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Efficacy and safety of montelukast in adults with asthma and allergic rhinitis

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Summary Several clinical studies have confirmed the effectiveness of montelukast 10 mg orally in adults with both asthma and allergic rhinitis. The objective of this phase IV study was to investigate the efficacy and safety of montelukast 10 mg in adults with both asthma and allergic rhinitis in a real-life setting. Data from 5855 patients (mean age: 42.8 ± 15.4 years) were collected and analyzed following treatment for 4–6 weeks. Efficacy was analyzed by comparing baseline values of: general, day- and night-time improvement in asthma symptoms, need for rescue medication or inhaled corticosteroids (ICSs), general and specific improvement in allergic rhinitis symptoms, reduction in rhinitis medication use, and general and specific quality of life (QoL) improvement with values collected at the end of the observation period of 4–6 weeks. Following treatment with 10 mg montelukast 86.5% ($n = 4547$) of patients reported a strong or marked improvement in day-time asthma symptoms and 88.5% ($n = 4367$) reported improvement in night-time symptoms. A similarly high proportion of patients had a strong or marked improvement in all symptoms of allergic rhinitis (i.e. sneezing/itching (84%), rhinorrhea (81.7%), nasal congestion (79.3%), watery eyes (78.4%) and red or burning eyes (77.7%). The use of asthma and rhinitis medication was also reduced. 92.3% ($n = 5685$) of all patients intended to continue montelukast therapy. Overall QoL was "very good" or "good" in 85.2% of patients ($n = 4991$) and a "strong" or "marked" improvement in each of the four domains of sleep, work, everyday life and physical activity. Montelukast was well tolerated. Adverse drug reactions occurred in 14 out of 6158 patients. None of the adverse events was serious. Accordingly, montelukast 10 mg is a safe and effective treatment for patients with both asthma and allergic rhinitis.

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Introduction

The prevalence of asthma and allergic rhinitis has risen markedly worldwide in recent years.[1] Asthma is estimated to affect ~4–11% of the general population, while allergic rhinitis is estimated to affect between 10% and 30% of the general population.[2,3] Comorbidity of asthma and rhinitis has been well documented, suggesting a link between upper and lower airway disease and the hypothesis that asthma and rhinitis represent a systemic disease (i.e. one airway one disease).[4–6] The finding of nasal inflammation in asthma and bronchial inflammation and hyperresponsiveness in rhinitis further supports this hypothesis.[4–6] The majority of patients with asthma also suffers from allergic rhinitis. It has been reported that up to 80% of patients with asthma also have rhinitis,[7] while a significant number of patients with rhinitis also have asthma.[7,8] In patients with asthma and allergic rhinitis healthcare costs are significantly increased while quality of life (QoL) is significantly worse.[9–11] In addition, patients with rhinitis have an increased risk of developing asthma.[12,13]

The Allergic Rhinitis and its Impact on Asthma (ARIA) Guidelines categorize patients' allergic rhinitis as either "intermittent" or "persistent" with regards to duration.[14] The severity of allergic rhinitis is subdivided into "mild" or "moderate-severe", depending on symptoms and QoL.[14] These guidelines suggest to use combined strategies for the treatment of upper and lower airways. They propose a stepwise approach according to symptom severity and treatment response. Leukotriene antagonists, such as montelukast, were included in these guidelines as a treatment option for allergic rhinitis[14] despite the fact that clinical studies about their efficacy were limited at the time of publication.

Since cysteinyl leukotrienes participate in the pathophysiology of both asthma and allergic rhinitis[15] it has been suggested that blocking the cysteinyl leukotriene receptor might be beneficial to patients with asthma *and* allergic rhinitis.[15] Accordingly, a recent study has shown that montelukast can improve symptoms of seasonal allergic rhinitis and asthma in patients with both diseases.[16] The aim of the present article was to evaluate the efficacy and safety of add-on montelukast (10 mg orally) to existing controller medication in the treatment of patients with asthma and allergic rhinitis.

Patients and methods

Study design

This multicentre, phase IV study with 3018 physicians was designed to investigate the efficacy of 10 mg montelukast in adults with asthma and allergic rhinitis. Current therapy for each patient was recorded for ~4–6 weeks of treatment between February 1st, 2004 and July 31st, 2004.

Patients

Patients were required to suffer from physician diagnosed asthma and allergic rhinitis. The minimum age of inclusion was 16 years. Montelukast was either used as a monotherapy or in addition to another anti-asthmatic therapy which was judged to be inadequate prior to the administration of the leukotriene receptor antagonist.

Baseline parameters

At visit 1 patients demographic data (gender and age), disease diagnosis and severity were recorded. Asthma severity was categorized according to recent guidelines as "intermittent", "mild" or "moderate" and rhinitis was subdivided into "intermittent" or "persistent". Asthma daytime symptoms (cough, wheezing, chest tightness and shortness of breath) and night-time symptoms (cough, shortness of breath and nocturnal awakenings), the need for rescue medication and inhaled corticosteroids (ICSs) were recorded together with symptoms of allergic rhinitis (sneezing/itching, runny nose, nasal congestion, watery eyes and red/burning eyes). Any recent medication and its perceived effectiveness to treat symptoms of rhinitis were also recorded. In addition, patients' overall QoL was assessed as "good", "satisfactory" or "reduced" and also more specifically according to the four domains of "difficulty sleeping", "difficulty with work", "difficulty with everyday life" and "limitation to daily activities".

Efficacy parameters

At the end of the observation period (4–6 weeks) the following efficacy parameters were collected: general improvement in asthma symptoms, improvement of day- and night-time asthma symptoms, need for rescue medication, need for ICSs, general and specific improvement in allergic rhinitis symptoms, reduction in medication to treat the symptoms of allergic rhinitis, and general and specific QoL improvement. General improvements were categorized as "very good", "good", "satisfactory", "sufficient" or "not sufficient". Specific improvements in symptoms or QoL domains were categorized as "strong", "marked", "moderate" or "none".

Safety parameters

Undesirable effects (UE) and adverse drug effects (ADE) were recorded during the treatment period with montelukast 10 mg.

Statistical analysis

The methods of descriptive statistics were employed to analyze results from this post-marketing surveillance study and all analyses were performed using SAS (Statistical Analysis System version 8.2 for Windows). Case reports were considered evaluable for efficacy (efficacy group) if the following criteria were met: documented therapy with montelukast (case report form filled out); data recorded for visit 2; patient aged at least 16 years; beginning of monitored study medication not earlier than February 1st, 2004. Case reports were considered evaluable for drug safety (drug safety group) when the following criteria were met: documented therapy with montelukast 10 mg. Undesirable effects were calculated on the "preferred term" level.

Results

Study population

In total, 6158 patients were identified by 3018 physicians. In all, 303 of these patients were not included into the study due to prior treatment with montelukast ($n = 140$), age < 16 years ($n = 175$) or missing data at visit 2 ($n = 4$). Patients (5855) ($n = 2487$ male; $n = 3299$ female) with a mean age of 42.8 ± 15.4 years met all inclusion criteria and were included in this post-marketing surveillance study (Table 1). The average duration of observation was 5.5 weeks.

The majority of patients (40.5%) had moderate asthma with both day- and night-time symptoms in the last weeks prior to enrolment (Table 1). Cough was the most frequently reported day- and night-time symptom; more than half of the patients (58%) had nocturnal awakenings due to asthma (Table 2). There was a fairly even spread of patients with intermittent and persistent allergic rhinitis (51.8% and 47.0%, respectively); almost all patients reported symptoms of allergic rhinitis in the weeks prior to enrolment (Table 1), namely sneezing/itching, rhinorrhea, nasal congestion, watery eyes and/or red/burning eyes. In 70% of all patients overall QoL was reduced due to symptoms of asthma and rhinitis; most patients reported difficulty sleeping, work-related

Table 1 Patient baseline characteristics.

Characteristic	*n* (%)
Gender	
Male	2487 (42.5)
Female	3299 (56.3)
No data	69 (1.2)
Age (years)	
Mean ± standard deviation	42.8 ± 15.40
Range	16–96
Asthma severity	
Intermittent	1728 (29.5)
Mild	1695 (29.0)
Moderate	2369 (40.5)
No data	63 (1.1)
Asthma symptoms in last weeks	
Day-time symptoms	5256 (89.8)
Night-time symptoms	4930 (84.2)
Allergic rhinitis	
Persistent	2754 (47.0)
Intermittent	3032 (51.8)
No data	69 (1.2)
Current rhinitis symptoms	5774 (98.6)

Table 2 Pre-study symptoms and quality of life (QoL).

Characteristic	*n* (%)
Day-time asthma symptoms	
Cough	4381 (75)
Wheezing	2598 (44)
Chest tightness	2485 (42)
Shortness of breath	2166 (37)
Night-time asthma symptoms	
Cough	3823 (65)
Shortness of breath	2062 (35)
Nocturnal awakening	3378 (58)
Allergic rhinitis symptoms	
Sneezing/itching	5521 (94)
Running nose	5218 (89)
Congested nose	4646 (79)
Watery eyes	5052 (86)
Red/burning eyes	4507 (77)
Overall QoL assessment	
Good	196 (3)
Satisfactory	1518 (26)
Reduced	4089 (70)
Individual QoL assessment	
Difficulty sleeping	5509 (94)
Difficulty with job	5262 (90)
Difficulty with everyday life	5639 (96)
Limitations to daily activities	5610 (96)

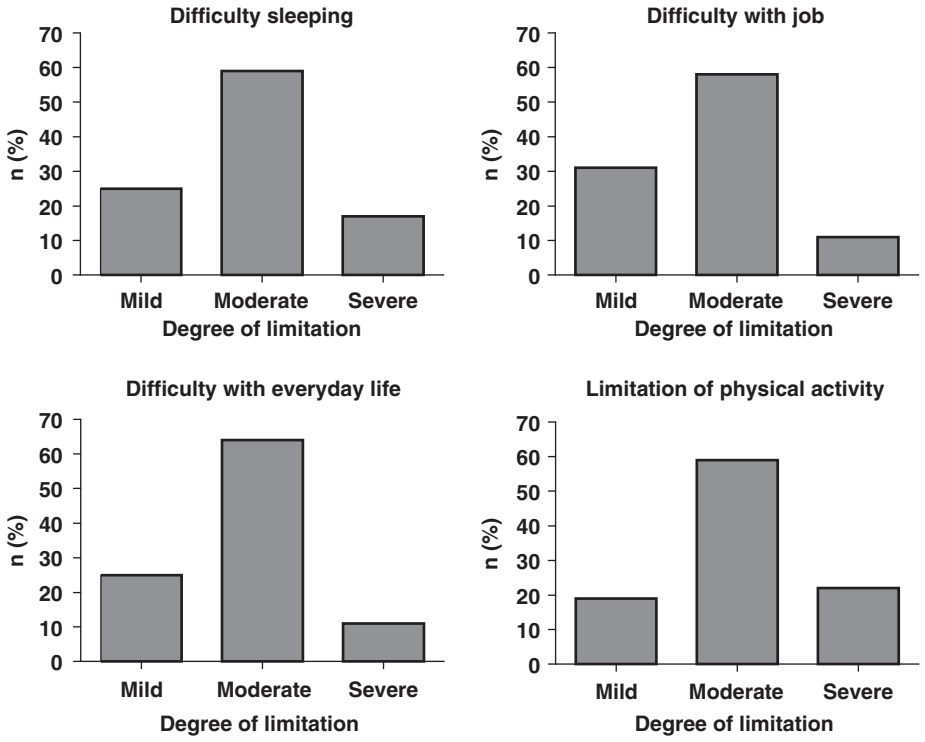

Figure 1 Pre-study degree of quality of life limitation.

problems, impairments during everyday life and a limitation in daily activities due to asthma and/or rhinitis (Table 2 and Fig. 1). Well over half (58%) of the patients reported a moderate limitation in each of the four QoL domains while 16.8% of patients reported severe impairment in sleeping, 10.9% had severe work-related difficulties and 10.8% and 22.1% of patients reported severe limitations in their every day lives and physical activity, respectively (Fig. 1).

Efficacy results

Asthma symptoms

Following treatment with 10 mg montelukast there was an overall improvement in asthma symptoms in the majority of patients, where 36.6% ($n = 2143$) rated this improvement as "very good", and 45.2% ($n = 2648$) as "good" (Fig. 2). Day-time symptoms improved "strongly" or "markedly" in 86.5% ($n = 4547$) of patients and 88.5% ($n = 4367$) reported an improvement in night-time symptoms (Fig. 2). This was accompanied by a reduction in the requirement for other asthma medications such as β_2-agonists and ICSs. The number of patients who needed additional asthma medication decreased by 19.9% ($n = 1,163$) for β_2-agonist use and by 14.8% ($n = 865$) for ICS use; in addition, the mean number of puffs per day of β_2-agonists was reduced from 4.0 to 1.9 and from 2.5 to 1.6 for ICSs.

Allergic rhinitis symptoms

Adding montelukast 10 mg to current asthma medication led to an overall improvement in allergic rhinitis symptoms in 86.5% of patients; 37.7% ($n = 2210$) rated this improvement as "very good" and 45.8% ($n = 2684$) as "good" (Fig. 3). Most patients reported a "strong" or "marked" improvement in all symptoms of allergic rhinitis; 77.7% ($n = 3502$) reported a "strong" or "marked" improvement in red/burning eyes, 78.4% ($n = 3961$) had a "strong" or "marked" improvement in watery eyes, and 79.3% ($n = 3682$) reported similar improvement in nasal congestion, while 81.7% ($n = 4266$) had a "strongly" or "markedly" improved rhinorrhea and 84% ($n = 4637$) similarly improved sneezing/itching (Fig. 3). This was accompanied by a reduction in rhinitis medication in 88.1% ($n = 4228$) of all patients ($n = 5855$). The strongest decrease was observed for nasal steroids with 77.1% ($n = 1566$ of a total of 2031 patients). The use of α-sympaticomimetics was reduced in 75.9% of patients ($n = 576$ of a total of 759 patients), the use of eye drops in 69% of patients ($n = 1616$ of a total of 2311 patients), anti-histamines in 69% of patients ($n = 2499$ of a total of 3621 patients) and

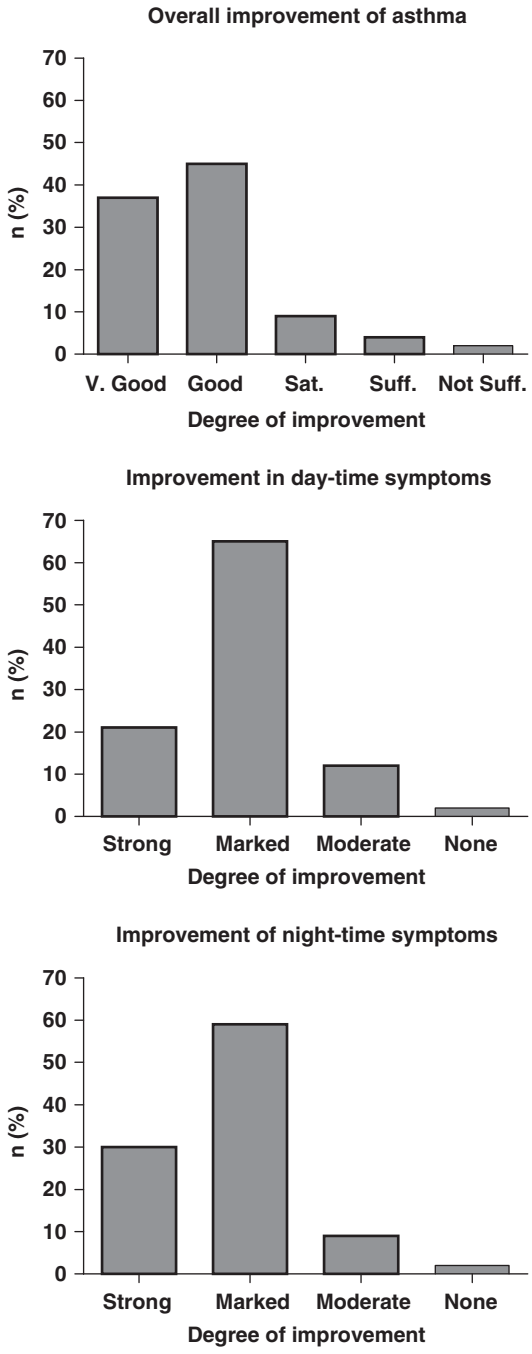

Figure 2 Improvement in asthma. Sat: satisfactory; Suff: sufficient.

other rhinitis medications in 67.1% of patients ($n = 336$ of a total of 501 patients).

Quality of life

There was a "very good" or "good" improvement in 85.2% of patients ($n = 4991$) in overall QoL and a "strong"/"marked" improvement in each of the four domains of sleep, work, everyday life and physical activity in 86.3% ($n = 4752$), 81.6% ($n = 4293$), 84.4% ($n = 4764$) and 82.1% ($n = 4605$) of patients, respectively (Fig. 4).

Other efficacy results

Almost all patients (92.3%, $n = 5685$) planned to continue montelukast therapy after the end of the observation period, while only 7.2% of patients ($n = 442$) discontinued montelukast. In 2.6% ($n = 160$) further treatment was not required due to either almost completely resolved symptoms or due to the fact that the hay fever season had ended. A similarly large percentage (2.3%, $n = 142$) discontinued therapy due to insufficient efficacy and 0.2% ($n = 10$) due to adverse events. 2.1% ($n = 130$) reported other or no reason for discontinuation.

Safety results

Montelukast was well tolerated in this large phase IV study. In 14 of 6158 patients (0.23%) 21 drug-related adverse events were reported. Most frequently headache, gastrointestinal infections and sleepiness were observed as single symptoms. None of the adverse events was serious.

Discussion

Asthma and allergic rhinitis have been linked clinically for many years. This has recently been acknowledged in the "one airway one disease" concept which underlines the hypothesis that both diseases share a common pathophysiology, characterized by inflammation of the respiratory mucosa by the same pro-inflammatory cells (e.g. eosinophils, Th2 lymphocytes and mast cells) and mediators (e.g. cytokines, histamine and leukotrienes).[4,5,17] Patients with asthma and rhinitis are twice as likely to require emergency care for asthma, and need more asthma-related hospitalizations and GP visits leading to higher asthma drug costs. In addition, patients with allergic asthma and rhinitis are significantly more likely to experience asthma attacks compared to patients with asthma alone.[11,18] Based on these findings it has been suggested that both conditions should be ideally treated together.[14] Montelukast, a leukotriene receptor antagonist, has been shown to improve both asthma and allergic rhinitis symptoms [15,16,21] and therefore has the potential to conveniently treat patients with asthma and rhinitis.[19,20]

In this phase IV study treatment with montelukast 10 mg for 4–6 weeks (added to existing controller medication) was effective and well tolerated in patients with mild-to-moderate

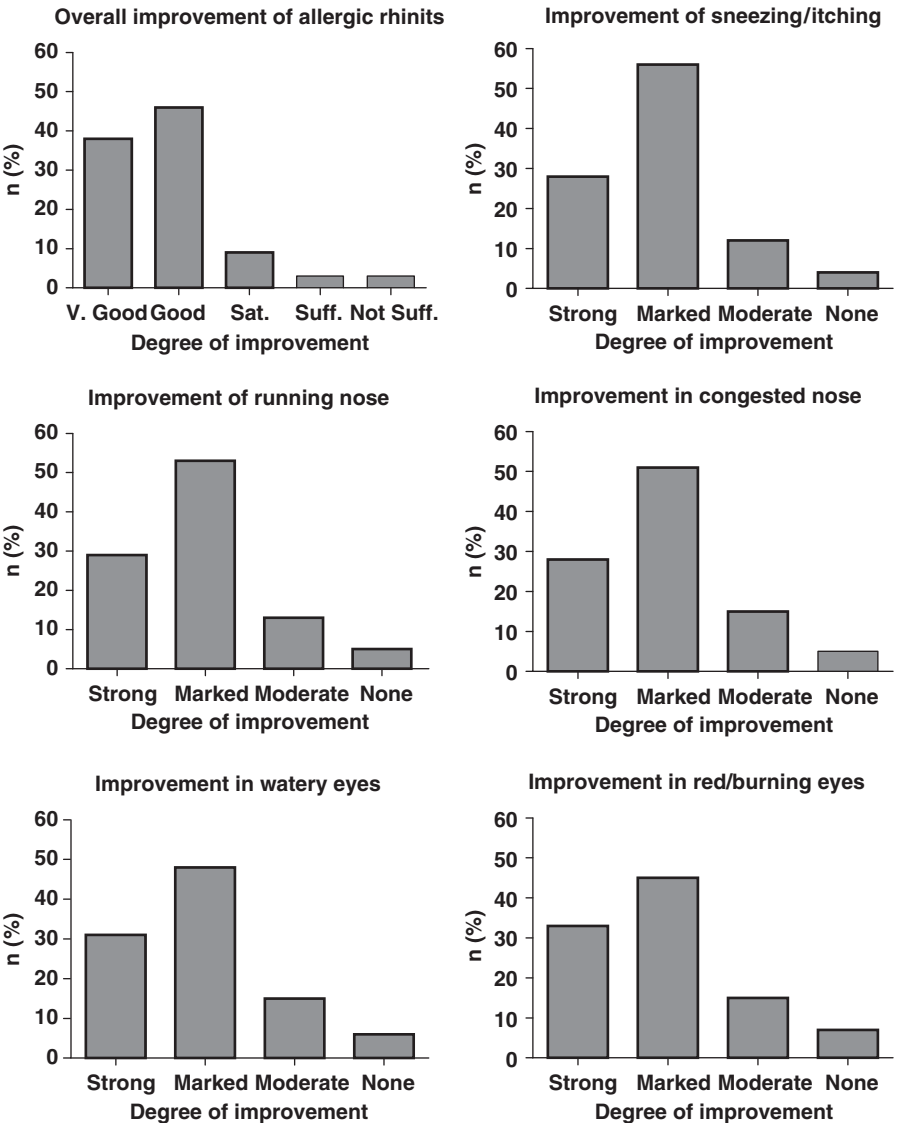

Figure 3 Improvement in rhinitis. Sat: satisfactory; Suff: sufficient.

asthma and allergic rhinitis. There was a ''strong'' or ''marked'' improvement in both day- and night-time asthma symptoms as well as the symptoms of allergic rhinitis. These improvements were associated with a reduction in both asthma and rhinitis medication. Similar results have been previously reported from studies in which montelukast was added to existing therapies.[16,21] Accordingly, a subgroup analysis from the Clinical Outcomes with Montelukast as a Partner Agent to Corticosteroid Therapy (COMPACT) study[21] suggested that the mean increase in pulmonary function in patients with persistent asthma and a physician-based diagnosis of allergic rhinitis was greater when montelukast was added to a previous regimen of 800 μg of budesonide/day versus doubling the dose of budesonide to 1600 μg/day.[21] Adding montelukast to existing maintenance therapy also significantly improved the symptoms of seasonal allergic rhinitis in patients with concomitant active asthma.[16] Furthermore, the addition of montelukast significantly ($P<0.001$) reduced daily rhinitis symptom scores, day-time nasal symptoms, nasal congestion, rhinorrhea and sneezing, night-time symptoms, especially nasal congesting upon awakening and day-time eye symptoms.[16] Both patients and physicians also reported significant improvements in the global evaluation of allergic rhinitis ($P\leqslant 0.001$) and asthma ($P\leqslant 0.05$). Similar to our findings patients who took montelukast needed significantly less rescue medication which is likely to impact on healthcare resource use[16] as has been suggested by a study from Italy in children under 14 years of age where montelukast decreased the

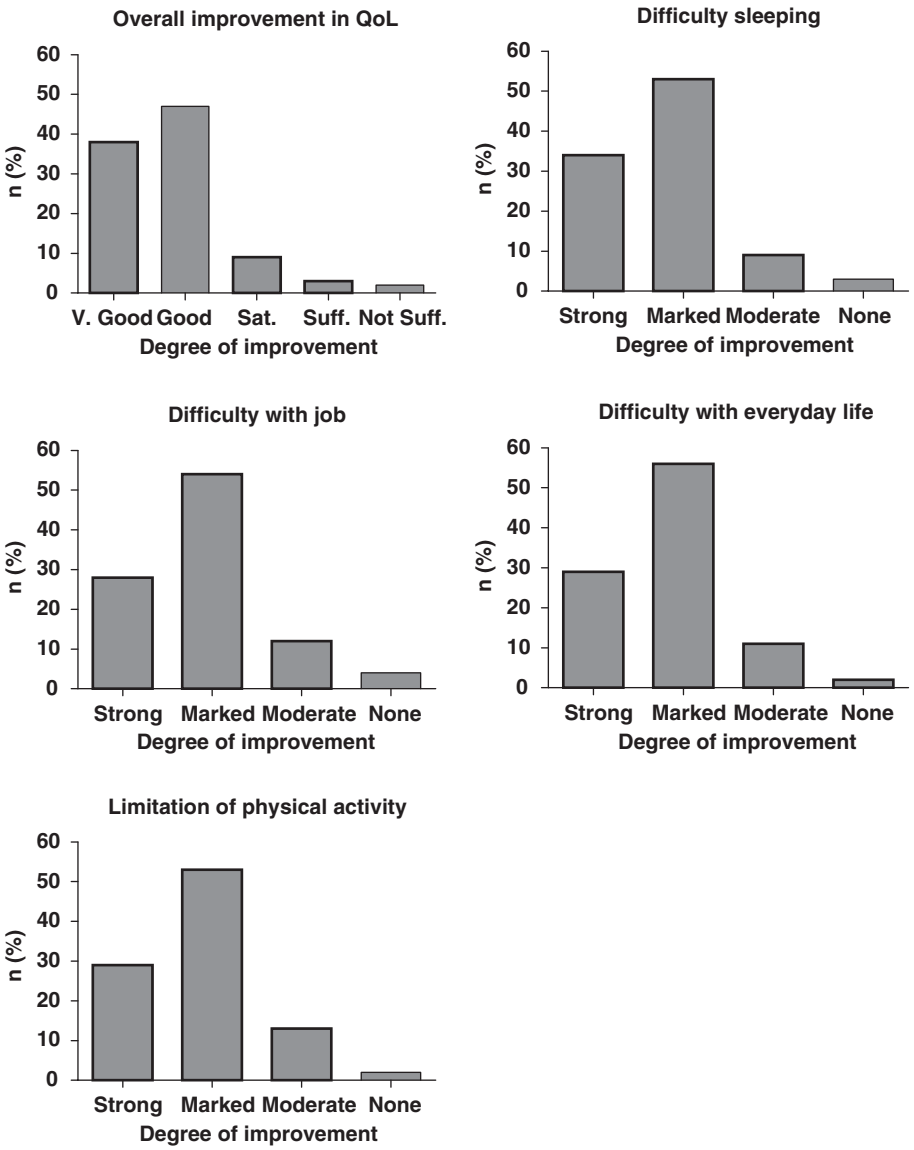

Figure 4 Improvement in quality of life (QoL). Sat: satisfactory; Suff: sufficient.

total use and costs of asthma rescues/acute and allergy medication over a 2-year period.[22] The results of these studies which are now expanded with our post-marketing surveillance study, add further proof to the effectiveness of montelukast not only in a clinical setting, but also in a real-life setting.

Both asthma and allergic rhinitis can impair QoL which is further reduced in patients with both diseases.[10] Patients treated in an open label setting with montelukast 10 mg orally reported a ''strong''/''marked'' improvement in their QoL most notably in the domains of sleep, work, everyday life and physical activity. Similar results have been obtained from controlled trials[16] which also showed that montelukast treatment improved rhinoconjunctivitis QoL overall score in patients with both asthma and allergic rhinitis. Significant ($P<0.05$ each) improvements were noted in the QoL domains of nasal symptoms, eye symptoms, activity, sleep, emotions and practical problems.[16]

In conclusion, based on previous findings asthma and allergic rhinitis often occur together and common treatment strategies have been recently suggested for both diseases. Our findings from a very large number of patients suggest that previous results from smaller, randomized controlled trials can be translated into a real-life setting, where montelukast is a safe and effective systemic treatment of both upper and lower airways in patients with both asthma and allergic rhinitis.

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