Int J Clin Exp Med 2020;13(7):5122-5129
www.ijcem.com /ISSN:1940-5901/IJCEM0108076

Original Article

The efficacy of montelukast sodium and budesonide on pulmonary function in infantile asthma

Chao Lin[1,2], Guoyan Lu[1,2], Dan Yu[1,2]

[1]Department of Pediatrics, West China Second University Hospital, [2]Key Laboratory of Birth Defects and Related Diseases of Women and Children of The Ministry of Education, Sichuan University, Chengdu, Sichuan Province, China

Received January 18, 2020; Accepted February 16, 2020; Epub July 15, 2020; Published July 30, 2020

Abstract: Objective: To analyze the clinical efficacy of montelukast sodium combined with budesonide on the pulmonary function of children with asthma. Methods: A prospective study was carried out on 100 children with asthma who were randomly divided into a control group (50 cases) and an experimental group (50 cases). The control group received budesonide, and the experimental group was given montelukast sodium and budesonide. We compared the two groups' clinical efficacy, their post-treatment clinical symptom scores, their adverse reactions, and their pulmonary function indices (forced expiratory volume in one second (FEV_1), peak expiratory flow (PEF), and the percentage of FEV_1/forced vital capacity (FEV_1/FVC)). Results: After the treatment, the FEV_1, PEF, and FEV_1/FVC as well as the total effective rate in the experimental group were significantly higher than they were in the control group (all $P<0.05$). After the treatment, the daytime asthma control and the nighttime asthma control scores of the experimental group were significantly lower than they were in the control group ($P<0.05$). Though the incidence of adverse reactions in the experimental group was lower than it was in the control group, the difference was not statistically significant ($P>0.05$). In the one-year follow-up, the recurrence rate in the experimental group was significantly lower than it was in the control group. Conclusion: In children, the combination of montelukast sodium and budesonide can effectively improve the patients' pulmonary function indices, relieve their asthma symptoms, lower their incidence of adverse reactions, and reduce the recurrence rate.

Keywords: Montelukast sodium, budesonide, infantile asthma, pulmonary function, clinical efficacy

Introduction

Asthma is a complex chronic respiratory inflammatory disease [1]. Patients often suffer from the paroxysmal repeated attacks of airway obstruction, airway inflammation, hyperresponsiveness, and mucus hypersecretion [2], which induce coughing, gasping, chest distress, dyspnea, and other symptoms [3]. In the past decades, asthma has become one of the main factors affecting the life and health of children [4] as its incidence and hospitalization rate have been on the rise for years [5]. Without effective control, asthma may lead to a series of symptoms in children, such as growth retardation, nighttime gasping, and sleep deprivation, lower their quality of life, and cause economic burdens on their families [6, 7].

Infantile asthma can be managed with proper drug treatment, education for patients and their families, and environmental control [8]. Inhaled corticosteroids are the most common drugs used in the first-line treatment of infantile asthma [9-14]. Budesonide, a glucocorticoid, has extensive anti-inflammatory effects [15]. It is capable of controlling infantile asthma, but the inhibitory effect against leukotriene, which is the pathogenic factor of airway inflammatory reactions [16], is not significant. In addition, budesonide also has certain limitations, as the long-term use of the drug may cause side effects [17].

Montelukast sodium is a cysteinyl leukotriene receptor antagonist that can effectively inhibit the synthesis of leukotriene, alleviate inflammatory reactions [18], and serve as an adjuvant or alternative therapy in glucocorticoid drug treatment [19]. Studies have shown that montelukast sodium can relieve symptoms and improve pulmonary function [20]. Though many

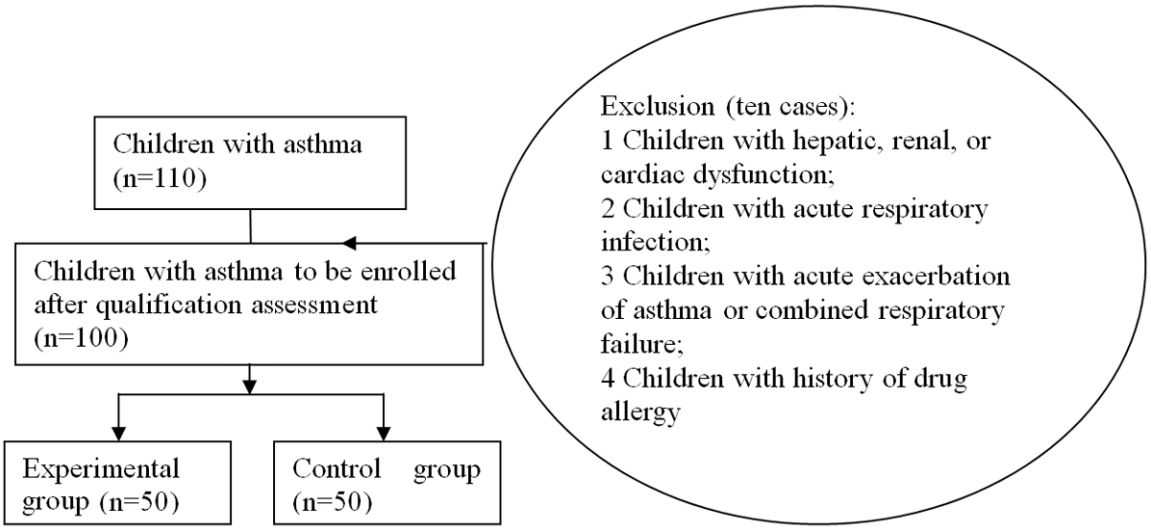

Figure 1. Flow chart of this study.

studies have explored the possibility of treating asthma with the combined treatment of montelukast sodium and budesonide, the effects of such treatment on pulmonary function in infantile asthma still needs more data. Therefore, this study enrolled 100 children with asthma to investigate the efficacy of such a combined treatment on the pulmonary function of children with asthma.

Methods

General information

This prospective analysis recruited 100 children with asthma who were admitted to the West China Second University Hospital, Key Laboratory of Birth Defects and Related Diseases of Women and Children of the Ministry of Education between January 2018 and July 2019. These children were randomly divided into the experimental group and the control group. We obtained the informed consent of the parents of these children, and the study was approved by the Ethics Committee of West China Second University Hospital, Key Laboratory of Birth Defects and Related Diseases of Women and Children of the Ministry of Education. See the flow chart of this study in **Figure 1**.

Inclusion and exclusion criteria

Inclusion criteria: Only subjects meeting all of the following criteria were enrolled: patients meeting with the diagnostic standards of the *Guidelines on the Diagnosis and Prevention of Bronchial Asthma in Children (2016)* established by the editorial board of the *Chinese Journal of Pediatrics* under the Subspecialty Group of Respiratory Diseases, the Society of Pediatrics, Chinese Medical Association [21]; patients with symptoms such as dyspnea, cough, and gasping, and clinically diagnosed with asthma; patients whose parents signed the informed consent form; patients who did not use any other drugs in the three months before their enrollment in the study.

Exclusion criteria: Children with any of the following conditions were excluded: patients with hepatic, renal, or cardiac dysfunctions; patients with acute respiratory infections; patients with acute exacerbation of asthma or combined respiratory failure; patients with a history of drug allergies.

Methods

Children in the control group were prescribed the inhalation of budesonide aerosol (20 mg/100 sprays, 200 μg/spout; manufactured by Shanghai Sine Pharmaceutical Laboratories Co., Ltd.) at the dose of one spray/time, bid. Those in the experimental group were treated with both budesonide aerosol and montelukast sodium chewable tablets (5 mg/tablet, manufactured by Lunan Beite Pharmaceutical Co., Ltd.). Montelukast sodium chewable tablets was administered orally at the dose of one tab-

Table 1. General information

Related factors	Experimental group	Control group	t/χ^2	P
Age			0.043	0.836
<7	32	31		
≥7	18	19		
Gender			0.049	0.826
Male	35	36		
Female	15	14		
Severity of asthma			0.544	0.762
Mild	23	25		
Moderate	15	16		
Severe	12	9		
Average course of the disease (years)	2.6±0.5	2.5±0.5	0.381	0.674
History of smoking			0.060	0.806
Yes	10	11		
No	40	39		
History of medication			0.198	0.656
Yes	15	13		
No	35	37		
History of asthma in parents			0.078	0.799
Yes	7	8		
No	43	42		

let/time. All the children received three-month treatment, and they were not allowed to take any other adjuvant drugs, and they all were followed up for one year.

Observation indices

Pulmonary function: A spirometer (model: SP-1, Schiller AG) was used to compare the pulmonary function changes of the two groups of children before and after the treatment [22]. Indices: forced expiratory volume in one second (FEV_1); forced vital capacity (FVC); percentage of FEV_1 in forced vital capacity (FEV_1/FVC); peak expiratory flow (PEF).

Efficacy: Markedly effective: cough, pulmonary wheeze, dyspnea, and other clinical symptoms nearly disappeared with an increase of FEV_1 over 35% after the treatment; Effective: the clinical symptoms were relieved to some extent with a 25%-35% increase in FEV_1 after the treatment; Ineffective: the symptoms showed no relief, and there was no improvement in the pulmonary function indices, or the condition of the disease was aggravated. Total effective rate % = (number of markedly effective cases + number of effective cases)/total cases number * 100 [21].

Asthma control scores during the daytime and nighttime: The daytime asthma control scores were calculated using a scale of 0-3 according to the number of occurrences of gasping, dyspnea, chest distress, and other symptoms; a higher score indicates a more severe disease condition. The nighttime asthma control scores were calculated using a scale of 0-4 according to the number of occurrences of nighttime choking during sleep and early awakening [23].

Adverse reactions: Oral candidiasis, hoarseness, scratchy sore throat, growth retardation, and adrenal suppression in children are defined as adverse reactions. In such cases, the children were asked to rinse out their mouths after taking the drug, and the adverse reactions were observed after the drug's reduction and withdrawal. In severe cases, the child was immediately sent to a hospital. The incidence of an adverse reaction % = number of cases with adverse reactions/total cases number * 100.

Recurrence rate after withdrawal: After the withdrawal, a one-year follow-up was performed to observe the recurrence rate [24]. The recurrence rate % = number of recurrent cases/total cases number ×100; non-recurrence rate % = number of non-recurrent cases/total cases number ×100.

Statistical methods

SPSS 22.0 statistical software (IBM, USA) was adopted for the data processing. The measurement data were expressed in the form of ($\bar{x}$ ± sd), and the comparisons between two groups used independent sample t-tests, while the intra-group comparisons used paired t-tests. The enumeration data were expressed as case number/percentage (n/%), and the comparisons between two groups used χ^2 tests. $P< 0.05$ indicates that a difference is statistically significant.

Table 2. Comparison of the pulmonary function indices in the two groups before and after the treatment

Group	Experimental group	Control group	t	P
FEV_1 (L)				
Before treatment	0.59±0.11	0.60±0.10	-0.476	0.635
After treatment	0.91±0.26a	0.80±0.25b	2.156	0.033
FVC (L)				
Before treatment	2.18±0.33	2.17±0.32	0.154	0.871
After treatment	2.93±0.51a	2.42±0.61b	4.636	0
PEF (L/s)				
Before treatment	59.21±17.32	59.09±17.33	0.035	0.972
After treatment	91.00±19.67a	81.94±20.21b	2.272	0.025
FEV_1/FVC (%)				
Before treatment	63.79±3.06	63.81±3.05	-0.033	0.974
After treatment	89.56±2.05a	73.65±2.03b	38.995	0

Note: FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; PEF: peak expiratory flow. Comparison with the same group before the treatment, aP<0.05, bP<0.05.

Table 3. Comparison of the clinical efficacy in the two groups [n (%)]

Group	n	Markedly effective	Effective	Ineffective	Total effective rate (%)
Experimental group	50	45	3	2	48 (96.00%)
Control group	50	30	9	11	39 (78.00%)
χ^2					7.162
P					0.007

Table 4. Comparison of the two groups' asthma control scores before and after the treatment during the daytime and nighttime ($\bar{x}$ ± sd)

Group	Experimental group	Control group	t	P
n	50	50		
Daytime				
Before treatment	14.2±2.1	13.8±2.2	0.93	0.355
After treatment	2.7±1.1c	7.6±1.3d	-20.346	0
Nighttime				
Before treatment	8.9±2.0	9.1±2.1	-0.488	0.627
After treatment	2.2±0.4c	4.6±1.2d	-13.416	0

Note: Comparison with the same group before the treatment, cP<0.05, dP<0.05.

Results

The comparison of the two groups' general information

Table 1 provides a comparison of the two groups' general information. The experimental group included 35 male children and 15 female children, with an age span of 2-10 and an average age of (5.1±2.1). There were 32 children under age 7, and 18 at or above age 7. The average course of the disease was (2.6±0.5) years. The experimental group's cases were categorized into 23 mild cases, 15 moderate cases, and 12 severe cases. The control group included 36 male children and 14 female children, with an age span of 2-12 and an average age of (5.1±2.0). There were 31 children under age 7, and 19 at or over age 7. The average course of the disease was (2.5±0.5) years. The experimental group's cases were categorized into 25 mild cases, 16 moderate cases, and nine severe cases. There was no statistical difference between the two groups in terms of the children's general information (P>0.05).

The children treated with combination therapy had better pulmonary function indices

Before the treatment, there was no statistically significant difference between the two groups in terms of their pulmonary function indices, FEV_1, FVC, PEF, and FEV_1/FVC (all P>0.05). After the treatment, the pulmonary function indices in both groups were significantly higher than they were before the treatment, but the experimental group's indexes were higher than the control group's (all P<0.05). See the details in **Table 2**.

Children treated with combination therapy showed better clinical efficacy

The total effective rate of the control group (78.00%) was significantly lower than the rate of the experimental group (96.00%, P = 0.007). See the details in **Table 3**.

Table 5. Comparison of the two groups in their incidences of adverse reactions (n/(%))

Group	n	Oral candidiasis	Hoarseness	Scratchy sore throat	Growth retardation	Incidence of adverse reactions (%)
Experimental group	50	0	1	1	0	2 (4.00%)
Control group	50	1	2	1	1	5 (10.00%)
χ^2						0.122
P						0.727

Table 6. Comparison of the two groups in their asthma recurrence rates at one year after withdrawal [n (%)]

Group	n	Non-recurrence	Recurrence
Experimental group	50	44 (88.00%)	6 (12.00%)
Control group	50	35 (70.00%)	15 (30.00%)
χ^2			4.882
P			0.027

The children treated with combination therapy had better asthma control scores before and after the treatment during the daytime and nighttime

Before the treatment, there were no statistically significant differences between the two groups in their daytime or nighttime asthma control scores (P>0.05). After the treatment, both groups had significantly larger drops in their daytime and nighttime asthma control scores, but the changes in the experimental group were more significant (P<0.05). See the details in **Table 4**.

The children treated with combination therapy had fewer adverse reactions

After the treatment, the incidence of adverse reactions in the experimental group was lower than it was in the control group, but the difference was insignificant (χ^2 = 0.122, P = 0.727). See details in **Table 5**.

The children treated with combination therapy had lower recurrence rates

One year after the treatment, the experimental group had an asthma recurrence rate of 12.00%, which was significantly lower than the rate in the control group (30.00%, P = 0.027). See the details in **Table 6**.

Discussion

Montelukast sodium is a novel, efficient leukotriene receptor inhibitor [25] that can selectively inhibit the activity of leukotriene peptides in the smooth airway muscles, prevent and inhibit the increased vascular permeability, eosinophil infiltration, and airway spasms induced by leukotriene, reduce the inflammatory substances caused by airway allergies, and alleviate bronchial hyperresponsiveness [26-28]. The combination of montelukast sodium with the glucocorticoid drug budesonide makes better use of their respective advantages. Many related studies have found that combining montelukast sodium and budesonide improves the total effective rate in asthma treatment [29, 30].

Our results showed that after treatment, the FEV_1, FVC, and PEF, FEV_1/FVC indices of the experimental group were significantly higher than of the indices in the control group, suggesting that the combined treatment of montelukast sodium and budesonide can effectively improve pulmonary function in children with asthma, a finding consistent with the conclusions of other studies that found that combined leukotriene receptor antagonists with inhaled corticosteroids can more effectively improve pulmonary function in children with asthma than using inhaled corticosteroids alone [31]. In addition, montelukast sodium has a good compliance [32], so combining it with budesonide can create a supplementary effect and improve treatment efficacy. This also indirectly testifies to the limitations of budesonide used alone in improving FEV_1 and other pulmonary function indices, which have also been mentioned in other studies [34].

In our study, the total effective rate of the experimental group was significantly higher than of the rate in the control group, indicating that the combined treatment had a significant effect on asthma in children. The combination therapy can effectively relieve clinical symptoms, comprehensively inhibit the synthesis of leukotriene and other inflammatory substances, inhibit the secretions of airway mucus, and promote the stretching of the smooth tracheal

muscles [35]. After the treatment, the daytime and nighttime asthma control scores in the experimental group were significantly lower than of the scores in the control group, indicating that the combined treatment had a better effect at controlling asthma. Previously studies have also found that the combination of montelukast sodium and budesonide can effectively lower asthma control scores and improve patients' quality of life [36]. The mechanism may be that montelukast sodium can bind with leukotriene receptors, and budesonide binds with glucocorticoid receptors, so the anti-inflammatory effect is strengthened, the secretions of airway mucus are reduced, and the frequency of asthma attacks is lowered [37].

We also found that the combined treatment can lower the incidence of adverse reactions such as oral candidiasis, hoarseness, and other phenomena. Local and systemic adverse reactions are common in the use of glucocorticoid drugs [38], so the administration of glucocorticoids should be controlled [39]. Related studies have shown that montelukast sodium has a sound tolerance. Even though the given dose of montelukast sodium was as high as 200 mg/d, which is far above the maximum dose recommended in clinical practice (10 mg/d), the incidence of adverse reactions is still relatively low [40]. In addition, we found that the recurrence rate of the experimental group was significantly lower than the rate in the control group. Due to the heterogeneity of asthma, using glucocorticoid drugs alone has the defects of poor responses and poor prognosis, so the combination of glucocorticoid and leukotriene receptor modulators should be considered [41] In addition, using glucocorticoid drugs alone has trigger factors that may cause the recurrence of asthma [42].

However, due to the small sample size of this study, the study results are inadequate, so further studies should be performed to verify our findings and further details on the mechanisms of this combination therapy should be explored.

In conclusion, giving montelukast sodium and budesonide to children with asthma can significantly improve their pulmonary function indices, lower their incidence of adverse reactions, reduce the recurrence rate, and achieve better clinical efficacy, so it is worthy of clinical promotion.

Disclosure of conflict of interest

None.

Address correspondence to: Dan Yu, Department of Pediatrics, West China Second University Hospital, Sichuan University, Chengdu, Sichuan Province, China; Key Laboratory of Birth Defects and Related Diseases of Women and Children of The Ministry of Education, Sichuan University, No. 20 Section 3, Renmin South Road, Wuhou District, Chengdu 610041, Sichuan Province, China. Tel: +86-15928-623580; E-mail: yudanhx2h@163.com

References

[1] GBD 2015 Chronic Respiratory Disease Collaborators. Global, regional, and national deaths, prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990-2015: a systematic analysis for the Global burden of disease study 2015. Lancet Respir Med 2017; 5: 691-706.

[2] Elliot JG, Jones RL, Abramson MJ, Green FH, Mauad T, McKay KO, Bai TR and James AL. Distribution of airway smooth muscle remodelling in asthma: relation to airway inflammation. Respirology 2015; 20: 66-72.

[3] Chen JB, Hong ZD and Zhang XY. Clinical observation on the treatment of acute attack period of bronchial asthma with Xiweiping asthma decoction. Chin J Trad Med Sci Techno 2019; 26: 236-237.

[4] Casas L, Tischer C and Taubel M. Pediatric asthma and the indoor microbial environment. Curr Environ Health Rep 2016; 3: 238-249.

[5] Sulaiman I, Lim JC, Soo HL and Stanslas J. Molecularly targeted therapies for asthma: current development, challenges and potential clinical translation. Pulm Pharmacol Ther 2016; 40: 52-68.

[6] Lodha R, Puranik M, Kattal N and Kabra SK. Social and economic impact of childhood asthma. Indian Pediatr 2003; 40: 874-879.

[7] Ferrante G and La Grutta S. The burden of pediatric asthma. Front Pediatr 2018; 6: 186.

[8] Sockrider M. Management of asthma in young children. Curr Allergy Asthma Rep 2002; 2: 453-459.

[9] Bateman ED, Hurd SS, Barnes PJ, Bousquet J, Drazen JM, FitzGerald JM, Gibson P, Ohta K, O'Byrne P, Pedersen SE, Pizzichini E, Sullivan SD, Wenzel SE and Zar HJ. Global strategy for asthma management and prevention: GINA executive summary. Eur Respir J 2008; 31: 143-178.

[10] Kaur S and Singh V. Asthma and medicines - long-term side-effects, monitoring and dose titration. Indian J Pediatr 2018; 85: 748-756.
[11] Ye Q, He XO and D'Urzo A. A review on the safety and efficacy of inhaled corticosteroids in the management of asthma. Pulmonary Therapy 3: 1-18.
[12] Reddel HK, Busse WW, Pedersen S, Tan WC, Chen YZ, Jorup C, Lythgoe D and O'Byrne PM. Should recommendations about starting inhaled corticosteroid treatment for mild asthma be based on symptom frequency: a post-hoc efficacy analysis of the START study. Lancet 2017; 389: 157-166.
[13] Castro-Rodriguez JA, Custovic A and Ducharme FM. Treatment of asthma in young children: evidence-based recommendations. Asthma Res Pract 2016; 2: 5.
[14] Chang C. Asthma in children and adolescents: a comprehensive approach to diagnosis and management. Clin Rev Allergy Immunol 2012; 43: 98-137.
[15] Rottier BL and Duiverman EJ. Anti-inflammatory drug therapy in asthma. Paediatr Respir Rev 2009; 10: 214-219.
[16] Peters SP, Bleecker ER, Canonica GW, Park YB, Ramirez R, Hollis S, Fjallbrant H, Jorup C and Martin UJ. Serious asthma events with budesonide plus formoterol vs. budesonide alone. N Engl J Med 2016; 375: 850-860.
[17] Turpeinen M, Pelkonen AS, Nikander K, Sorva R, Selroos O, Juntunen-Backman K and Haahtela T. Bone mineral density in children treated with daily or periodical inhaled budesonide: the Helsinki early intervention childhood asthma study. Pediatr Res 2010; 68: 169-173.
[18] Otunctemur A, Ozbek E, Cekmen M, Cakir SS, Dursun M, Polat EC, Somay A and Ozbay N. Protective effect of montelukast which is cysteinyl-leukotriene receptor antagonist on gentamicin-induced nephrotoxicity and oxidative damage in rat kidney. Ren Fail 2013; 35: 403-410.
[19] Knorr B, Franchi LM, Bisgaard H, Vermeulen JH, LeSouef P, Santanello N, Michele TM, Reiss TF, Nguyen HH and Bratton DL. Montelukast, a leukotriene receptor antagonist, for the treatment of persistent asthma in children aged 2 to 5 years. Pediatrics 2001; 108: E48.
[20] Wang XP, Yang LD and Zhou JF. Montelukast and budesonide combination for children with chronic cough-variant asthma. Medicine (Baltimore) 2018; 97: e11557.
[21] Subspecialty Group of Respiratory Diseases Society of Pediatrics; Chinese Medical Association; Chinese Journal of Pediatrics Editorial Board. Guideline for the diagnosis and optimal management of asthma in children. Zhonghua Er Ke Za Zhi 2008; 46: 745-53.
[22] Ali AM, Selim S, Abbassi MM and Sabry NA. Effect of alfacalcidol on the pulmonary function of adult asthmatic patients: a randomized trial. Ann Allergy Asthma Immunol 2017; 118: 557-563.
[23] Gao XY. Analysis of clinical efficacy and safety of montelukast and budesonide treatment of children with bronchial asthma. Med Recap 2016; 22: 3712-3714.
[24] Zhu J and Hu XP. Effects of continuingcare on family education-environmental improvement for compliance, life quality and recurrence rate of children with asthm. Med High Vocat Edu Moder Nurs 2018; 1: 280-283.
[25] Nagao M, Ikeda M, Fukuda N, Habukawa C, Kitamura T, Katsunuma T and Fujisawa T. Early control treatment with montelukast in preschool children with asthma: a randomized controlled trial. Allergol Int 2018; 67: 72-78.
[26] Montecucco F, Liberale L, Bonaventura A, Vecchie A, Dallegri F and Carbone F. The role of inflammation in cardiovascular outcome. Curr Atheroscler Rep 2017; 19: 11.
[27] Majak P, Rychlik B, Pulaski L, Blauz A, Agnieszka B, Bobrowska-Korzeniowska M, Kuna P and Stelmach I. Montelukast treatment may alter the early efficacy of immunotherapy in children with asthma. J Allergy Clin Immunol 2010; 125: 1220-1227.
[28] Kim CK, Callaway Z, Park JS, Nishimori H, Ogino T, Nagao M and Fujisawa T. Montelukast reduces serum levels of eosinophil-derived neurotoxin in preschool asthma. Allergy Asthma Immunol Res 2018; 10: 686-697.
[29] Shin J, Oh SJ, Petigara T, Tunceli K, Urdaneta E, Navaratnam P, Friedman HS, Park SW and Hong SH. Comparative effectiveness of budesonide inhalation suspension and montelukast in children with mild asthma in Korea. J Asthma 2019; 1-11.
[30] Wei H, Li W, Jiang Z, Xi X and Qi G. Clinical efficacy of montelukast sodium combined with budesonide or combined with loratadine in treating children with cough variant asthma and influence on inflammatory factors in the serum. Exp Ther Med 2019; 18: 411-417.
[31] Liccardi G, Salzillo A, Calzetta L, Cazzola M, Matera MG and Rogliani P. Can bronchial asthma with an highly prevalent airway (and systemic) vagal tone be considered an independent asthma phenotype? Possible role of anticholinergics. Respir Med 2016; 117: 150-3.
[32] Ding B, Lu YM and Li YQ. Efficacy of treatment with montelukast, fluticasone propionate and budesonide liquid suspension for the prevention of recurrent asthma paroxysms in children with wheezing disorders. Exp Ther Med 2019; 18: 3090-3094.

[33] Li Y, Wong K, Giles A, Jiang J, Lee JW, Adams AC, Kharitonenkov A, Yang Q, Gao B, Guarente L and Zang M. Hepatic SIRT1 attenuates hepatic steatosis and controls energy balance in mice by inducing fibroblast growth factor 21. Gastroenterology 2014; 146: 539-549, e537.

[34] Casale TB, Aalbers R, Bleecker ER, Meltzer EO, Zaremba-Pechmann L, de la Hoz A and Kerstjens HAM. Tiotropium respimat(R) add-on therapy to inhaled corticosteroids in patients with symptomatic asthma improves clinical outcomes regardless of baseline characteristics. Respir Med 2019; 158: 97-109.

[35] Zhang Y and Wang H. Efficacy of montelukast sodium chewable tablets combined with inhaled budesonide in treating pediatric asthma and its effect on inflammatory factors. Pharmazie 2019; 74: 694-697.

[36] Baig S, Khan RA, Khan K and Rizvi N. Effectiveness and quality of life with montelukast in asthma - a double-blind randomized control trial. Pak J Med Sci 2019; 35: 731-736.

[37] Assmann G. Lipid metabolism disorder: detection and treatment. 5: treatment of hyperlipidemia in manifest coronary heart disease, diabetes mellitus and hypertension. National cholesterol initiative. Fortschr Med 1991; 109: 361-363.

[38] Pinto CR, Almeida NR, Marques TS, Yamamura LL, Costa LA and Souza-Machado A. Local adverse effects associated with the use of inhaled corticosteroids in patients with moderate or severe asthma. J Bras Pneumol 2013; 39: 409-417.

[39] Ye T and Zhan SS. Adverse reaction of treating bronchial asthma with inhaled corticosteroids. Med Recap 2012; 18:1511-1514.

[40] Bonsignore MR, La Grutta S, Cibella F, Scichilone N, Cuttitta G, Interrante A, Marchese M, Veca M, Virzi M, Bonanno A, Profita M and Morici G. Effects of exercise training and montelukast in children with mild asthma. Med Sci Sports Exerc 2008; 40: 405-412.

[41] Ten Brinke A, Zwinderman AH, Sterk PJ, Rabe KF and Bel EH. "Refractory" eosinophilic airway inflammation in severe asthma: effect of parenteral corticosteroids. Am J Respir Crit Care Med 2004; 170: 601-605.

[42] Grzela K, Zagorska W, Krejner A, Litwiniuk M, Zawadzka-Krajewska A, Banaszkiewicz A, Kulus M and Grzela T. Prolonged treatment with inhaled corticosteroids does not normalize high activity of matrix metalloproteinase-9 in exhaled breath condensates of children with asthma. Arch Immunol Ther Exp (Warsz) 2015; 63: 231-237.