increase in the ‘other’ controller group (Fig. 2).

Discussion

This long-term retrospective pre- post-cohort study, based on primary care records of GPs from France, evaluated concomitant asthma/allergy medication use over 1-yr period among asthmatic children and found no differences in use in children adding montelukast or ‘other’ controllers (high-dose ICS, LABA, ICS + LABA), while subgroup with allergic rhinitis using montelukast had significantly lower use of asthma/allergy medications. Over the 2-yr observation period, the costs of asthma/rescue medications for patients taking montelukast remained stable compared with those taking ‘other’ controllers, which slightly increased particularly because of significant increase in use of nasal steroids. In patients with comorbid allergic rhinitis, overall costs for asthma/rescue, allergy and acute medications remained stable for patients taking montelukast, and increased significantly in children taking ‘other’ controllers. These evaluations support the concept that leukotriene modifiers and ICS are both effective therapeutic options for long-term control of persistent asthma in children, and a suitable alternative to addition of LABA or increase in ICS dose. There appears to be improved response to montelukast in children with concomitant allergic rhinitis.

Current therapeutic guidelines for the management of asthma recommend the use of ICS in patients with chronic mild to severe asthma with the option of addition of LABA or a leukotriene modifier if symptoms are not controlled (GINA). However, the guidelines do not specify which of the optional therapies provide the best clinical outcome or cost effectiveness. Additionally, the asthma guidelines have been developed from experience with results from large clinical trials. Data from these trials specifically address only efficacy and safety endpoints in a highly selected cohort of patients. Observational studies can supplement efficacy data and help determine the effectiveness of therapies in a real-world setting with heterogeneous populations and their subsequent behaviors.

In the current study, the actual use of concomitant asthma-related medications to manage symptoms and improve asthma control was similar among montelukast, high-dose ICS, ICS plus LABA or LABA treatment groups. Asthma/allergy medication costs remained stable in the montelukast group, and increased in the 'other' groups, especially in children with allergic rhinitis suggesting additional allergy control provided by montelukast. The results of this analysis support previous findings from observational studies suggesting similar or reduced use of asthma- and allergy-related resources in children on montelukast vs. ICS and in adults. Similarly, data suggest that adding montelukast to ICS vs. using other controller agents (high-dose ICS, ICS + LABA) resulted in similar reductions in asthma attacks, hospitalizations and concomitant medication use in children (12) and in similar reductions in asthma-related resource use in adults (20–24).

In this study approximately 50% of patients had concomitant allergic rhinitis. In this subpopulation, montelukast had a marked advantage over 'other' controllers. Over 1-yr follow-up period, patients with asthma and allergic rhinitis using montelukast had significantly lower use of OCS and AB ($p = 0.014$), and a nearly significantly lower use of allergy medications ($p = 0.071$) compared with those treated with other controllers. There was a significant difference in cost trends of asthma-rescue/acute medications and allergy medications ($p = 0.015$), acute medications ($p = 0.038$) and as well as AB ($p = 0.042$) and nasal steroids ($p = 0.001$) in children on montelukast compared with 'other' controller therapies. In this group, the increase in costs for SABA was smaller in the montelukast group compared with 'other' controllers ($p = 0.065$). A stable trend in the use and costs of concom-

itant asthma and allergy medications in this population treated with montelukast, as opposed to significant increases in costs in the 'other' controller group, is particularly noteworthy as both adult (25–27) and young (7, 8, 26, 28) asthmatics with comorbid allergic rhinitis have a greater burden in terms of increased likelihood of asthma attacks and increase health care costs because of their asthma compared with asthmatics without allergic rhinitis. Recent studies have demonstrated that treatment of allergic rhinitis improves asthma-related health-care utilization (29, 30). The interrelationship between asthma and allergic rhinitis is supported by the results of this subgroup analysis. Montelukast is the only therapeutic agent approved for treatment of asthma and allergic rhinitis in a single formulation (oral) (Singulair package insert). It is possible that the added benefit in the montelukast treated group (asthma and allergic rhinitis) was because of better control of inflammation because of allergies resulting a reduction in need for asthma-related medications. Recent clinical trials have shown that montelukast was protective against lower and upper airway responses during antigen challenge (31) and significantly relieved allergic rhinitis symptoms while reducing β -agonist use in patients with asthma and allergies (32). Further elucidation of the clinical and economic impact one disease has on the other will provide health-care providers with information on how best to allocate resources.

The long-term observational design of this study and the large size of the population provide additional evidence of the effectiveness of therapies evaluated in this analysis. Cohort studies using health information databases have shown to be accurate in classifying severity and distinguishing various respiratory diseases from each other (33). However, there are limitations to the use of medical records and prescriptions from any database in drawing conclusions about treatment effects. First, evaluation of medication use is based on analysis of prescribed medications rather than actual consumption (includes filling the prescription and adherence/persistence). However, when studies are comparing outcomes across treatment groups, the same measurement conditions apply to all medications under evaluation and this bias is minimized. Secondly, patients are identified by an analysis of claims and not randomized into respective groups, which may lead to an imbalance in patient allocation. To adjust for confounder bias, this study used propensity scores (13) to match patients at baseline. In a review of 43 studies comparing propensity scoring to traditional

regression modeling to adjust for confounding, Shah and colleagues determined that both methods generally gave similar results (34). The propensity score in this study contained variables pertinent to the group studied that best described the model including variables for age, gender, comorbidities, asthma and allergy medications, ICS use, and asthma severity scores. By using the propensity scores and probabilistic matching there were no significant differences in any patients' characteristics after matching suggesting comparable groups for the analysis of outcomes in this study.

Asthma severity, defined by an asthma severity algorithm (14) based on prescriptions for β -agonists and OCS for the 12-month prior to the index date, may also be a limitation. Definition based on prior medication use may be one of the reasons for a large proportion of patients being classified as 'intermittent', which may be inconsistent with the fact they were all commencing GINA-Step 3 therapy recommended by their GP. Although the algorithm has been validated vs. clinical endpoints, it may be subject to a slight 'floor effect'. However, this severity classification served as descriptive parameter and worked consistently across exposure groups (montelukast vs. 'other') suggesting no differences even prior to matching ($p = 0.64$), and therefore comparison of outcomes in this study remains valid and is not subject to confounding by severity.

Another limitation may be the use of exposure groups in this study. As per French guidelines and labeling, montelukast should have been added to ICS, as should LABA. However, treatment practices in this study suggest that this may be the case in a portion of the patients but not everyone. It is also possible that physicians taper off the dose of ICS, especially in children, particularly because of potential side effects of ICS (growth, adrenal suppression, etc.). In order to ensure validity of the results we conducted *post hoc* analyses of ICS + montelukast vs. ICS + LABA and ICS + montelukast vs. high-dose ICS. The results were comparable to those of the main analysis where a proportion of patients on montelukast were not receiving ICS, suggesting that treatment practices of French physicians are tailored to the needs of their patients and at the same time do not jeopardize the outcomes.

Conclusions

This study demonstrated that initiating montelukast therapy in children with asthma, a proportion of whom also used ICS, resulted in similar overall use of concomitant asthma and

allergy medications over 1 yr compared with children increasing the ICS dose, adding LABA or starting ICS + LABA combination therapy. This suggests comparable asthma control. Children with asthma and concomitant allergic rhinitis experienced improved outcomes, for example significantly lower use of OCS and AB, if they were treated with montelukast, suggesting improved asthma control. Costs of concomitant asthma/allergy medications over a 2-yr observation period remained stable in children treated with montelukast and increased in children treated with high-dose ICS, LABA or ICS plus LABA, especially if children also had allergic rhinitis. The latter suggests favorable economic profile of montelukast therapy as an alternative to other GINA-Step 3 recommended medications.

References

1. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: the International Study of Asthma and Allergies in Childhood (ISAAC). *Lancet* 1998; 351: 1225–32.
2. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. Worldwide variation in the prevalence of asthma symptoms: the International Study of Asthma and Allergies in Childhood (ISAAC). *Eur Respir J* 1998; 12: 315–35.
3. MAZIAK W, BEHRENS T, BRASKY TM, et al. Are asthma and allergies in children and adolescents increasing? Results from ISAAC phase I and phase III surveys in Münster Germany. *Allergy* 2003; 58: 572–9.
4. LOZANO P, SULLIVAN SD, SMITH DH, WEISS KB. The economic burden of asthma in US children: estimates for the National Medical Expenditure Survey. *J Allergy Clin Immunol* 1999; 104: 957–63.
5. VAN GANSE E, LAFOREST SL, PIETRI G, et al. Persistent asthma: disease control, resource utilization and direct costs. *Eur Respir J* 2002; 20: 260–7.
6. LAFOREST L, ERNST P, PIETRI G, et al. Asthma-related costs relative to severity and control in general practice. *Pediatr Asthma Allergy Immunol* 2005; 18: 36–45.
7. GRUPP-PHELAN J, LOZANO P, FISHMAN P. Health care utilization and cost in children with asthma and selected comorbidities. *J Asthma* 2001; 38: 363–73.
8. SAZONOV KOCEVAR V, THOMAS J III, JONSSON L, et al. Association between allergic rhinitis and hospital resource use among asthmatic children in Norway. *Allergy* 2005; 60: 338–42.
9. ALLEN-RAMEY FC, ANSTATT DT, RIEDEL AA, MARKSON LE. Comparison of asthma-related resource use in patients initiating montelukast or fluticasone propionate: an age-stratified analysis. Presented at the 2003 Annual Conference of the American college of Asthma Allergy and Immunology (ACAAI), New Orleans, LA.
10. DAVIES GM, DASBACH EJ, SANTANELLO NC, KNORR BA, BRATTON DL. The effect of montelukast versus usual care on health care resource utilization in children aged 2 to 5 years with asthma. *Clin Ther* 2004; 26: 1895–904.

11. LUSKIN A, BUKSTEIN D, SAZONOV KOCEVAR V, YIN D. Asthma rescue and allergy medication use among asthmatic children with prior allergy prescriptions who initiated asthma controller therapy. *Ann Asthma Allergy Immunol* 2005; 95: 129–36.
12. STURKENBOOM MCJM, PICELLI G, SCAMARCIA A, et al. Asthma exacerbations in children receiving montelukast vs. other controllers in Italy. *Eur Respir J* 2005; 26 (Suppl. 49): 618s (P3932).
13. RUBIN DB. Estimating causal effects from large data sets using propensity scores. *Ann Intern Med* 1997; 127: 757–63.
14. LEIDY NK, PARAMORE LC, WARTROUS ML, et al. Development of algorithm for scoring severity of asthma in administrative databases. *Value Health* 1999; 2: 394 (abstract).
15. ALLEN-RAMEY FC, DUONG PT, REIDEL AA, et al. Observational study of the effects of montelukast and fluticasone in subjects matched at baseline. *Ann Allergy Asthma Immunol* 2004; 93: 373–80.
16. ALLEN-RAMEY FC, DUONG PT, GOODMAN DC, et al. Outcomes of patients treated with ICS propionate or montelukast sodium. *Manag Care Interface* 2003a; 16: 30–5.
17. ALLEN-RAMEY FC, ANSTATT DT, SAJJAN SG, et al. Asthma-related health care resource use among patients starting fluticasone or montelukast therapy. *Pharmacotherapy* 2005; 25: 1752–60.
18. BUKSTEIN DA, HENK HJ, LUSKIN AT. A comparison of asthma-related expenditures for patients started on montelukast versus fluticasone propionate as monotherapy. *Clin Ther* 2001; 23: 1589–600.
19. STEMPEL DA, MAUSKOPF J, McLAUGHLIN T, et al. Comparison of asthma costs in patients starting fluticasone propionate compared to patients starting montelukast. *Respir Med* 2001; 95: 227–34.
20. PRICE D, WOLFE S. Montelukast: clinical and cost effectiveness in primary care. *Am J Respir Crit Care Med* 1999; 159: A640.
21. PRICE DB, BEN-JOSEPH RH, ZHANG Q. Changes in asthma drug therapy costs for patients receiving chronic montelukast therapy in the U.K. *Respir Med* 2001; 95: 83–9.
22. ANSTATT D, ALLEN-RAMEY FC, KORELITZ JJ, BETHEL J, SAJJAN S, MARKSON LE. Asthma control with montelukast or salmeterol as add-on therapy to inhaled corticosteroid treatment of asthma. *Chest* 2003; 124: 94S.
23. TRAVIER N, SAZONOV KOCEVAR V, YIN DD, LAFOREST L, VAN GANSE E. Cost of asthma rescue/acute and allergy medications among asthmatic patients on controller therapy. *Eur Respir J* 2004; 24 (Suppl. 48): 344S (P2165).
24. BORDERIAS L, MINCEWICZ G, PAGGIARO P, GUILERA M, SAZONOV KOCEVAR V, BADIA X. Improvement in asthma control and reduction in medical resource use following treatment with montelukast (Practical Study). *Eur Respir J* 2005; 26 (Suppl. 49): 576s (P3692).
25. HALPERN MT, SCHMIER JK, RICHNER R, GUO C, TOGIAS A. Allergic rhinitis: a potential cause of increased asthma medication use, costs, and morbidity. *J Asthma* 2004; 41: 117–26; *J Clin Epidemiol* 2005; 58: 550–9. Epub 2005 Apr 19.
26. YAWN BP, YUNGINGER JW, WOLLAN PC, REED CE, SILVERSTEIN MD, HARIS AG. Allergic rhinitis in Rochester Minnesota residents with asthma: frequency and impact on health care charges. *J Allergy Clin Immunol* 1999; 103: 54–9.
27. PRICE DB, ZHANG Q, SAZONOV KOCEVAR V, YIN D, THOMAS M. Effect of a concomitant diagnosis of allergic rhinitis on asthma-related health care use by adults. *Clin Exp Allergy* 2005; 35: 282–7.
28. THOMAS M, ZHANG Q, SAZONOV KOCEVAR V, YIN D, PRICE DB. Health care resource use by children with asthma and co-morbid allergic rhinitis in general practice in the United Kingdom. *Pediatrics* 2005; 115: 129–34.
29. CRYSTAL-PETERS J, NESLUSAN C, CROWN WH, TORRES A. Treating allergic rhinitis in patients with comorbid asthma: the risk of asthma-related hospitalizations and emergency department visits. *J Allergy Clin Immunol* 2002; 109: 57–62.
30. CORREN J, MANNING BE, THOMPSON SF, HENNESSY S, STROM BL. Rhinitis therapy and the prevention of hospital care for asthma: a case-control study. *J Allergy Clin Immunol* 2004; 113: 415–9.
31. PERRY TT, CORREN J, PHILIP G, et al. Protective effect of montelukast on lower and upper respiratory tract responses to short-term cat allergen exposure. *Ann Allergy Asthma Immunol* 2004; 93: 431–8.
32. PHILIP G, NAYAK AS, BERGER WE, et al. The effect of montelukast on rhinitis symptoms in patients with asthma and seasonal allergic rhinitis. *Curr Med Res Opin* 2004; 20: 1549–58.
33. MCKNIGHT J, SCOTT A, MENZIES D, BOURBEAU J, BLAIS L, LEMIERE C. A cohort study showed that health insurance databases were accurate to distinguish chronic obstructive pulmonary disease from asthma and classify disease severity. *J Clin Epidemiol* 2005; 58: 206–8.
34. SHAH BR, LAUPACIS A, HUX JE, AUSTIN PC. Propensity score methods gave similar results to traditional regression modeling in observational studies: a systematic review. *J Clin Epidemiol* 2005; 58: 550–9.