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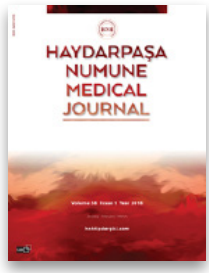

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ORIGINAL ARTICLE

Comparison of The Treatment Efficacy of Montelukast and Zafirlukast in Children with Asthma

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Abstract

Introduction: Asthma is one of the most common respiratory disorders in clinical practice, affecting up to 13% of people worldwide. Leukotriene antagonists have long been used in the treatment of asthma. This study was conducted to compare the effectiveness of the montelukast and zafirlukast treatment in children diagnosed with asthma.

Methods: Sixty-one patients diagnosed with asthma in the age group of 6-14 years were included in the study. Patients were consecutively divided into 2 groups, and the first group was given 5 mg of montelukast before sleep and the second group received 10 mg/day of zafirlukast in two doses. The patients were followed up monthly for 6 months. Short acting beta agonist and inhaled corticosteroid use, daytime symptoms, night awakenings, admission to the emergency department and FEV1 value were compared before and after the treatment and between two groups.

Results: Significant improvement was observed in both groups during post-treatment period when compared to the pre-treatment period in terms of the short acting beta agonist and inhaled corticosteroid use, daytime symptoms, night awakenings, mean FEV I. However, no statistical difference was determined between two groups.

Discussion and Conclusion: It was found that monteluksat and zafirlukast were effective in asthma treatment and there was no difference between their effects.

Keywords: Asthma; montelukast; zafirlukast.

Asthma is one of the most common chronic diseases in childhood and one of the leading chronic diseases that cause absenteeism at school. In 30% of the patients, the onset is around 1 year old, and the first symptoms appear before the age of 4-5 in 80-90%[1]. Medications used in asthma treatment are divided into two groups as relieving and disease-controlling drugs[2]. Symptom-relieving drugs are inhaled beta-2 agonists, inhaled short-acting anticholinergic drugs, short-acting theophylline, short acting oral beta-2 agonists, magnesium and systemic steroids. Disease-controlling drugs include inhaled systemic steroids, long-acting inhaled beta-2 agonists used in conjunction with inhaled steroids, leukotriene antagonists, slow-release theophylline, and long-acting anticholinergics. Disease-controlling drugs are used daily and for a long time, mainly to keep asthma under control through

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their anti-inflammatory effects. There are studies in the literature investigating the advantages of these treatment methods[3-5].

Leukotrienes are mediators that are synthesized in inflammatory cells such as eosinophils, basophils and mast cells in the bronchial mucosa and have important roles in asthma pathogenesis. Leukotriene antagonists (zafirlukast, montelukast) are drugs used in the treatment of asthma for a long time. Studies have been published reporting that these drugs reduce symptoms, reduce the need for bronchodilators and increase FEV1 in patients with mild persistent asthma[6-8]. Although there are many studies on the treatment efficacy, tolerability and side effects of montelukast and zafirlukast, which are the leukotriene receptor antagonists separately, there are no studies comparing these two drugs with each other in the literature; therefore, this study was planned. We aimed to compare the effectiveness of both treatments by administering these two drugs to patients who were admitted to our clinic with a diagnosis of partially controlled asthma.

Materials and Methods

In this study, 61 patients between the ages of 6-14 who admitted to the Pediatric Health and Diseases Clinic of Dr. Lütfi Kırdar Kartal Training and Research Hospital and who were diagnosed with partially controlled asthma according to the control level, were included. Complete blood count, peripheral blood eosinophil count, sedimentation, PPD, stool parasite test, nasal smear eosinophil count, total IgE level, aspartate transaminase (AST), alanine transaminase (ALT) tests were performed in these patients at the admission; and PA chest X-ray and Waters' view were obtained. Twenty-one parameter prick test including testing aeroallergens was used as an allergy skin test. Pulmonary function tests were performed with spirometry.

Patients were randomly divided into two groups according to the order of admission to the outpatient clinic for treatment. The first group was started on 5 mg montelukast once a day before going to bed at night, and the second group was started on a total of 10 mg zafirlukast twice a day. Patients in both groups were followed up monthly. Nighttime symptoms, daytime symptoms, occurrence of asthma episodes, need for short-acting beta-2 agonists, and inhaled steroid use were questioned at each visit; pulmonary function tests were performed every three months. Pulmonary function tests of the patients were performed at any time during the day by the same person. The efficacy of both treatments was compared considering nighttime symptoms, daytime symptoms, occurrence of asthma episodes, need for short-acting beta-2 agonists, inhaled steroid use, and FEV percentage parameters. Local Ethics Committee Approval was obtained for the study.

Statistical Analysis

Statistical analyses were performed using the SPSS (Statistical Package for Social Sciences) for Windows 15.0 program. P value <0.05 was considered statistically significant. Besides descriptive statistical methods (mean, standard deviation), student t test was used for independent groups in normal distribution; Analysis of Variance in Repeated Measures was used in the evaluation according to in-group follow-up times; Paired Samples t test was used in post HOC evaluations. Mann Whitney U test was used for independent groups which are not normally distributed, Friedman test was used for evaluations according to in-group follow-up times; Wilcoxon signed-rank test was used in post hoc comparisons. Chi-square test and Fisher's exact test were used for comparison of qualitative data, and McNemar's test was used for evaluations of dependent groups. Results were accepted at 95% confidence interval.

Results

Thirty patients with partially-controlled asthma (median age:8.5 years, 70% male) receiving montelukast treatment were included in the study as group I and 31 patients with partially-controlled asthma (median age:10 years, 45.2% male) receiving zafirlukast treatment as group II. The mean follow-up period of group 1 was 8.1 months, and group 2 was 8.4 months. When the treatment groups were compared in terms of initial tests, no statistically significant difference was found in skin prick test results, nasal eosinophil positivity, serum Ig E level, percentage of peripheral blood eosinophils and FEV1 results (p>0.05).

Pre-treatment Parameters

There was no statistically significant difference between the two groups in terms of use of short-acting beta-2 agonists 3 months before the initiation of anti-leukotriene treatment, the number of nighttime symptoms, the number of daytime symptoms, the number of episodes in the day, and the presence of symptoms with exercise (Table 1).

Evaluation of Response to Treatment

1. **Number of episodes:** There was no statistically significant difference between the groups in terms of the number of episodes before and during the first three

Table 1. Evaluation of beta agonist use and symptoms by groups

	Group I (n=30)	Group II (n=31)	*p
Beta agonist use			
Pre-treatment (PT)	8.83±6.63	8.19±6.83	0.451
3rd month	4.60±5.98	4.09±4.83	0.958
6th month	7.06±8.18	3.38±5.09	0.097
9th month	3.75±4.43	2.41±3.33	0.251
**p value			
PT-3rd month	0.003	0.001	
PT-6th month	0.145	0.001	
PT-9th month	0.003	0.001	
Number of nighttime episodes			
Pre-treatment	7.40±5.10	3.80±3.91	0.913
3rd month	2.43±3.23	1.52±2.25	0.432
6th month	4.03±6.97	2.13±6.32	0.038
9th month	2.64±3.66	1.51±3.69	0.130
**p value			
PT-3rd month	0.001	0.007	
PT-6th month	0.017	0.025	
PT-9th month	0.001	0.023	
Number of daytime episodes			
Pre-treatment	9.23±6.5	5.90±4.77	0.004
3rd month	3.03±4.85	3.29±4.76	0.551
6th month	7.73±9.64	4.51±7.94	0.149
9th month	3.25±3.97	1.93±3.49	0.139
**p value			
PT-3rd month	0.001	0.017	
PT-6th month	0.222	0.074	
PT-9th month	0.001	0.004	

* : Mann Whitney U test; **: Friedman test; binary comparisons Wilcoxon Signed Rank test.

months of treatment (p>0.05). The second trimester of treatment was valuable among the groups according to their number within cases of Group I. (p<0.05). There was no statistically significant difference between the groups in terms of the number of episodes in the third 3 months of treatment (p>0.05). When compared before and after treatment, a significant decrease in the number of episodes was found in both groups (Fig. 1).

2. **Use of short-acting beta-2 agonists:** There was no significant difference between the groups in the measurements taken before the treatment and at the 3rd month of the treatment (p>0.05); Although beta-2 agonist use was higher in Group I in the 6th month, there was no statistically significant difference (p>0.05). In the 9th month, there was no significant difference again between the number of beta-2 agonists use of the groups (p>0.05). The decrease in the number of beta-2 agonist use in the 3rd and 9th months in both groups compared to the pre-treatment preiod was found to be statistically significant (p<0.05); While there was no significant change in the 6th month measurements after the treatment in group I compared to pre-treatment period (p>0.05); a statistically significant decrease was detected in group II (p<0.05) (Table 1).

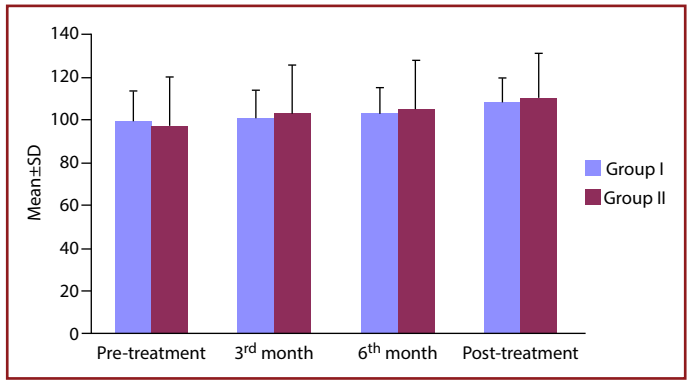

Figure 1. Distribution of the groups according to the number of episodes.

3. **Inhaled steroid use:** When the patients were evaluated at the 3rd, 6th and 9th months of the treatment, it was found that the rate of steroid use decreased in both groups. There was no significant difference between the groups in terms of steroid use (p>0.05) (Fig. 2).
4. **Number of nighttime symptoms:** The number of nighttime symptoms did not differ significantly between the groups in the pre-treatment period and in the 3rd and 9th months of treatment (p>0.05); The rate of nighttime symptoms in Group I in the 6th month was found to be statistically significantly higher than Group II (p<0.05). The decrease in the number of nighttime symptoms in the 3rd, 6th and 9th months of the treatment in Groups I and II, compared to the pre-treatment period was found to be statistically significant (p<0.01) (Table 1).

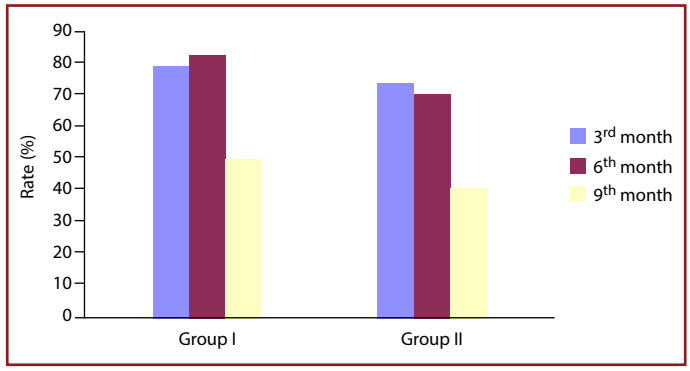

Figure 2. Distribution of steroid usage rates by groups.

5. **Number of daytime symptoms:** Number of daytime symptoms in Group I before treatment was found to be significantly higher than in Group II ($p<0.01$). 3rd, 6th and 9th month post-treatment measurements did not differ significantly between groups ($p>0.05$). In both groups, the decrease in the number of daytime symptoms in the 3rd month and the 9th month compared to the pre-treatment period was found to be statistically significant ($p<0.01$) (Table 1).
6. **FEV1 levels:** There was no statistically significant difference between the groups in terms of % FEV1 values at the beginning of the treatment, at the 3rd and 6th months of the treatment and after the treatment ($p>0.05$). While there was no significant change in the 3rd and 6th months compared to the beginning of the treatment in group I; the increase in % FEV1 measurements at the end of the treatment was found to be statistically significant ($p=0.001$; $p<0.01$). In Group II, the increase in % FEV1 measurements at the 3rd month, 6th month and at the end of the treatment was statistically significant, compared to the beginning of the treatment ($p=0.026$; $p=0.026$; $p=0.001$) (Fig. 3).

Discussion

As a result of this study, the leukotriene antagonists montelukast and zafirlukast treatments were found to have no difference in their efficacy in patients who were followed up with a diagnosis of partially-controlled asthma. Today, asthma remains an important childhood health problem that affects approximately 10% of children. It negatively affects the academic achievement and social communication of children by causing school absenteeism[9]. Despite the increase in preventive health services, most of the children have frequent epoisodes and the rates of admission to the emergency department and hospitalization are high.

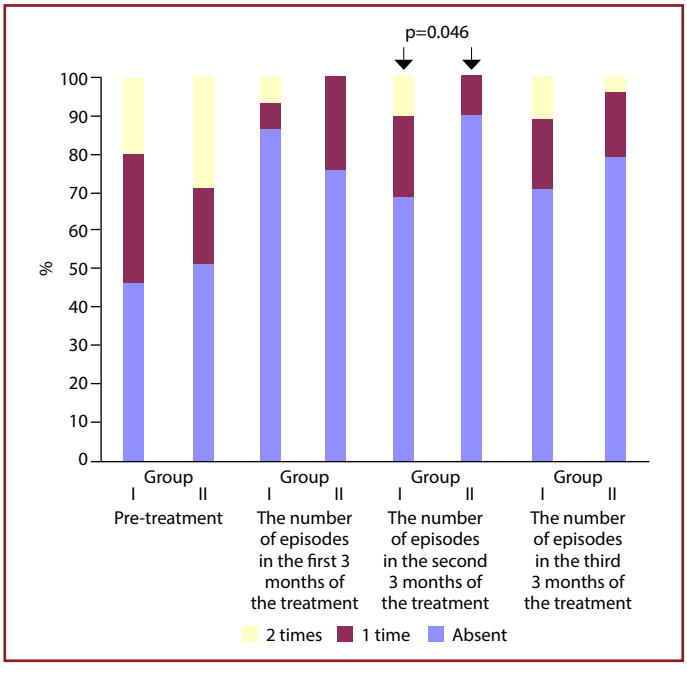

Figure 3. Distribution of FEV 1% measurements by groups.

The aim of the treatment of asthma is to ensure that children can do activities similar to healthy children while the symptoms are under control, to prevent the negative effects of exacerbations on lung functions and growth, and to minimize the risks such as the occurrence of adverse effects due to drugs[1]. Asthma treatment is based on regular preventive treatment and the use of relieving medication when necessary. The clinical benefits of asthma treatment in children are limited by the narrow therapeutic index of the drugs, long-term tolerability and administration frequency and/or difficulty[10]. The current treatments we have today do not have an affect on both the development and the natural course of asthma, but they can control the disease.

Leukotrienes are mediators that are synthesized in inflammatory cells such as eosinophils, basophils and mast cells in the bronchial mucosa and have important roles in asthma pathogenesis. They cause bronchoconstriction, eosinophil infiltration, increased mucus secretion and vascular permeability[11]. Leukotriene receptor antagonists (montelukast, zafirlukast) have been used in the treatment of asthma for over thirty years. They achieve their effects by blocking the Cys LT1 receptor, which is involved in arachidonic acid metabolism and is found in lung tissue and blood cells. Studies examining leukotriene-blocking receptor antagonists and 5-lipoxygenase inhibitors have shown improvement in asthma control in children. In studies comparing zafirlukast with placebo, it was reported that patients with chronic asthma using zafirlukast had an improvement in daytime symptom scores, a decrease in nighttime awakenings, and a decrease in the use of short-acting beta-2 agonists needed daily[12,13]. In the literature, it has been reported that the total daily use of short-acting beta-2 agonists and the number of asthma episodes during day and night were lower in chronic asthma patients aged 2-5 years with chronic asthma treatment with montelukast, compared to the group using placebo[10,14]. In our study, it was found that the need for use of short-acting beta-2 agonists, daytime and nighttime symptom frequency and the number of episodes were lower in patients followed up with a diagnosis of partially controlled asthma after montelukast or zafirlukast treatment, and that neither treatment method

was superior to each other.

In children followed up with a diagnosis of persistent asthma, after treatment with leukotriene antagonists (montelukast, zafirlukast), a significant improvement was found in pulmonary function tests, PEF and FEV 1 levels compared to placebo[13,15-17]. In our study, a significant increase was observed in the FEV1 values of the patients after both montelukast and zafirlukast treatment. There was no significant difference between the two groups in terms of increase in FEV1 value.

It has been reported that montelukast leads to an improvement in airway obstruction and daily symptom scores, a decrease in night awakenings, the rate of asthma episodes, and the use of total daily beta-2 agonists, and this effect was reported to be similar to the effect obtained with inhaled steroids[5,18]. In our study, it was observed that approximately thirty percent of the patients who were initiated montelukast or zafirlukast treatment did not need inhaled steroid treatment they were using and stopped, and no statistically significant difference was found between the two groups in the rate of discontinuation steroid treatment. In both groups, no side effects that led to treatment discontinuation were observed. Our study showed that the addition of leukotriene antagonists to corticosteroid treatment in partially controlled asthma would have a positive effect on the course of asthma and reduce the need for steroids.

Cysteinyl leukotrienes play an important role in the pathogenesis of asthma. The high patient compliance due to oral use of one or two doses per day, having both bronchodilator and anti-inflammatory effects, controlling asthma symptoms with a single drug, and not having serious side effects known to date, provide advantages of leukotriene antagonists to have an advantage over other drugs used in the treatment of asthma. As a result of our study, it was determined that montelukast and zafirlukast in children with a diagnosis of partially controlled asthma were easy to use and safe and their effects were not different from each other. Due to its ease of use, the rate of compliance with treatment was found to be high. When used in combination with inhaled steroids, it was found that it allowed the reduction of the steroid treatment dose or the discontinuation of the steroid treatment and it did not have significant side effects.

Ethics Committee Approval: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept: B.V., A.G.T.; Design: B.V., A.G.T.; Data Collection or Processing: B.V., P.B.; Analysis or Interpretation: B.V., S.Ö.; Literature Search: B.V., A.G.T., P.B.; Writing: B.V., A.G.T., S.Ö.

Conflict of Interest: None declared.

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