Real-Life Effectiveness of Singulair® (Montelukast) in 506 Children with Mild to Moderate Asthma

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Abstract

Background: Based on the outcome of several randomized controlled trials, the orally active leukotriene receptor antagonist montelukast (Singulair®, Merck) has been licensed for treatment of asthma. The drug is favored for treating childhood asthma, where a therapeutic challenge has arisen due to poor compliance with inhalation therapy.

Objectives: To assess the efficiency of and satisfaction with Singulair® in asthmatic children under real-life conditions.

Methods: Montelukast was prescribed for 6 weeks to a cohort of 506 children aged 2 to 18 years with mild to moderate persistent asthma, who were enrolled by 200 primary care pediatricians countrywide. Four clinical correlates of childhood asthma – wheeze, cough, difficulty in breathing, night awakening – were evaluated from patients' diary cards.

Results: Due to under-treatment by their physicians, almost 60% of the children were not receiving controller therapy at baseline. By the end of the study, which consisted of montelukast treatment, a significant improvement over baseline was noted in asthma symptoms and severity, as well as in treatment compliance. The participating pediatricians and parents were highly satisfied with the treatment.

Conclusions: The results of this extensive study show that the use of montelukast as monotherapy in children presenting with persistent asthma resulted in a highly satisfactory outcome for themselves, their parents and their physicians.

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Asthma is the most common chronic disease in children [1] and pediatricians are frequently faced with this serious public health problem, which severely limits the daily activities and school attendance of many children. Asthma is now considered an inflammatory disorder of the airways involving many tissues and cellular elements. Even in mild to moderate asthma, a strong inflammatory process is present which is believed to be the underlying cause of airway hyper-responsiveness and the propensity to airway obstruction.

Corticosteroids are potent anti-inflammatory agents, yet they do not block the release of inflammatory mediators such as the cysteinyl leukotrienes [2]. Montelukast (Singulair®, Merck, USA) is a new agent that blocks these mediators by binding to the leukotriene receptors. Also, in contrast to steroids that are usually administered by aerosolization, anti-leukotriene agents are given by mouth. It is proposed that this difference greatly affects compliance and is a major factor in the successful treatment of children. Several randomized controlled trials have demonstrated the efficacy of montelukast in childhood asthma [3-5]. While these trials were performed under strict and rigorous conditions, their implications for effectiveness, as opposed to efficacy, in real-life situations may be limited [6].

The present study was undertaken together with general community pediatricians to assess the effectiveness and acceptance of montelukast therapy among children with mild to moderate persistent asthma. The study was performed as a real-life study with minimal restrictions imposed. This also enabled us to evaluate current asthma practice among participating pediatricians.

Patients and Methods

A group of 200 pediatricians working in primary care clinics in Israel were asked to enroll patients and offer them 6 weeks of Singulair® (montelukast) treatment. Inclusion criteria were children aged 2–18 years with mild to moderate persistent asthma, as judged by the pediatrician, and that required controller therapy.

Pediatricians participated voluntarily and did not receive payment. Patients were enrolled at the discretion of the individual pediatrician and enrollment was also voluntary and unpaid. Informed consent was obtained for each patient, and ethics committee approval was obtained at each clinic. Patients with mild to moderate persistent asthma were eligible for this open-label observational study, but those with chronic lung diseases, severe asthma, and/or already taking montelukast were excluded.

The study intervention consisted of montelukast therapy (4, 5, and 10 mg for 2–5 year olds, 6–14 year olds, and 15–18 year olds, respectively) once daily at bedtime for 6 weeks. Montelukast was prescribed either as monotherapy (for patients on no-controller therapy) or as add-on therapy to existing inhaled corticosteroid therapy.

Outcome measures were symptoms and the need for rescue medications. These were measured at baseline based on patients' reports regarding the month prior to enrollment, and at the end of the study using a written questionnaire that was completed by the patients and, in the case of young patients, by their parents. Physicians classified subjectively the degree of their patients' asthma, as well as assessing objectively the severity of the asthma as based on patients' reported symptoms. Asthma was classified according to GINA (Global Initiative for Asthma) guidelines. Physician and parent satisfaction were evaluated at

the end of the study using a linear scale of 1 to 5 (very unsatisfied to very satisfied).

Compliance was assessed by a forgetting scale whereby the patients, or parents in case of very young patients, were requested to admit forgetting to take their medications.

Statistical analysis

Differences in symptoms between the pre- and post-study periods were analyzed by a chi-square test for independence. The degree of statistical significance was expressed as a *P* value, which was considered significant if less than 0.05.

Results

The study group comprised 200 pediatricians who enrolled 568 patients. A total of 506 patients completed the full study. Patients' parameters as recorded by the pediatricians are presented in Table 1.

Symptoms

- *The first visit*: The main complaint in this sample was cough, cited by 61% of the patients [Table 2]. Six percent reported having an Emergency Room or hospital admission in the month prior to enrollment and 27% reported using oral corticosteroids in this period. With regard to wheezing, 25% of patients (126/506) reported having wheezed more than twice a week, 46% less than twice a week, and 29% reported no wheeze. Regarding cough, 44% of patients (221/506) reported having coughed more than twice a week, 40% less than twice a week, and 16% reported no cough. Shortness of breath was experienced by 20% more than twice a week, 38% less than twice a week, and 42% reported no shortness of breath. Twenty-five percent of patients (129/506) reported having night awakening from asthma more than once a week, 27% less than twice a month, and 48% reported no night awakening. A total of 196 patients reported that they used bronchodilators during the week preceding the study.

When questioned during their first visit, the most common single presenting complaint was cough (61%), followed by shortness of breath (14%, n = 69) and wheeze (3%, n = 13).

- *The end of the treatment period*: Following 6 weeks of montelukast therapy there was a significant improvement in the following symptoms: wheeze, cough, breathing difficulty and night awakening [Figure 1]. Only 3% of patients (16/506) reported having wheezed more than twice a week, 13% less than twice a week and 84% reported no wheeze. With regard to cough at the end of the treatment period, 8% of patients (41/506) reported having coughed more than twice a week, 27% less than twice a week, and 65% reported no cough. Shortness of breath was experienced by 2% more than twice a week, 8% less than twice a week, and 90% reported no shortness of breath. Two percent of patients (11/506) reported having night awakening from asthma more than once a week, 10% less than twice a month, and 88% reported no night awakening. Fifty-nine patients reported having used bronchodilators during the last week of the study (mean = 5 times, SD = 5).

Table 1. Patients' baseline characteristics (%)

Gender	
Male	60
Female	40
Age (yrs) mean (SD)	7.0 (4.0)
2–5	48
6–14	46
15–18	6
Family history of asthma	37
Allergy background	36

Table 2. Symptoms and severity (%)

Main complaint at baseline	
Cough	61
Shortness of breath	14
Wheezing	3
ER or hospital admission	6
Oral corticosteroids	27
Exercise-induced asthma	17
Asthma severity (at baseline, according to physician)	
Mild	56
Moderate	42
Severe	2

Asthma severity classification

At the first visit, asthma severity classification by pediatrician assessment was 56% (283/506) mild, 42% (211/506) moderate, and

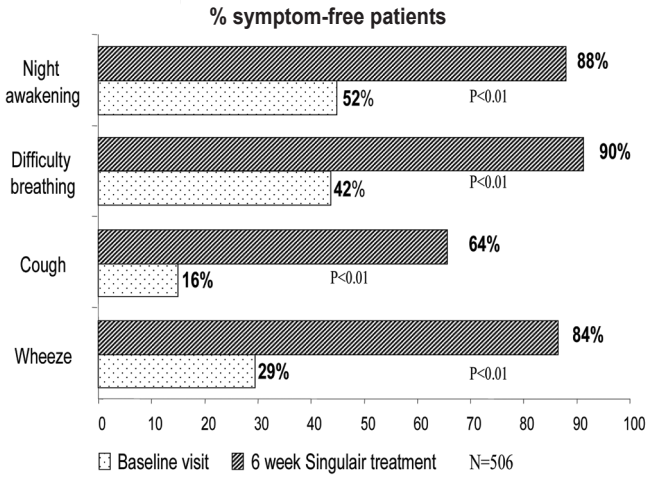

Figure 1. Percent of symptom-free patients before and after the intervention

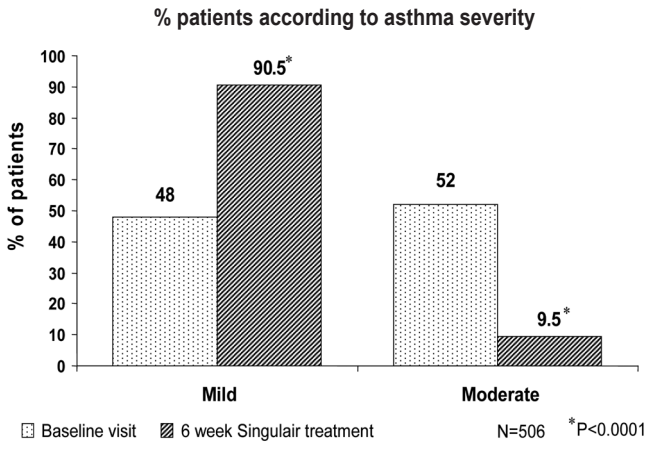

Figure 2. Percent of mild asthma or moderate asthma patients before and after the intervention

2% (12/506) severe. Asthma severity by patients' history (GINA definition of patients' reported symptoms): 48% (243/506) were classified as mild persistent, and 52% (n=263) as moderate persistent. At the second visit after 6 weeks of montelukast therapy, asthma severity (GINA definition) was 90.5% (458/506) mild and 9.5% (48/506) moderate [Figure 2].

Therapy

Almost 60% of the patients were not receiving a controller therapy at baseline despite being symptomatic and defined by their pediatricians as being mild persistent to moderate persistent asthmatics. The most common preventive therapy was budesonide (78%) (267/344 prescribed), while 7% (24/344) of patients were receiving salbutamol as preventive therapy.

Initiation of montelukast as monotherapy was much more common than as an add-on among those perceived by their pediatricians as having mild asthma (76% versus 24%). It was less common as add-on however, among those perceived by pediatricians as having moderate asthma (46% vs. 54%).

Initiation of montelukast as monotherapy was more common than as add-on among those perceived by patients and/or parents as having mild asthma (63% vs. 35%), and in contrast to pediatricians' perception, montelukast as monotherapy was more common as add-on among patients perceived as having moderate asthma (60% vs. 40%). Montelukast was equally effective as a monotherapy or when used concurrently with other asthma treatment

- *Compliance*: At the first visit, 65% of patients who had been on controller therapy prior to enrollment (155/240) reported that in the previous week they had not missed their maintenance therapy, while 25% reported missing it one to three times, and 10% reported missing it more than three times. When compared to patients who received budesonide, 61% (82/135) reported that in the previous week they had not missed their maintenance therapy, 26% reported missing it one to three times, and 13% reported missing it more than three times. At the end of the treatment period, 81% of patients (280/344) reported never having missed their maintenance therapy in the past week, 16% reported missing it one to three times, and 1% reported missing it more than three times.
- *Satisfaction*: With regard to parent and physician satisfaction scores after 6 weeks of treatment based on a five point scale (0 = very dissatisfied, 5 = very satisfied), 88% of parents and pediatricians were satisfied (grades 4 and 5), and only 6% of parents and 4% of pediatricians were dissatisfied (grades 1 and 2).

Discussion

This study reports one of the first large-scale trials of Singulair® (montelukast) in children performed in a real-life situation. Randomized controlled trials are designed to evaluate the efficacy of therapy. They are performed under strict and rigorous conditions and require a high degree of controlled conditions. Most of these also include a placebo or other treatment group for comparison. A milestone example of this form of RCT is that of Knorr et al. [3], which evaluated the clinical effect of montelukast in 6 to 14 year old asthmatic children. The degree of a controlled situation imposed in this study can be easily appreciated from some of the inclusion criteria: namely, forced expiratory volume in the first second of 50–85% of the predicted value, a 15% response to bronchodilators, a minimum symptoms score, a minimum of rescue medication uptake, adequate competence and understanding of diaries on the part of patients, peak flow meters, and spirometry. There were many exclusion criteria, including acute sinus disease prior to the study, no visits to the emergency room for asthma or admission within 1 to 3 months prior to the study, and no use of corticosteroids, cromolyn and several other medications. There were restrictions for immunotherapy, no change or addition of new asthma medications were allowed, oral corticosteroids during the study were not allowed more than once, and there were also restrictions on the use of concomitant inhaled corticosteroids.

It is very difficult, if at all possible, to include such a patient within the setting of primary care pediatrics because this type of RCT requirements is far from a real-life situation. An RCT may have the advantage of proving the efficacy of a medication under very controlled and strict conditions but its implications for the practicing pediatrician are limited. In real-life situations the more important factor is effectiveness rather than efficacy, despite their interchangeable usage. These so-called effectiveness trials more closely reflect routine clinical practice. They use a more flexible dosage regimen, a more relaxed protocol to allow physicians and patients to use the drug, and monitor patients in ways that reflect routine clinical practice and usual care more closely, instead of a placebo comparator. Enrolled patients are more representative of actual practice and outcomes including utility

GINA = Global Initiative for Asthma

RCT = randomized controlled trial

measures. They are more suited to provide the data needed to estimate the real benefit of the treatment in actual care [6].

Effectiveness is influenced by many factors that cannot be addressed by an RCT. Nevertheless, one major component in a well-performed trial is treatment compliance. Thus it follows that compliance will affect effectiveness in a real-life study but not efficacy as in an RCT.

The present study was designed to assess clinical intervention of montelukast under real-life conditions with minimal restrictions. It therefore may have more implications for the pediatrician in general practice by taking into account rather than ignoring all the data documented by previously reported RCTs. The present study showed that under real-life conditions montelukast was an effective and highly accepted treatment for children with mild to moderate persistent asthma, and the degree of improvement of symptoms following the prescribing of this drug was remarkable.

It is acknowledged that this was not a placebo-controlled study and therefore part of the improvement might have been due to participation in the study. On the other hand, from a real-life perspective, no placebo is given in clinical practice. The fact that Singulair® was so effective establishes it as an attractive and proven real-life alternative treatment. Some of the enrolled patients were having mild intermittent, rather than persistent asthma according to their symptoms. Nevertheless, the pediatricians' decision to initiate controller therapy typifies a real-life situation.

This study offered an opportunity to highlight important issues in the management of asthma. For example, we noted a significant gap or discrepancy in the definition of severity by pediatricians according to patients' symptoms. This gap conformed to previous studies [7,8]. In the present study, primary care pediatricians tended to underestimate asthma severity in their patients. This gap appears relatively small and this may have been due to the fact that pediatricians were required to apply a structured table based on GINA guidelines in the present study, which may have contributed to a better and more accurate classification. In practice, pediatricians do not employ such instruments, thus the real underestimation of severity may have been even higher. In order to improve agreement in severity assessment between doctors and patients, it may be useful in the future to use similarly structured symptom scoring or analysis within pediatric practice.

The relatively large number of patients who required oral corticosteroids, visited the emergency room, or were admitted in the month preceding the study should be noted. This may represent an under-recognized severity in patients who were not on controller therapy. It must be noted that even patients with mild asthma can experience significant unpredictable and potentially life-threatening exacerbations [9]. The severity underestimation in the present study may also be associated with the under-treatment observed in our study – almost 60% of the patients were not receiving controller therapy at study entry despite being symptomatic and were defined by their pediatricians as having mild persistent to moderate asthma. Physicians tend both to underestimate asthma severity and under-treat their patients. Consequently, among patients receiving montelukast as monotherapy, there were more mild cases according to pediatricians' assessment, while according to their symptoms there were more patients with moderate asthma.

Non-compliance with medication is a major issue in asthma management particularly in children, and poor compliance correlates with loss of asthma control [10]. Many studies have underlined a low adherence to inhalation therapy. One study that investigated the compliance of patients with concurrent prescriptions for inhaled corticosteroids compared to oral theophylline [11] found that patients were significantly more compliant with the prescribed oral medication than with the inhaled drug. The long-term effect of oral Singulair® was compared with inhaled beclomethasone in two long-term extension studies, one of which was double blind and the other open label. In both studies, montelukast and inhaled corticoisteroid treatments improved asthma control, and while montelukast was equally effective during the entire course of both extension studies, the effect of beclomethasone gradually decreased from the outset of the open-label study to the end of its follow-up treatment period. This effect was not observed in the double-blind study. These results emphasize the bias of RCTs in which compliance is optimized and does not reflect the patients' real-life situation. Our results are in agreement with a 6 month open-label extension study comparing beclomethasone with montelukast, where almost twice as many children on montelukast than on beclomethasone were compliant (82% vs. 45%) [12].

In conclusion, under real-life conditions, montelukast, a controller therapy, was shown to be effective in reducing asthma severity and ameliorated all four measured symptoms (wheeze, cough, difficulty breathing and night awakening) to the satisfaction of physicians and parents.

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