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Original article

Evaluation of 3–5 months' add-on therapy with montelukast in patients with non-controlled asthma in Austria: the STAR open-label, real-world, observational study

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Abstract

Objective:
To assess the current state of asthma management in Austria and evaluate improvement of symptoms and quality of life (QoL) in asthma patients by adding the controller substance montelukast to existing therapy.

Research design and methods:
Office-based pneumologists across Austria were invited to participate in an open-label, multicenter observational study. Male and female patients aged from 12–50 years with mild or moderate persistent asthma according to GINA guidelines and $FEV_1 > 70\%$ predicted were included if they were on concurrent asthma treatment, but still had persistent symptoms and reduced quality of life. Asthma control was assessed at time of patient anamnesis and subsequent follow-up visits. In addition, a physical examination was performed, lung function (FEV_1) was measured and two types of validated QoL questionnaires were used: the Juniper Asthma Control Questionnaire was evaluated and documented by the physicians at each study visit and the Asthma Quality of Life Questionnaire was completed by the patients following each visit.

Results:
A total of 851 patients (343 males, 508 females) were included and 328 patients were eligible for evaluation 3–5 months after completing at least two study visits. QoL rating by patients was available for 263 at baseline and for 216 patients after 3–5 months. The physicians' rating of asthma-related QoL showed improvements between 6.66 and 11.80% in the categories: nocturnal awakening, morning asthma symptoms, reduction of daily activities, wheezing and dyspnoea, but no reduction in the use of short acting β_2-agonists (SABA). The QoL judged by the patients by means of the QoL-Q showed statistically significant improvements in 13 of 15 parameters of QoL. The categories: response to cigarette smoke and response to air pollution showed positive trends (not significant) while the improvement of shortness of breath, response to dust, frustration, cough, anxiety, chest pressure, sleep quality, worries about asthma, wheezing, symptoms at heavy and moderate exercise and impairment of daily activities and activities at work reached statistical significance.

Conclusion:
This open-label, multicenter observational study shows significant improvement in six QoL parameters evaluated by the physicians and in 13 out of 15 QoL categories judged by the patients 3–5 months after adding montelukast to the ongoing asthma treatment in patients with mild or moderate persistent asthma. Limitations to these conclusions are the lack of a placebo control group (as this was an open-label study) and the continuing basal asthma therapy, which might contribute to improvement of asthma control.

Introduction

During the past 20 years, a large number of scientific advances have led to an improved understanding of the pathophysiology of asthma. This led to the development of new therapeutic approaches and to extended treatment options to manage and control the disease. In order to implement this into clinical practice several national and international guidelines for the assessment, diagnosis and management of asthma have been developed[1–3].

In 1993 the National Heart, Lung and Blood Institute, in collaboration with the World Health Organization, issued a common Report on a Global Strategy for Asthma Management and Prevention[4]. At the same time the Global Initiative for Asthma (GINA) was implemented in order to incorporate results of scientific studies into asthma care and to disseminate and promote information about the care of asthma patients. The first GINA report was issued in 1995, revised in 2002 and updated in November 2006[5].

The goals and objectives of this initiative were to carefully review and improve management of asthma, based on disease severity (severity classification) with treatment options to step up and step down when there was a change in the course of disease. In the recent GINA report this strategy was adapted to the growing evidence that this approach did not lead to an overall control of the disease in many patients. Asthma still has a substantial impact on patients' quality of life (QoL).

The definition of asthma control is mainly based on symptoms control, defined by quality of life parameters like no or minimal day and night symptoms, no limitations on activities (including physical exercise), no or minimal requirements for rescue medications and a near normal lung function and no or infrequent exacerbations.

Numerous studies were initiated to evaluate the proportion of patients whose asthma is totally or well controlled in different regions all over the world. For instance, the Asthma Insight and Reality survey of Europe (AIRE[6]) and the Asthma Insight and Reality survey In the Asian Pacific region (AIRIAP[7]) provided important data on the proportion of patients with regard to their asthma control. Remarkably, they showed that only a minority of patients received appropriate levels of controller therapy.

The Satisfaction with Treatment of Asthma patients in Real life Study (STAR) was designed to evaluate the magnitude of improvement with regards to quality of life and symptoms control through adding a leukotriene receptor antagonist (LTRA) to the existing medication in a real-life setting. In this study, an established step up approach was evaluated and documented under daily life conditions. Airway inflammation and symptoms often persist in asthma patients despite treatment with inhaled corticosteroids (ICSs) and/or long acting $ß_2$-agonists (LABAs).

Besides true lack of response to treatment, poor compliance with medications and deficits in environmental control could be responsible for persistence of inflammation.

Patients and methods

Study objectives

The Satisfaction with Treatment of Asthma patients in Real life Study (STAR) was aimed to assess patterns of actual control of asthma in treated patients in a real-life setting. In Austria, treatment of asthma patients by a pneumonologist reflects 'real life', as patients may see the specialist directly if they choose so, or are referred by a primary care physician to the specialist for further treatment if still symptomatic.

An additional objective was to evaluate the quality of life in patients where montelukast had been added to the existing controller therapy. Quality of life was measured in terms of symptoms control by means of the standardized Juniper Asthma Control Questionnaire (ACQ) (nocturnal awakening, symptoms in the morning, limitations in daily activities, and shortness of breath, wheezing and the usage of short acting $ß_2$-agonists). In terms of patients' functional impairments it was measured by the standardized Juniper Asthma Quality of Life Questionnaire (AQLQ) (symptoms, emotions, exposure to environmental stimuli and activity limitation).

Treatment of comorbidities and improvement of environmental factors, if feasible, were supported by the physician.

Patients

The study was implemented prior to the change of GINA Guidelines in November 2006. With the publication of the GINA Guidelines 2006, the protocol has been amended in order to fit with the qualitative classification as controlled, partly controlled and uncontrolled symptoms.

Data for the asthma control questionnaire (ACQ) as quantified by the physician are depicted in Tables 1a and 1b. The highest achievable sum of points would be 36 according to Table 1b.

In order to compare our results with the recent update of GINA guidelines (November 2006) the classification categories were allocated in the following way:

Symptoms 'never' or 'almost never' were considered as 'controlled', 'rarely' and 'occasionally' as 'partly controlled' and 'frequently', 'most of the time' and 'always' were considered as 'uncontrolled'. Accordingly the number of SABA puffs was categorized as shown in Table 1b.

Table 1a. The six categories of the Asthma Control Questionnaire (ACQ).

1	Nocturnal awakening caused by asthma
2	Morning asthma symptoms
3	Reduction of daily activities
4	Shortness of breath
5	Wheezing
6	Use of short acting β_2-agonists (SABA)

Table 1b. Quantification for QoL categories in the Asthma Control Questionnaire (ACQ).

Points	Symptoms	Use of SABA puffs	GINA classification
0	Never	None	Controlled
1	Almost never	1–2	
2	Rarely	3–4	Partly controlled
3	Occasionally	5–8	
4	Frequently	9–12	Uncontrolled
5	Most of the time	13–16	
6	Always	>16	

SABA: short acting β_2-agonists; GINA: global initiative on asthma; QoL: Quality of Life

This observational trial was designed as an open-label, multi-center study in adolescent and adult asthmatic patients, treated by office based pneumologists in Austria. Sixty pneumologists participated in this program and documented 851 male and female outpatients aged between 12 and 50 years over a period of up to 24 months.

Patients were recruited between April and November 2005. Eligible patients had a documented clinical diagnosis of mild to moderate asthma and an $FEV_1 > 70\%$ according to the GINA guidelines valid in the year 2005. All patients were on concurrent asthma treatment. They could be enrolled by their physicians if symptoms still persisted or significant quality of life impairment prevailed under concurrent treatment and the physician therefore decided to initiate additional treatment with montelukast in an oral dose of 10 mg per day. The add-on treatment with montelukast was only administered to patients who had not been on this drug before. Of the originally screened patients a proportion of 32% had been on montelukast at some time prior to the screening process. These patients were excluded from enrolment. Asthma control was assessed at patient history evaluation (first visit) by measurement of lung function (FEV_1) and by means of the standardized Juniper Asthma Control Questionnaire (ACQ), a validated questionnaire that has strong evaluative and discriminative properties[8].

The questionnaire evaluates six items at each visit which are documented by the physician (Table 1a). Each item was scored on a 0–6 scale (0 = best, 6 = worst, i.e. seven levels) and the ACQ score was expressed as the sum of the six items (0 = best-controlled symptoms, 36 = worst controlled symptoms). As in daily practice, the ACQ score was a common basis for the physicians' decision to add montelukast 10 mg to the current treatment.

Table 2. The four domains of the patients' AQLQ.

Symptoms	Emotions about their asthma
○ Shortness of breath	○ Frustrated
○ Cough	○ Anxiety
○ Chest pressure	○ Worries about asthma
○ Sleep quality	
○ Wheezing	
Activity limitation	Exposure to environmental stimuli
○ Heavy exercise	○ Response to dust
○ Moderate exercise	○ Response to cigarette smoke
○ Daily activities	○ Air pollution
Activities at work	

AQLQ: Asthma Quality of Life Questionnaire

At follow-up visits, which were scheduled every 3 months (up to four visits per year) FEV_1 was measured and asthma control was assessed by evaluation of symptoms. Quality of life was assessed by means of the standardized Juniper ACQ. Data were entered online or in a hard copy version during the patients' visits.

In addition, patients were asked to fill in the standardized Juniper Asthma Quality of Life Questionnaire (AQLQ) at each visit, a 15-item questionnaire which has been developed to measure the functional impairments that are most important for adults with asthma[9]. The items cover four domains which are symptoms, emotions, exposure to environmental stimuli and activity limitation. The questionnaire had to be completed following each visit either online or in a hardcopy version (Table 2).

Statistical analysis

Continuous variables were described by mean and standard deviation, discrete variables by absolute and relative frequencies. Frequencies were compared using the chi-squared test. For continuous variables the *t*-test was used. Because of some missing values different sample sizes have to be considered for some variables.

Results

At baseline evaluation the sample size of patients who were included in the study and received add-on therapy with montelukast was 851. During the time period of 3–5 months after the start of add-on montelukast, 328 patients were still eligible for evaluation by their physician (these results are shown in Figures 2–4). This drop-out rate reflects the fact that many patients did not show up for their scheduled follow up visits, either because they were satisfied with the upgraded therapy or for some other reason.

Table 3a. Demographic data of included patients ($n = 851$).

	Mean	SD	Male	Female
Age	32.5	11.4	31.7	33.1
Weight (kg)	70.6	16.7	77.5	66.0
Height (cm)	169.6	10.4	176.1	165.2

Table 3b. Smoking habits, concomitant allergic rhinitis and FEV_1 of included patients ($n = 851$, for smoking habit $n = 803$).

Smoking habit (%)	Currently	At any time before	Never
	18.1	14.2	67.7
Allergic rhinitis % of 57% total	Perennial	Seasonal	Not allocated
	24.8	29.2	46.1
Allergic rhinitis % of 57% total	Mild	Moderate/ Severe	
	60	40	
Pulmonary function FEV_1 in % predicted	Males	Females	
	81.4	81.1	

FEV_1: Forced expiratory volume in one second

The number of patients who completed and returned the AQLQ was 263 at the beginning and 216 after 3–5 months (Figures 5 and 6).

Demographic data at first evaluation

A total of 851 patients, 343 males (m) and 508 females (f), were included in the study and completed at least two visits after enrolment.

Means and standard deviations of patients' age, weight and height are shown in Table 3a. Additional features such as smoking habits, concomitant allergic rhinitis and pulmonary function are shown in Table 3b.

Smoking habits could be evaluated in 803 patients (325 m, 478 f): 18.1% were currently smoking, 14.2% had smoked at some time previously and 67.7% had never smoked. There was no significant difference between males and females.

Concomitant allergic rhinitis was reported by 57.3% of all asthmatic patients; 24.8% of these had perennial, 29.2% had seasonal rhinitis and in 46.1% the rhinitis could not be associated with either category. Sixty percent of all patients with allergic rhinitis were classified as mild (60.6% in males and 59.6% in females) and 40% as moderate or severe (39.4% in males and 40.4% in females).

Other documented relevant concomitant diseases were: atopic dermatitis in 34 patients, sinusitis in 31, gastroesophageal reflux in 30 and arterial hypertension in 20 patients.

Pulmonary function, measured as FEV_1 in percentage predicted, was 81.4% in males and 81.1% in females.

Asthma medications taken by the patients prior to administration of montelukast as add-on treatment are documented in Figure 1. A great majority of the patients had been treated with a combination of inhaled corticosteroids and long acting $ß_2$-agonists (ICS + LABA).

Asthma control and Quality of Life during add-on therapy with montelukast

Physicians' rating

Figure 2 shows the comparison of asthma control assessed by the physicians prior to and 3–5 months after add-on therapy with montelukast. Fifty percent to 95% of patients, according to the quality of life parameter, are uncontrolled or partly controlled under their concurrent asthma treatment. Poorest asthma control was achieved in shortness of breath and limitations in daily activities.

Figure 3 shows the differences after 3–5 months' add-on montelukast compared to baseline values. It demonstrates a substantial reduction in the number of uncontrolled cases and accordingly an increase in the number of partly controlled and controlled patients.

If all categories of quality of life are compiled to one category 'overall quality of life' a significant improvement in this overall score can be demonstrated. As shown in Figure 4 the mean overall quality of life score improves from 71.6% to 83.5% after 5 months' add-on treatment with montelukast ($p < 0.001$) in all categories (100% defined as 0 = no symptoms).

Patients' rating

The patients' own judgments according to the validated questionnaire containing 15 questions on symptoms, environmental stimuli, emotional functions and limitation of different activities prior to and after 3–5 months of add-on therapy with the LTRA montelukast are shown in Figure 5.

Differences are shown in Figure 6. As can be seen, there is a substantial increase in the number of ratings qualified as controlled asthma. This is evident in all 15 questions and in most of them the increase in score is 10% to 29%.

Tests for statistical significance showed that with the exception of questions 7 (Response to cigarette smoke) and 11 (Response to weather change and air pollution) the improvements were statistically significant at $p < 0.05$.

Discussion

We were able to demonstrate in this open-label, real-world, observational study that adding montelukast to the concurrent asthma treatment leads to a substantial

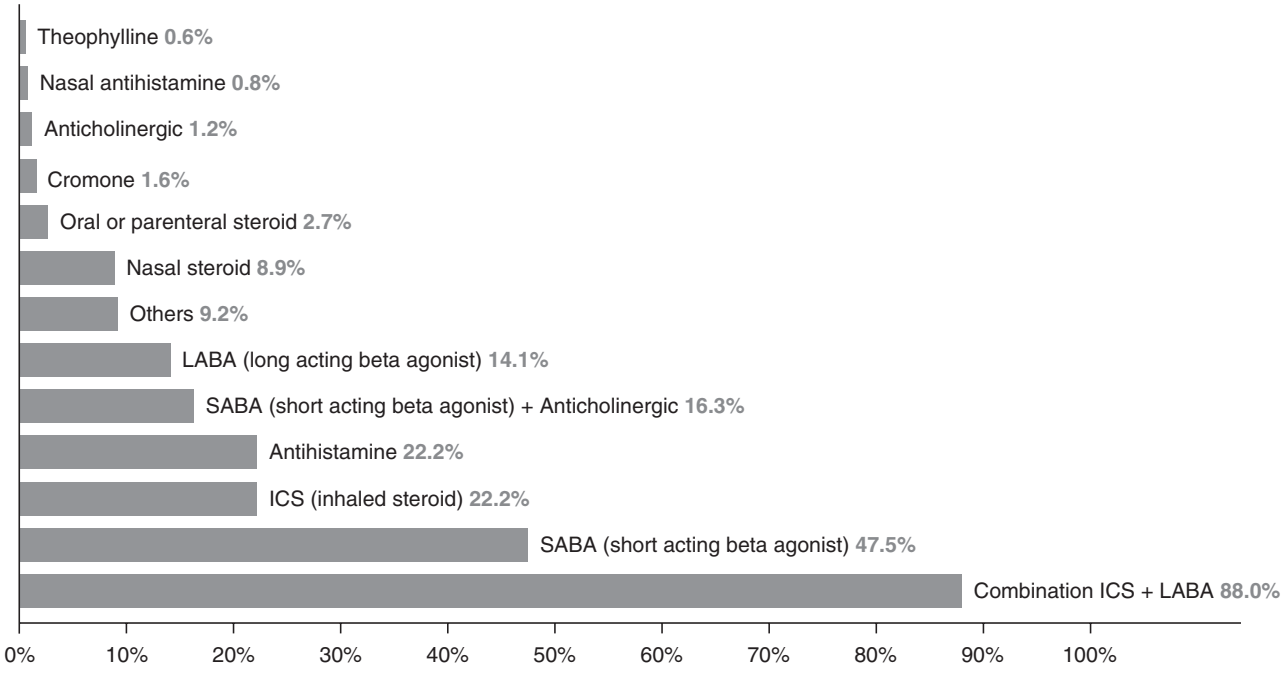

Figure 1. Asthma medication prior to add-on therapy with montelukast ($n = 851$).

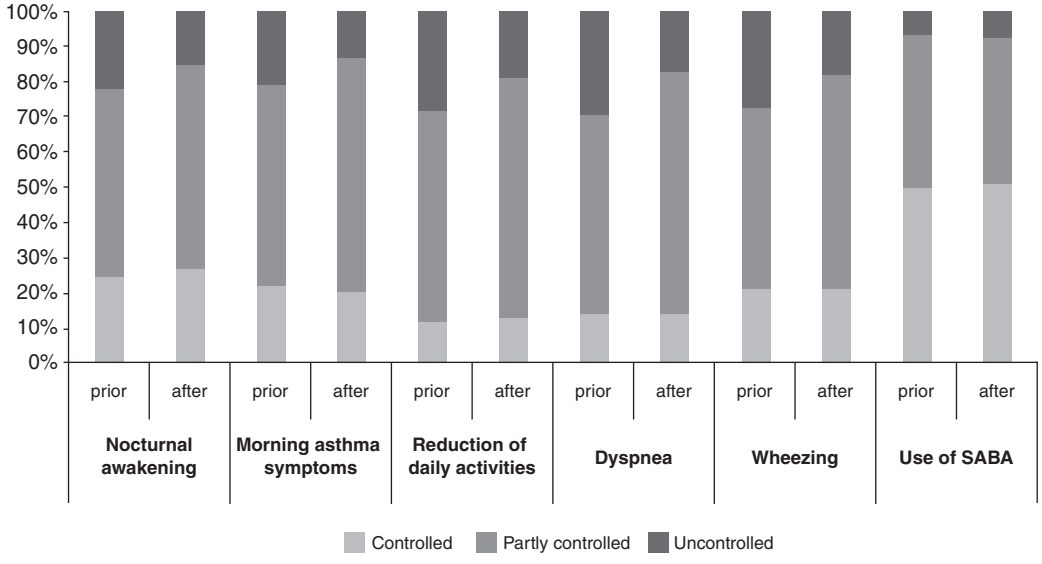

Figure 2. Doctors' rating of Quality of Life (asthma control) prior to and 3–5 months after add-on montelukast ($n = 328$). SABA: short acting beta agonists.

improvement in the overall quality of life in patients who were not sufficiently controlled with ICS or ICS/LABA treatment. However, there are some limitations, as an undetermined number of patients, who were well controlled, were lost to follow up and severe asthmatics did not fulfill inclusion criteria.

Aside from the clinical and economic implications such as suffering from symptoms and absence from school or work due to the disease, there is an additional reason to strive for optimal control: perceiving asthma as a fundamentally inflammatory disorder has led to the notion that this disease process is a biological continuum leading from occasional symptoms to irreversible structural change of the airways which are usually labeled with the term 'airway remodeling', which may finally cause chronic need for treatment[10].

There is now increasing awareness that optimal treatment of asthma should provide a level of control of the

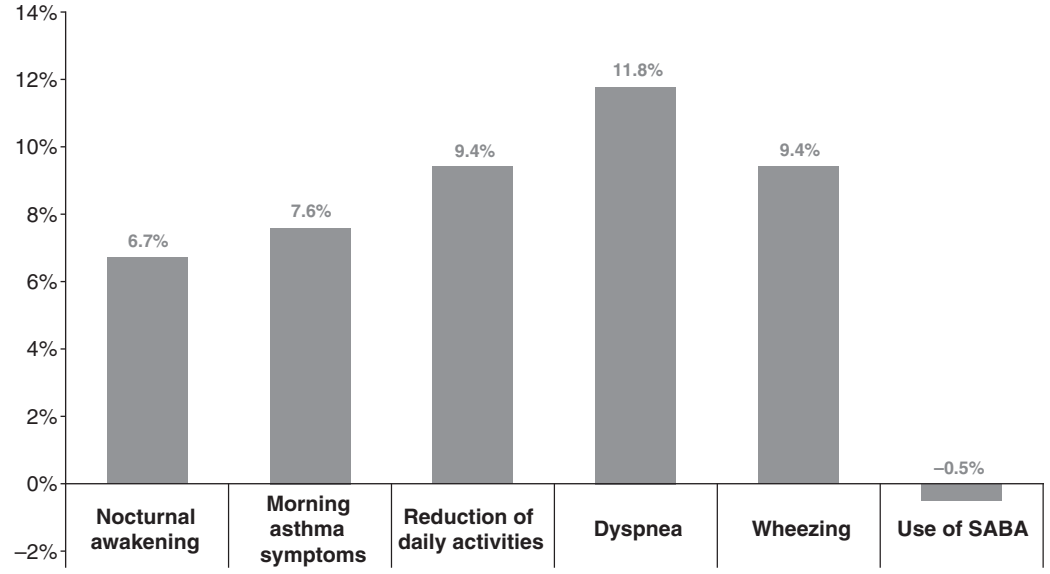

Figure 3. Improvement of Quality of Life from uncontrolled to controlled or partly controlled after 3–5 months' add-on montelukast compared to baseline ($n = 328$). SABA: short acting beta agonists.

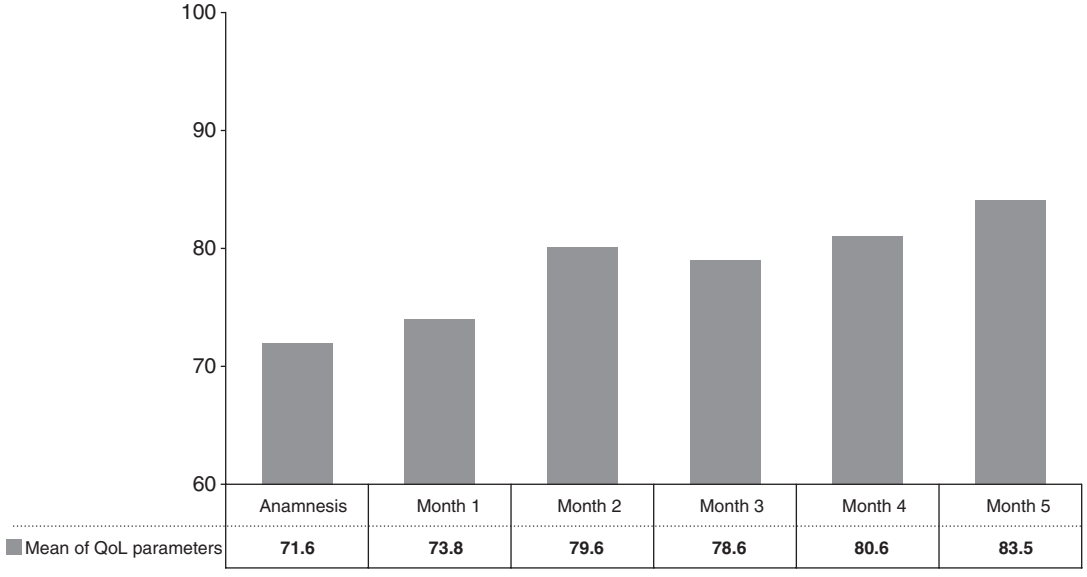

Figure 4. Overall Quality of Life (QoL) score per month after add-on montelukast ($n = 328$).

disease that would prevent the above described irreversible changes of the airway mucosa. Applying guideline-based treatment regimens have so far not proven sufficient to reach this aim. On the contrary, it has been shown in large international multicenter studies and also by our own survey of Austrian asthma patients that there is an alarming rate of symptoms and physical and emotional limitations that indicate insufficient control[6,7].

Although the term 'asthma control' may be defined to indicate disease prevention or even cure, neither of these are realistic options at present. So we define it as control of the manifestations of disease.

Several major attempts to improve asthma control have been undertaken in recent years. A 10 year national community intervention program in Finland was launched in 1994 with the goal of decreasing the percentage of patients with severe and moderate asthma from 40% to 20% and reduce the annual treatment costs per patient by 50%[11]. Important measures for achieving these goals included early diagnosis, active treatment and guided self management by the patient. This program has not completely reached its goals but has still resulted in a substantial clinical and economic improvement of asthma management in Finland[12].

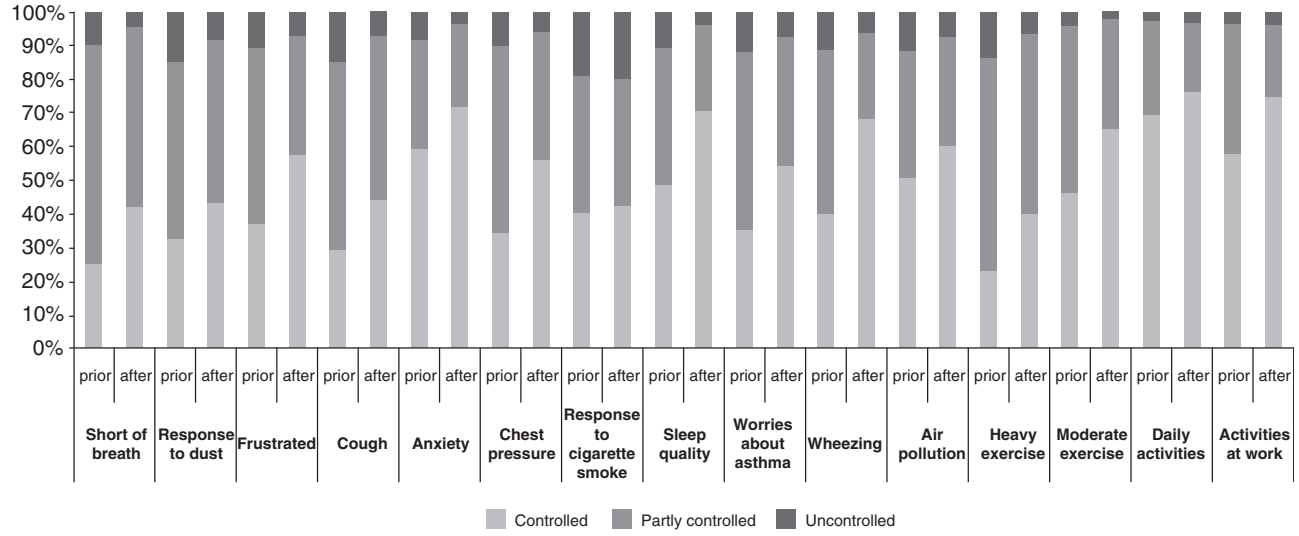

Figure 5. Patients' Questionnaire Quality of Life prior to and 3–5 months after add-on montelukast ($n = 216$).

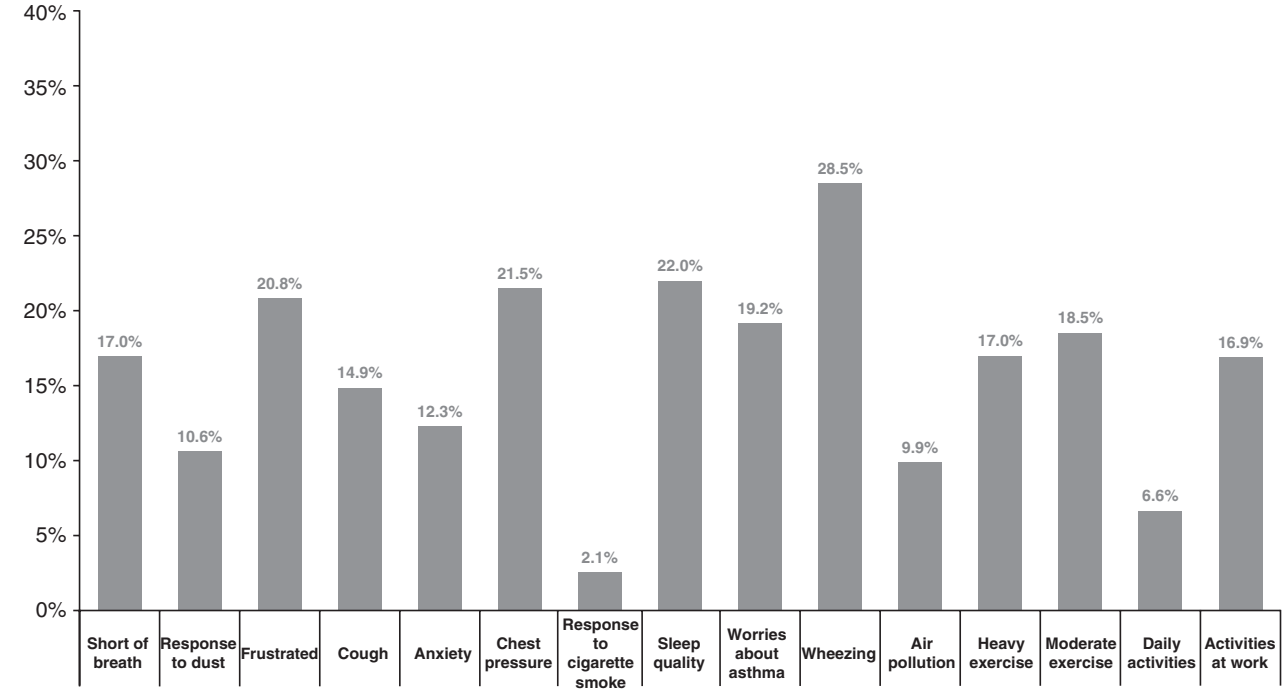

Figure 6. Differences between 'controlled' and 'uncontrolled' or 'partly controlled' at 3–5 months versus prior to add-on montelukast ($n = 216$).

In France the adequacy of acute asthma management was evaluated in a prospective study and an asthma program was launched in 2002 with the main objectives of developing information on asthma, improvement of the quality of asthma care, follow-up of chronic asthmatic patients, detection of new cases and collection of epidemiologic and economic data[13].

The GOAL study is a prospective study to evaluate the concept of achieving complete clinical control based on the goals of treatment described in international treatment guidelines (GINA)[14]. The major emphasis was put on health related quality of life (HRQoL) and it was shown that 'total control' was associated with near maximal levels of HRQoL. In this study eligible patients were allocated to one of three strata based on their dose of inhaled corticosteroid (ICS) in the previous 6 months (stratum 1: no ICS, stratum 2: ≤500 µg beclomethasone daily or equivalent, stratum 3: 500–1000 µg beclomethasone daily or

equivalent). During phase I fluticasone propionate (FP) or salmeterol/fluticasone combination (SFC) dose was increased in a stepwise manner every 12 weeks until guideline derived total control was achieved or the maximum dose of study medication was reached. Patients were then maintained at the final dose level for the remainder of the study (phase II). Thus, the duration of the dose titration phase I ranged between 12 to 36 weeks and the following phase II ranged between 16 to 40 weeks. 'Total control' was achieved in all strata in 31% of patients with SFC and in 19% with FP in phase I and in 41 with SFC and 28% with FP after 1 year (end of phase II). 'Well controlled' were 63% with SFC and 50% with FP at end of phase I and 71% vs. 59% at end of phase II.

This means that even with continuing high dose combination treatment 29% of patients and with FP alone 41% are still not well controlled. This fact is probably not surprising as the study included a number of severe asthmatics. What may be a limitation, however, is the unsolved question, whether such high doses of ICS should be maintained forever, as the concept of 'step down' was eliminated in this study. In fact, relevant suppression of adrenal function with reduction of bone mineral density cannot be excluded when high doses of ICS are administered for years. In the GOAL study and in other studies reduction of mean cortisol levels in 24-h urine were demonstrated, although in 92% of patients they still remained within normal limits.

A similar approach, though aimed less at complete control had been taken in the Formoterol and Corticosteroid Establishing Therapy (FACET) study[15].

In our own study (STAR) we pursued an alternative approach which is the combination of current treatment with ICS or ICS + LABA with a leukotriene receptor antagonist (LTRA). A huge body of evidence has been established for the effectiveness and safety of this class of agents in asthma treatment. Hence, LTRAs are recommended as a treatment standard in all international guidelines for asthma and also allergic rhinitis management (GINA, PRACTALL, ARIA).

The efficacy of the LTRA montelukast in combination with ICS has been shown in two large multicenter studies: in the IMPACT Investigation of Montelukast as a Partner Agent for Complementary Therapy–trial montelukast (ML) 10 mg/day or salmeterol (S) 100 μg/day were combined with the inhaled steroid fluticasone 200 μg/day for 48 weeks[16]. Both combination treatments were equally effective in preventing asthma attacks completely (79.9% for ML, 80.9% for S) and also, when not completely prevented, the distribution and number of asthma attacks was not different in the two groups, nor was there a significant difference in reduction of nocturnal awakenings or use of medical resources such as unscheduled visits to doctors or emergency rooms or hospitalization. ML was as effective as S in asthma specific QoL. However, montelukast therapy had a substantial impact on inflammatory activity with a significant reduction in blood eosinophils and sputum eosinophil counts and significantly fewer drug related adverse events and serious adverse events in the ML group.

However, another study showed greater improvement in asthma control of symptomatic patients on low dose ICS therapy when switched to a combination of fluticasone with salmeterol as compared to adding montelukast to ICS[17].

The second large study is a randomized controlled trial of montelukast 10 mg/day plus inhaled budesonide 800 μg/day vs. doubling the dose of inhaled budesonide (1600 μg/day) for 12 weeks (COMPACT study)[18]. Both groups showed progressive improvement in several measures of asthma control such as mean morning peak expiratory flow (AM-PEF) with a faster onset of improvement during days 1–3 in the ML group. Both groups showed similar improvements with respect to 'as needed' $ß_2$-agonist use, mean daytime symptom score, nocturnal awakenings, exacerbations, asthma free days, peripheral eosinophil counts and asthma specific QoL. Both combinations were generally well tolerated.

The main site of activity of cys-leukotrienes may be the small airways. Evidence from high resolution CT, histological analyses of resected lung tissue, autopsy lung specimens and transbronchial biopsies has backed up the concept that inflammation in asthma is not confined to the large bronchi but extends to the entire bronchial tree, and that the inflammatory changes in the peripheral airways are even more severe[19–21]. In addition, inflammation in the distal lung compartment is probably undertreated by using inhaled corticosteroids, whereas LTRA administered orally reach both the central and distal airways.

In addition to the proven clinical effect of antileukotrienes there are biochemical explanations that speak in favor of these agents. The inflammatory process in asthma is known to be complex and caused by many factors. The anti-inflammatory actions of corticosteroids obviously do not cover all of them. Corticosteroids at any dose do not block leukotrienes in the airways of asthmatic patients. Therefore a combined therapy may enforce anti-inflammatory action and assure the efficiency of asthma treatment.

Favorable results under real-life conditions were published in a German multicenter phase IV study describing the efficacy and safety of montelukast 10 mg in adults with both asthma and allergic rhinitis[22]. At the end of the observation period of 4–6 weeks, 86.5% of 5855 patients reported strong or marked improvement in daytime asthma symptoms and a similar high proportion of patients had improvement in night-time symptoms. They also had

fewer symptoms of allergic rhinitis and had reduced their asthma and rhinitis medication.

These data were supported in a recent open-label observational study demonstrating improvement of asthma and allergic rhinitis symptoms in patients not adequately controlled on a fixed association of ICS/LABA[23].

Additionally a Canadian group demonstrated that montelukast add-on therapy is effective for managing asthma and allergic rhinitis symptoms in patients who were previously uncontrolled with ICS or ICS/LABA treatment[24].

Although the results of the STAR study are encouraging, the nature of the study design limits the interpretation of the data to the accepted constraints of an open-label trial. The lack of a placebo control group and the office based study conditions limit the validity of the findings. Similarly, all patients were continued on their existing asthma therapy which might also result in a continuous improvement of asthma control. Moreover, the patient symptom component of the ACQ is subject to bias in an open-label trial. A final question is, why the number of uncontrolled patients in our study was lower when compared to other surveys. This is most likely due to the selection criteria, as only patients with mild or moderate asthma had been enrolled. In addition, most patients had already been treated by a specialist and not by a primary care physician. Therefore, a randomized, double-blind, placebo controlled trial would be required to confirm the beneficial effect of adding montelukast to various treatment combinations to improve the quality of life of asthmatic patients.

Conclusion

The study shows that despite concurrent asthma treatment a group of patients in Austria faces limited quality of life. The main objective of our investigation was to find out whether the favorable results of the quoted randomized studies with LTRA as add-on therapy can improve the quality of life of those patients.

In this study the open-label add-on treatment with montelukast resulted in a significant improvement in quality of life and asthma control. We could demonstrate that adding montelukast to the previously administered treatment leads to a substantial improvement in the overall quality of life score and an improvement in five out of six quality of life parameters from uncontrolled to controlled and partly controlled after 3–5 months' add-on therapy with montelukast.

The patients' own judgment according to the validated questionnaire containing 15 questions on symptoms, environmental stimuli, emotional functions and limitation of different activities showed improvements in all 15 items after 3–5 months of add-on therapy with montelukast.

Transparency

Declaration of funding

This study was supported by a grant from MSD Merck Sharp & Dohme Ges.m.b.H, Vienna, Austria.

Declaration of financial/other relationships

W.S. has disclosed that he received sponsorship from MSD and acted as a consultant to MSD. W.P. has disclosed acting as a board or advisory board member for Boehringer Ingelheim, MSD, Mundipharma, Nycomed and Meda, and receiving consultancy fees from AstraZeneca. W.P. has served on speakers bureaus for AstraZeneca, Boehringer Ingelheim, Glaxo SmithKline, MSD, Chiesi, Pfizer Inc., Actelion, Nycomed and AlkAbello. K.P. has disclosed acting as a statistical advisor for MSD. K.A. has disclosed receiving research grant funding from Allmirall, AstraZeneca, Bayer, Boehringer, Eli Lilly, GSK, Nycomed, Pfizer, Roche and acting as consultant to Boehringer Ingelheim, GSK, MSD, Pfizer and Torrex Chiesi. G.F. has disclosed no relevant financial relationships. M.K. has disclosed acting as a consultant to GSK, Boehringer Ingelheim, Nycomed, Meda Pharma, AstraZeneca, Pfizer, Bayer and AOP Orphan. H.Z. has disclosed receiving research grant funding from AstraZeneca, Boehringer Ingelheim and EUMEDICS.

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