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

Israel Amirav MD

Department of Pediatrics, Ziv Medical Center, Safed, and Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel

Key words: asthma, inflammation, montelukast, real-life study

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.

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.

- **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).

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

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 parents 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, 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.

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.

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 requires 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.

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).

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, 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.

RCT = randomized controlled trial

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].

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

- % patients according to asthma severity

<table>
<thead>
<tr>
<th>% of patients</th>
<th>Mild</th>
<th>Moderate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline visit</td>
<td>52</td>
<td>48</td>
</tr>
<tr>
<td>6 week Singulair treatment</td>
<td>50</td>
<td>49</td>
</tr>
</tbody>
</table>

GINA = Global Initiative for Asthma

RCT = randomized controlled trial
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 Singular® 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 corticoesteroid 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.

Acknowledgment. This study was funded by MSD.

References

Correspondence: Dr I. Amirav, Dept of Pediatrics, Ziv Medical Center, Safed 13110, Israel.
Phone: (972-4) 682-8712
email: amirav@012.net.il

Beware of little expenses. A small leak will sink a great ship
Benjamin Franklin (1706-1790), one the most important and influential Founding Fathers of the United States. A noted polymath, Franklin was a leading author and printer, satirist, political theorist, politician, scientist, inventor, civic activist, statesman and diplomat

Capsule

Regulating ovulation
In mammals, the ability of a female to remain fertile for an extended period depends on the continuous awakening of primordial follicles from their dormant state in the ovary. Menopause, or the natural end of female reproductive life, occurs when the pool of primordial follicles has been depleted. The mechanisms controlling follicular activation have remained unknown. Reddy and associates reveal that follicle activation is controlled by the oocyte PTEN (phosphatase and tensin homolog deleted in chromosome 10)-phosphatidylinositol 3-kinase pathway. In a mouse model where Pten is deleted specifically in oocytes, the entire pool of primordial follicles is prematurely activated and subsequently depleted in early adulthood, which results in premature ovarian failure.

Science 2008;319:611
Eitan Israeli

Capsule

Orexin, narcolepsy and anesthesia
What do narcolepsy and anesthesia have in common? Almost a decade ago, a mouse model for human narcolepsy was developed on the basis of results demonstrating that the neuropeptide orexin promoted wakefulness and that genetic ablation of orexinergic neurons yielded mice with behavioral and physiological symptoms remarkably like those of narcoleptic humans. Anesthesia, on the other hand, can be induced by a wide variety of agents such as isoflurane or sevoflurane but has resisted efforts to identify its neural loci of action. In their mouse model, Kelz et al. found that the neural systems innervated by orexinergic neurons are central in the emergence from (though not the induction of) an anesthetized state. Both isoflurane and sevoflurane reduced the percentage of active orexin neurons to the levels seen during non-rapid eye movement sleep, yet an orexin receptor antagonist surprisingly did not change the rate of entry into anesthesia. Nevertheless, the same antagonist did markedly delay recovery from an anesthetized state, and a similar delay was observed in orexin-deficient mice and also is seen in some human narcoleptic patients.

Proc Natl Acad Sci USA 2008;105:2257
Eitan Israeli