Montelukast in Asthma Treatment in Croatia

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A B S T R A C T

The aim of this study was to determine the efficacy and safety of montelukast added to previous medication in the treatment of a mild and moderate asthma. Data were obtained via questionnaires given to the physicians and given further to their patients. Patients were divided in two groups, first followed 4 weeks (612 patients) and second followed 8 weeks (91 patients). We found out that there was a significant improvement in FEV_1 (forced expiratory volume in first second) and general condition of patients and decreased number of salbutamol inhalations after using montelukast. In the second group of patients we find out the same significant improvement in FEV_1, general condition and decrease in salbutamol inhalations after 4 weeks of using montelukast and further improvement after the next month of therapy. We conclude that montelukast is an efficient drug with little side effects and with a good compliance. Montelukast managed to achieve a good asthma control; therefore it has a significant place in asthma therapy.

Key words: *montelukast, asthma, treatment, Croatia*

Introduction

Asthma is one of the most common chronic diseases in the world with prevalence of 10–15% in children and 5–10% in adults in the western world[1]. In Croatia, 3–4 % of patients suffer from asthma[2]. Despite development in understanding mechanisms of the disease and availability of inhalation therapy asthma frequency is increasing both in children and adults. Therefore, during 90's GINA (Global Initiative for Asthma)[3] was created to help health care professionals and public health officials to reduce asthma prevalence, morbidity and mortality. Asthma is today defined as a chronic inflammatory disease of the airways. Chronically inflamed airways are hyper-responsive, they become obstructed and airflow is limited (by bronchoconstriction, mucus plugs, edema and increased inflammation) when airways are exposed to various stimuli or triggers. Common asthma triggers include viral infections, allergens such as domestic dust mites, animals with fur, cockroaches, pollens, tobacco smoke, air pollution, exercise, strong emotional expressions and chemical irritants. Asthma attacks are episodic but airway inflammation is chronically present. Therefore, asthma requires a long-term management and cannot be cured but should be well controlled. It can be treated and controlled so that patients can prevent day and night symptoms, prevent serious attacks, need little or no quick-relief medications, have productive, physically active lives and have (near) normal lung function. According to GINA asthma is classified in two major groups: intermittent and persistent asthma. Persistent is further divided into mild, moderate and severe[3]. This classification is done according to the presence of day and night symptoms and lung function (PEF, FEV_1).

Regarding the GINA guidelines, asthma therapy is applied. Today, there are many drugs used for asthma treatment. All medications are divided in two groups: quick-relief medications (or relievers) that work fast to stop attacks or relieve symptoms, and long-term preventive medications with anti-inflammatory effects (or controllers). In both groups inhaled medications are preferred because of their high therapeutic ratio: high concentrations of drug are delivered directly to the airways with potent therapeutic effects and with few systemic side effects. Corticosteroids, sodium chromoglycate, nedocromil, long-acting β_2 agonists, sustained release theophylline and ketotifen are long-term preventive medications. Inhaled steroids are the most effective anti-inflammatory therapy[4]. And drugs like short-acting β_2 agonists, anticholinergics and short-acting theophylline

are quick-relief medications. All mentioned drugs have been used for asthma treatment for many years.

Therefore, many inflammatory molecules take part in pathophysiology of asthma: IL-4, IL-5, IL-13, histamine, leukotrienes, chemochines, etc.[5] In the last twenty years, only one new group of drugs has been discovered and implemented in everyday practice for asthma management – leukotriene antagonists[6]. History of leukotrienes can be tracked back to classical pharmacology studies in late 1930s. Leukotrienes were then named slow released substance (SRS)[7]. Decades later, Brocklerhurst (1960)[8] renamed it in SRS – A (Slow-reacting substance of anaphylaxis). Two pivotal discoveries were required before the importance of SRS – A in allergic responses were proven. The first was the discovery in 1973 by Augstein et al.[9], when SRS – A antagonist called FPL 55712 was discovered, and the second was elucidation of the structure of SRS – A as a 5-lipooxygenase product of arachidonic acid, which was termed cysteinyl leukotriene[10]. Since then, great efforts were done to try to inhibit leukotriene synthesis by inhibiting 5-lipooxygenase or to block leukotriene receptors. Therefore, first was discovered leukotriene receptor antagonist zafirlukast (1990)[11], then leukotriene-synthesis inhibitor zileuton (1991)[12] and finally in 1995 another leukotriene receptor antagonist montelukast[13]. The first leukotriene antagonist registrated in Croatia was montelukast.

The aim of this study was to determine the efficacy and safety of montelukast in treatment of a mild and moderate persistent asthma.

Subjects and Methods

Sample selection

The study was done between October 2000 and March 2001 all over Croatia. Data were obtained by questionnaires given to pulmonologists all over Croatia. Each pulmonologist was given ten questionnaires to give it further to their patients. Study population consisted β 703 patients from 83 pulmonologists. Study population was further divided in two groups. One group of patients consisted of 612 patients from 73 pulmonologists and was followed in two time points (before and 4 weeks after using montelukast). The second group consisted of 91 patients from 10 pulmonologists and was followed at three time points (before using montelukast, then 4 and 8 weeks after using montelukast). Severity of asthma was classified according to GINA criteria (intermittent and mild, moderate and severe persistent asthma). In all patients montelukast was prescribed as add on therapy to previous asthma medication that they have taken during the last three months. The montelukast (10 mg) was taken at 9 p.m. and FEV_1 was measured at 9 a.m..

Questionnaire

The questionnaire contained questions about asthma therapy (prescribed drugs and their combinations, taken drugs and their combinations) and presence of asthma symptoms before and after use of montelukast. The set of questions in group of patients followed in two time points were as follows: What drugs do you prescribe? What drugs do you take? Perception of well being before and after using montelukast (scale from –3.0 to +3.0, where –3.0 is the worst and +3.0 is the best)? Number of inhalations of salbutamol per day before and after use of montelukast? FEV_1 before and after use of montelukast? Physicians' evaluation of benefit of montelukast usage? Benefit of montelukast on frequency of night symptoms of asthma? Benefits and side effects of montelukast according to physicians and patients?

The set of questions in the group of patients followed in three time points (patients were followed before and 4 and 8 weeks after use of montelukast) was as follows: General condition of patients before and after use of montelukast? FEV_1 before and after using montelukast? Number of salbutamol inhalations before and after using montelukast?

Statistical analysis

The data are presented in absolute and relative frequencies of various answers. The statistical significance was assessed by the test of the significance of the differences of proportions and the Kruskal-Wallis ANOVA test. Statistical analyses were performed using the SPSS software for Windows (SPSS Inc., Chicago, Illinois, USA). The results were considered statistically significant for p values less than 0.05.

Results

We analyzed 612 questionnaires completed by 612 patients from 73 pulmonologist followed in two time points and 91 questionnaires completed by 91 patients and 10 pulmonologists followed in three time points.

The most often prescribed drugs for therapy of asthma are as follows: inhaled corticosteroids which were prescribed in 483 patients (79%), then long-lasting β_2-agonists (437 patients, 71%), long-lasting theophyllines (203 patients, 33%), oral corticosteroids (86 patients, 14%), antihistamines (60 patients, 10%), intravenous aminophylline (10 patients, 2%) and chromones (6 patients, 1 %).

The patients in the first group were followed in two time points, before and after use of montelukast. In the first group there were 73 pulmonologists with ten questionnaires each, and the questionnaires were at the end given to 612 patients.

We compared FEV_1 before and after using montelukast for four weeks in 462 patients regarding level of asthma according to GINA classification. In the group of patients with intermittent asthma (27 patients) there was improvement in FEV_1 from 89% to 94%. In patients with a mild persistent asthma (185 patients) we noticed improvement from 79% to 85% in FEV_1, and in the patients with a moderate persistent asthma (250 patients)

FEV_1 was improved from 64% to 73%. Differences in all groups were statistically significant, p<0.05, (Figure 1).

Further, we compared number of salbutamol inhalations per day in 381 patients before and after use of montelukast regarding level of asthma according to the GINA guidelines. In the group of patients with intermittent asthma (19 patients) a number of salbutamol inhalations remained the same before and after use of montelukast, 0.7 per day. In the group of patients with a mild persistent asthma (157 patients) we noticed decrease in salbutamol inhalations per day from 1.4 to 1.0 after use of montelukast which was statistically significant, p<0.05. And in the group of patients with a moderate persistent asthma (205 patients) we also noticed statistically significant (p<0.05) decrease in salbutamol inhalations per day from 2.7 to 1.9, (Figure 2).

Next we compared a general condition (scale –3.0 to 3.0) of 474 patients before and after use of montelukast regarding level of asthma according to GINA. In the patients with intermittent asthma (29 patients) there was improvement from score 1.3 to 2.2. In the patients with a mild persistent asthma (190 patients) we noticed improvement from 0.9 to 2.0. In the patients with a moderate persistent asthma (255 patients) there was increase from score –0.2 to 1.5. Changes in general condition in all groups were statistically significant, p<0.05, (Figure 3).
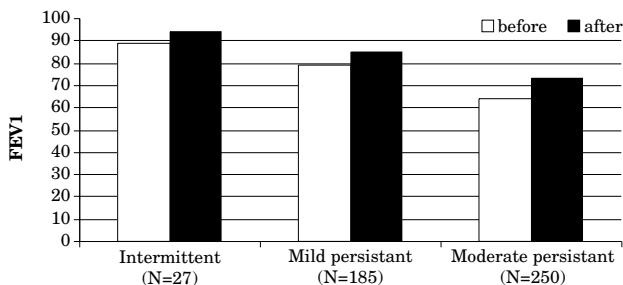

Fig 1. FEV1 (forced expiratory volume in first second) before and 4 weeks after use of montelukast (differences in all groups are statistically significant, p < 0.05).
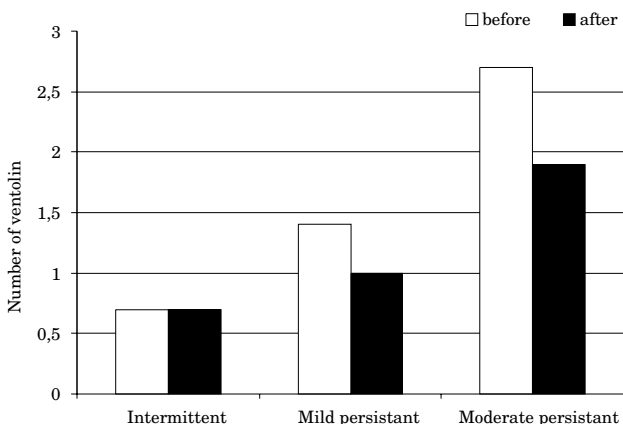

Fig. 2. Number of salbutamol inhalations before and 4 weeks after using montelukast (differences in all groups are statistically significant, p < 0.05).
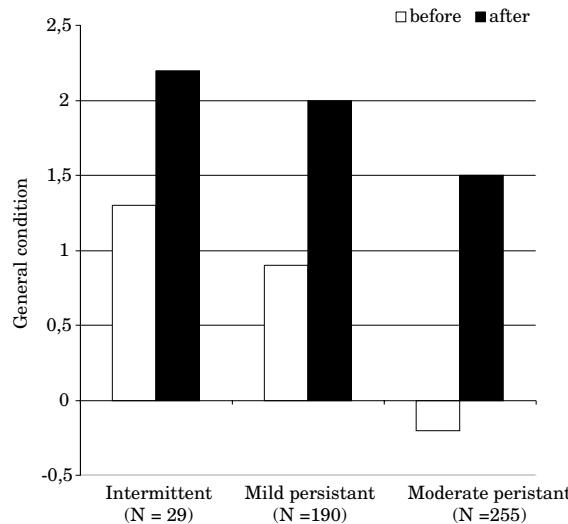

Fig. 3. Patients general condition before and 4 weeks after use of montelukast (scale from –3.0 to 3.0).

Further, we tried to estimate the benefit of montelukast on a general condition of patients from pulmonologists' point of view using the same questionnaires. Benefit of montelukast estimated by pulmonologists was as follows: 110 patients were estimated as 3,0 (21%), 165 patients 2,0 (33%), 109 patients 1,0 (21%), 46 patients had 0 (9%), 27 patients had – 1,0 (5%), then 15 patients – 2,0 (3%) and 41 patients had – 3,0 (8%). In total, 46 patients (9%) have no changes in their condition after use of montelukast, 384 patients (75%) have improvement in their condition after use of montelukast, and only 83 patients (16%) have worsening in their condition although they have used montelukast.

The benefits of montelukast estimated by pulmonologists were as follows: decreased use of standard therapy (inhaled corticosteroids, β_2-agonists) in 135 patients (22%), improvement in FEV_1 in 85 patients (14%), disappearance of night symptoms and cough in 72 patients (12%), quick acting in 49 patients (8%), no need for salbutamol in 48 patients (8%), dealing better with physical activity in 34 patients (6%), possibility of reducing dosage of inhaled corticosteroids in 28 patients (5%), normal physical findings over lung in 27 patients (4%), reduced number of worsening of asthma, shorter and less intense asthma attacks in 21 patients (3%) and reduced number of exacerbations in 10 patients (2%), (Table 1).

The benefits of montelukast observed by patients were as follows: I feel good, stoppage of cough in 130 patients (21%), stoppage of night symptoms in 80 patients (13%), decreased number and less intense and shorter attacks of dyspnea in 71 patients (12%), less using salbutamol in 65 patients (11%), no dyspnea in physical activity in 59 patients (10%), I feel healthy, have better quality of life, satisfied in 51 patients (8%), I feel no problems with my nose nor breathing in 50 patients (8%), I breath easily, feeling of heaviness in lungs have decreased in 24 patients (4%), decreased need for corticosteroid and antihistamines in 4 patients (1%), (Table 2).

TABLE 1

BENEFITS OF MONTELUKAST IN PHYSICIANS' POINT OF VIEW

	N	%
Decreased need for asthma therapy (ICS, B2A)	135	22
Improvement in FEV_1, no symptoms	85	14
Disappaerance of night symptoms, no functional changes	65	11
Quick acting, patient without symptoms	49	8
No need for salbutamol	48	8
No use, no changes, non significant	39	6
Improvement in physical activity	34	6
Possibility to decrease corticosteroid dose	28	5
Normal auscultatory findings, patient stable	27	4
Less intense, shorter attacks	21	3
Good effect on lower and upper airways	12	2
Less exacerbations	10	2

FEV_1 – forced expiratory volume in first second

TABLE 2

BENEFITS OF MONTELUKAST IN PATIENTS POINT OF VIEW

	N	%
I feel good, no cough	130	21
Dissapaerance of night symptoms	80	13
Less intense and shorter asthma attacks	71	12
Decreased need for Ventolin	65	11
No change	63	10
No dyspnea in physical activity	59	10
I feel healthy, better quality of life	51	8
No problems with nose or breathing	50	8
I breath easier, less weigth in lungs	24	4
Vomitting, nausea, vertigo, headache		9
I feel worse	5	1
Decreased dose of corticosteroids or claritine	4	1
Financial reasons, the drug is to expensive	3	0

Fig. 4. *FEV₁ (forced expiratory volume in first second) before and 4 and 8 weeks after using montelukast.*

Fig. 5. *Number of salbutamol inhalations before and 4 and 8 weeks after using montelukast.*

Fig. 6. *Improvement in patients' general condition after 4 and 8 weeks of using montelukast (scale from –3.0 to 3.0).*

The second group of patients (91 patients from 10 physicians) was followed at three time points, before using montelukast and 4 and 8 weeks after using montelukast. We compared FEV_1, number of salbutamol inhalations and general condition of patients before, and one and two months after use of montelukast.

FEV_1 before use of montelukast was 71%. Four weeks after using montelukast average FEV_1 increased to 79% (p<0.001) and to 80% after 8 weeks of using montelukast (statistically significant difference comparing to starting value, p<0.001), **(**Figure 4).

An average number of salbutamol inhalations per day before starting montelukast were 1.7. The average number of inhalations per day decreased to 1.3 after 4 weeks of using montelukast, decreasing further to 0.9 inhalations per day after 8 weeks of using montelukast. Differences between all groups were statistically significant with p<0.05, (Figure 5).
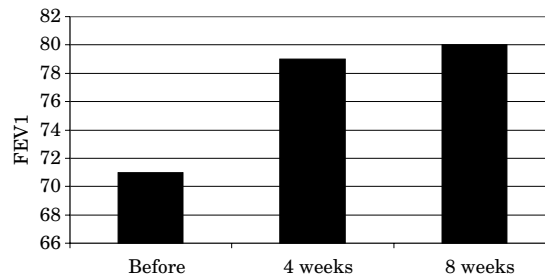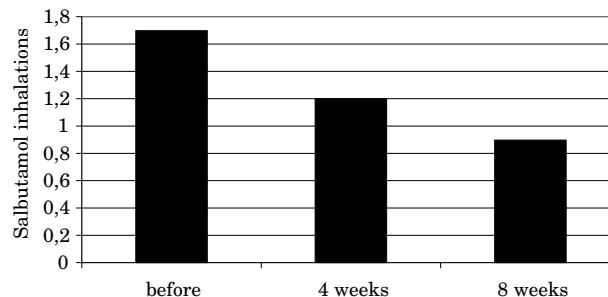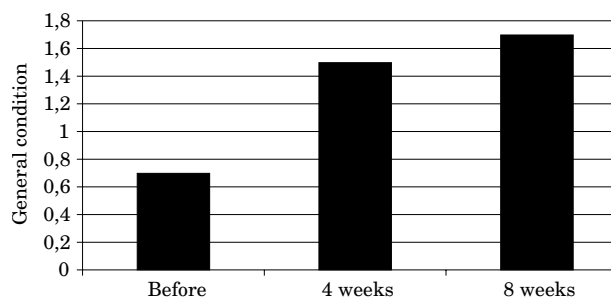
Then we compared general condition of patients before, and 4 and 8 weeks after use of montelukast. Before montelukast general condition of patients was at average graded as 0.7. One month after using montelukast average grade was 1.5 and this was a statistically significant difference, p<0.001. Two months after using montelukast a general condition was graded as 1.7 which is also significant improvement comparing with starting value (Figure 6).

Discussion

The present study was designed to determine the efficacy and safety of montelukast in asthma treatment. We also tried to find out what are the most commonly prescribed medications for asthma treatment.

According to the GINA classification asthma is divided in two major groups: intermittent and persistent

regarding presence of day and night symptoms and also regarding lung function. Persistent asthma is further divided to mild, moderate and severe.

The study was done from October 2000 to March 2001, and data were collected via questionnaire given to patients through their physicians. Patients were divided in two major groups: the first followed at two time points consisted of 612 patients and the second consisted of 91 patients followed in three time points.

Many drugs are used in asthma management today, and most commonly prescribed drugs in Croatia for asthma treatment are inhaled corticosteroids, long lasting β_2-agonists, long lasting theophyllins and oral corticosteroids. Other groups like antihistamines, aminophyllinum and chromones are much less prescribed.

Therefore, as leukotriene-antagonists are new group of drugs in asthma treatment we tried to determine the efficacy and safety of montelukast, one of the leukotriene-antagonists, in treatment of asthma.

We find out statistically significant improvement in patients' general condition after adding montelukast to asthma therapy and we also showed that need for salbutamol inhalations decreased after use of montelukast. Further we showed statistically significant improvement in FEV_1 after adding montelukast to a previous asthma therapy.

Further we showed statistically significant improvement in patients' general condition and in FEV_1 and decreased number of salbutamol inhalations per day after adding montelukast to asthma therapy in all levels of asthma severity according to the GINA criteria (intermittent, mild persistent and moderate persistent). The benefit of montelukast on asthma control was greater in more severe levels of asthma. The probable explanation for that is that in more severe asthma, inflammation is greater, regarding the fact that leukotrienes are inflammatory modulators. Montelukast is anti-inflammatory drug with synergistic and additive effect with steroids.

We also showed that 75% of patients have improved their condition and lung function after use of montelukast in combination with other drugs previously used for asthma treatment.

We tried to estimate the benefit of montelukast according to physicians. Most frequent benefit mentioned was a decreased need for other asthma drugs, improvement in FEV_1 and disappearance of night symptoms. Only in 6% of patients there was no improvement after using montelukast according to physicians.

The benefits of montelukast according to patients were most frequently mentioned stoppage of cough, dis-

appearance of night symptoms and decreased number of asthma attacks. Only 1% of patients, had side effects like vomiting, nausea, vertigo and headaches. That is in concordance with Rakusic et al. who noticed similar results in different asthma perception between physicians and patients in a previous study. Physicians focus on improvements in objective parameters (FEV_1) produced by efficient anti-asthmatic drugs, whereas patients focus on their inability to take part in daily activities and the emotional burden of their disease.

In the second group of patients, which was followed at three time points, before and then 4 and 8 weekss after adding montelukast to other asthma therapy we showed a clinically significant improvement in general condition and in FEV_1 4 weeks after starting to use montelukast. The difference between week 4 and week 8 was still present, though it was not clinically significant. Further, number of salbutamol inhalations decreased 4 and 8 weeks after starting to use montelukast. The differences were statistically significant. And in this group we also noticed that in majority of patients ther was a significant improvement between 4 and 8 weeks after starting to use montelukast.

Montelukast is leukotriene antagonist, a member of group of drugs for asthma treatment called controllers. Montelukast is used to control inflammation in the airway and therefore used to control asthma montelukast has quick action so we did not expect additional benefit after prolonged use of montelukast, (8 weeks after using montelukast). Prolonged use of long lasting β_2-agonists causes tachyphylaxis so we wanted to see is this phenomenon also present after prolonged montelukast usage. Our results have shown that benefit of montelukast is even greater after prolonged use of montelukast. We concluded that there was no tachyphylaxis after prolonged use due to even greater improvement in FEV_1 after prolonged use of montelukast. The additional benefit of montelukast in higher levels of asthma according to the GINA criteria is explainable that a longer period of time is required to achieve satisfactory asthma control.

Montelukast is a drug with few side effects, which is used once a day so compliance was very good. Good compliance also contributed and is necessary for further improvement in FEV_1 and a general condition after prolonged use of montelukast.

We conclude that montelukast is an efficient drug with little side effects and with a good compliance. Montelukast managed to achieve a good asthma control, therefore it has a significant place in asthma therapy.

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MONTELUKAST U LIJEČENJU ASTME U HRVATSKOJ

S A Ž E T A K

Cilj ove studije bio je odrediti učinkovitost i sigurnost montelukasta dodanog ostalim lijekovima za liječenje astme u bolesnika sa blagom i srednje teškom trajnom astmom. Podaci su sakupljeni preko upitnika koji su dani liječnicima i njihovim pacijentima. Bolesnici su bili podijeljeni u dvije grupe; prva, u kojoj su bolesnici praćeni kroz 4 tjedna (612 bolesnika) i druga, u kojoj su bolesnici praćeni kroz 8 tjedana (91 bolesnik). U praćenih bolesnika dokazali smo statistički značajno poboljšanje u FEV_1 (forsirani ekspiratorni volumen u 1. sekundi), poboljšanje općeg stanja bolesnika te smanjeno korištenje salbutamola. U drugoj skupini bolesnika, također smo dokazali poboljšanje u FEV_1 i općem stanju, te smanjenje korištenja salbutamola u prva 4 tjedna praćenja, te daljnji napredak u slijedeća 4 tjedna. Na temelju rezultata ove studije zaključujemo da je montelukast učinkovit lijek sa vrlo malo nuspojava. Montelukast je uspio postići dobru kontrolu astme, stoga ima značajno mjesto u liječenju bolesnika s astmom.