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Original Article

Effect of leukotriene receptor antagonist on clinical symptoms, Th1/Th2 cytokines and pulmonary function in children with bronchial asthma

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Abstract: Objective: To analyze the effects of leukotriene receptor antagonist (LTRA) on clinical symptoms, Th1/Th2 cytokines and pulmonary function in children with acute asthma attack. Methods: A total of 70 children with mild or moderate acute exacerbation of bronchial asthma were enrolled and randomly divided into control group and experimental group, with each group containing 35 patients. The control group received routine asthma treatment regimen which includes budesonide and ipratropium bromide inhalation. The experimental group received routine treatment regimen plus oral LTRA (montelukast sodium). Then total effective rate, time to symptom relief, Th1/Th2 cytokines, and pulmonary function index PEF%pred (percent-predicted values of peak expiratory flow) were compared between the groups. Results: The total effective rate of the experimental group was significantly higher than that of the control group ($P < 0.05$). The time to the relief of sibilant rhonchi, cough and wheezing of the experimental group were significantly shorter than those of the control group (all $P < 0.05$). Moreover, the serum interferon γ (IFN-γ) level was higher and interleukin-4 (IL-4) level was lower in the experimental group than those in the control group after treatment (both $P < 0.05$). The PEF%pred of the experimental group was also higher than that of the control group ($P < 0.05$). Conclusion: LTRAs could effectively restore the Th1/Th2 balance in children with acute exacerbation of bronchial asthma, thus improving pulmonary function and promoting symptom alleviation. LTRAs are highly recommended in clinical treatment of pediatric bronchial asthma.

Keywords: Leukotriene receptor antagonists, pediatric bronchial asthma, Th1/Th2, pulmonary function, clinical efficacy

Introduction

Infantile bronchial asthma is a common pediatric disease, which is now considered to be caused by a variety of inflammatory mediators and cytokines. The main feature of bronchial asthma is airway hyperresponsiveness and narrowing, resulting in a variety of symptoms such as cough, chest tightness, shortness of breath, and wheezing. Due to the long course of disease and the tendency to recurrence, bronchial asthma poses serious adverse effects on the physical and mental development of pediatric patients [1, 2]. The balance of Th1/Th2 cytokines is the basis for maintaining the normal immune fu-nction of the body. Th1 cells and Th2 cells interact to form a dynamic balance by secreting cytokines. Both Th1 cytokine interferon γ (IFN-γ) and Th2 cytokine interleukin-4 (IL-4) play an important role in immune cell proliferation and secretion. Once the Th1/Th2 cytokines are out of balance, it can lead to immune dysfunction and further lead to bronchial asthma. Clinical treatment regimen for bronchial asthma mainly consists of glucocorticoids and bronchodilators. However, the treatment effect is often not satisfactory in some patients. Leukotriene receptor antagonists (LTRAs) are new class of drugs for the clinical treatment of asthma, and their short-term and long-term efficacy are currently of high clinical concern. In view of this, we enrolled 70 pediatric patients with mild or moderate acute exacerbation of bronchial asthma, and conducted a randomized controlled trial to investigate the ef-

fects of LTRAs on clinical symptoms, Th1/Th2 cytokines and pulmonary function.

Materials and methods

Patients

A total of 70 pediatric patients with mild or mode-rate acute exacerbation of bronchial asthma, admitted to The Affiliated Nanhua Hospital, University of South China from December 2016 to December 2018 were enrolled in the study. Patients were divided into control group and experimental group based on random number table, with each group containing 35 patients. This study was approved by the ethics committee of The Affiliated Nanhua Hospital, University of South China, and informed consent was obtained for all patients.

Inclusion criteria: patients were diagnosed with mild or moderate acute exacerbation of bronchial asthma according to the Guidelines for the Diagnosis and Prevention of Bronchial Asthma in Children (2016 edition) [3]; patients were under 6 years old; patient's course of disease was under 3 months; patients could communicate with medical staff normally.

Exclusion criteria: patients had severe acute exacerbation of bronchial asthma; patients had respiratory failure or heart failure; patients had malignant tumor, congenital diseases, or immune diseases; patients had cough variant asthma; patients were treated for bronchial asthma before this study; patients had major organ dysfunction.

Methods

The control group was treated with budesonide (AstraZeneca Pty Ltd., China, 1 mg/2 mL) 1 mg and ipratropium bromide (Laboratoire Unither, 250 μg/2 mL) 100 μg mixed with 1 mL normal saline via oral inhalation 2 times a day, supplemented by oxygen and other symptomatic treatment. The treatment was continued for 4 weeks.

The experimental group was given montelukast sodium tablets (Sichuan Otasuka Pharmaceutical Co., Ltd., China) on the basis of the treatment regimen of the control group. The dose was 8 mg/day orally for 2-6 years old and 10 mg/day orally for 6 years old or above. Montelukast was given every morning and evening and continued for 4 weeks.

Observational indices

After 4 weeks of treatment, the total effective rate, time to symptom relief, Th1/Th2 cytokines, and pulmonary function were compared between the two groups.

Total effective rate

Criteria for determining clinical efficacy: daytime symptoms > twice per week (lasting a few minutes); any symptoms during night or when wakes up; need for rescue medication > twice per week; any limitation of activities (less running/playing than other children; easy to fatigue when walking/playing). Asthma is "well controlled" if there is no above criteria, "partially controlled" if there are 1 or 2 above criteria, and "uncontrolled" if there are 3 or 4 above criteria. Total effective rate = (well controlled + partially controlled)/total ×100% [4, 5].

Time to symptom relief

Time required to alleviate clinical symptoms including sibilant rhonchi, cough and wheezing.

Th1/Th2 cytokines

A volume of 5 mL fasting venous blood of all subjects was drawn before and after treatment. Blood samples were centrifuged at 3000 r/min for 10 min, and IFN-γ (interferon γ) and IL-4 (interleukin-4) were detected in the serum.

Pulmonary function

Pulmonary function index PEF%pred (percent-predicted values of peak expiratory flow) before and after treatment was compared between the groups.

Statistical analysis

All data were analyzed with SPSS 25.0 statistical package. Quantitative values were expressed as mean ± standard deviation. Differences between groups were evaluated using independent t-test and differences within group were compared using paired t-test; Enumeration

Table 1. Comparison of baseline condition

Group	Experimental group (n=35)	Control group (n=35)	t/χ^2	P
Gender			0.059	0.808
Male	21	20		
Female	14	15		
Age (year)	3.5±1.0	3.6±1.0	0.124	0.902
Duration of Disease (year)	4.6±2.1	4.9±2.0	0.062	0.951
Asthma Severity			0.2543	0.881
Mild	12	13		
Moderate	23	22		

Table 2. Comparison of total effective rate (n, %)

Group	Well controlled	Partially controlled	Uncontrolled	Total effective rate
Experimental group (n=35)	13 (37.14)	20 (57.14)	2 (5.71)	33 (94.29)
Control group (n=35)	7 (20.00)	16 (45.71)	12 (34.29)	23 (65.71)
χ^2				8.929
P				0.003

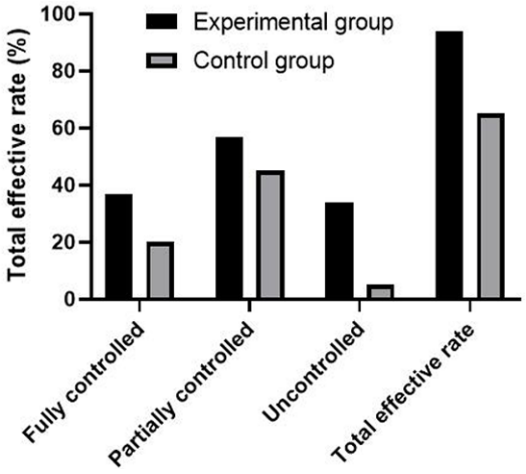

Figure 1. Comparison of total effective rate. *P < 0.05, compared with the control group.

data were expressed as number/percentage (n, %) and compared by X^2 test. P < 0.05 is considered statistically significant.

Results

Comparison of baseline condition

There was no significant difference in gender, age, duration of disease and asthma severity between the two groups (all P > 0.05), as shown in **Table 1**.

Comparison of total effective rate

The total effective rate of the experimental group was significantly higher than that of the control group (P < 0.05). See **Table 2** and **Figure 1**.

Comparison of time to symptom relief

The time to the relief of symptoms including sibilant rhonchi, cough and wheezing was significantly shorter in the experimental group than that in the control group (all P < 0.05). See **Table 3**.

Comparison of Th1/Th2 cytokines

There was no significant difference in Th1/Th2 cytokine levels between the two groups before treatment. However, after treatment, IFN-γ was significantly higher in the experimental group than that in the control group, while IL-4 was significantly lower in the experimental group than that in the control group (both P < 0.05). See **Table 4**.

Comparison of PEF%pred

There was no difference in the PEF%pred between the two groups before treatment (P > 0.05). After treatment, the PEF%pred of the experimental group was higher than that of the control group (P < 0.05). Moreover, the PEF%pred after treatment was significantly higher than that before treatment in both groups (both P < 0.05). See **Table 5**.

Discussion

Clinical studies have shown that the incidence of bronchial asthma in children is as high as 3-5% in China [6]. In recent years, the incidence of bronchial asthma in children has increased significantly due to the deteriorating living environment in China. Previous studies have shown that inflammatory cells in the airway, such as T lymphocytes, mast cells, eosinophils, and

Table 3. Comparison of time to symptom relief (mean ± sd)

Group	Sibilant rhonchi (d)	Cough (d)	Wheezing (d)
Experimental group (n=35)	1.6±0.2	2.1±0.3	1.9±0.3
Control group (n=35)	4.0±0.8	4.1±0.8	4.0±0.9
χ^2	16.473	13.836	13.582
P	<0.001	<0.001	<0.001

Table 4. Comparison of Th1/Th2 cytokines

Group	Experimental group (n=35)	Control group (n=35)	t/χ^2	P
IFN-γ (μg/L)				
Before treatment	1.01±0.08	1.00±0.09	0.491	0.625
After treatment	1.49±0.19	1.28±0.12	5.529	<0.001
t	13.775	11.043		
P	<0.001	<0.001		
IL-4 (ng/mL)				
Before treatment	1.38±0.11	1.39±0.13	0.347	0.729
After treatment	0.52±0.03	1.12±0.04	70.993	<0.001
t	44.623	11.744		
P	<0.001	<0.001		

Table 5. Comparison of PEF%pred

Group	Experimental group (n=35)	Control group (n=35)	t	P
Before treatment (%)	70.52±2.05	70.59±2.01	0.144	0.886
After treatment (%)	94.62±10.62	86.02±6.25	4.129	<0.001
t	13.182	13.904		
P	<0.001	<0.001		

their secretions, including leukotrienes, prostaglandins, histamine, interleukins, tumor necrosis factors (TNFs) etc., participated in the occurrence and development of bronchial asthma [7, 8]. Until now, the cause of bronchial asthma is still unclear. It is generally believed that the occurrence of this disease is closely related to heredity and environment. T helper cells are further divided into Th1 and Th2 cells according to different secreted cytokines. Imbalanced Th1/Th2 cell subsets may result in decreased Th1 cytokines and increased Th2 cytokines, which are fundamental causes of bronchial asthma [9, 10]. IFN-γ produced in Th1 cells can activate macrophages, enhance the phagocytic activity, and kill pathogenic microorganisms in a variety of cells [11, 12]. IL-4 produced in Th2 cells plays an important role in humoral immunity. IL-4 exerts its function by promoting the proliferation of B cells to produce IgE and IgG, thereby stimulating immune response. It has been found that the level of IL-4 was positively correlated with the severity of bronchial asthma [13, 14].

At present, it is generally believed that the imbalance of Th1/Th2 cytokines is closely related to the occurrence of bronchial asthma, especially the imbalance of IFN-γ and IL-4, which is manifested as IFN-γ lower than 1.21 μg/L and IL-4 higher than 1.01 ng/L [15]. Therefore, the current clinical treatment strategy of asthma has transitioned from alleviating respiratory tract spasm to restoring Th1/Th2 cytokine imbalance, so as to reduce the inflammation and airway response caused by Th1/Th2 cytokine imbalance. In this study, LTRA was effective in the treatment of bronchial asthma, and patients treated with LTRA were less likely to relapse. The reason is twofold. First, montelukast is characterized by good lipophilicity and absorbability. Montelukast specifically inhibits cy-steinyl leukotriene receptor as well as the production of histamine and oxide. As a result, eosinophil infiltration and vascular permeability could be reduced, which in turn enhanced airway cilia clearance and reduced airway resistance to facilitate sputum expectoration. All these effects were conducive to the control of disease progression [16-18]. Second, montelukast has stimulating effect on the proliferation of T lymphocyte, which can increase the number of T lymphocytes and contribute to the improvement of immune function in asthma patients. In addition, montelukast has a rapid onset and remarkable effect on the control of asthma symptoms. After administration, the IFN-γ level was increased and the IL-4 level was lowered, indicating that the airway inflammation was controlled and the Th1/Th2 imbalance was restored. Thus, patient's quality of life could be improved due to rapidly relieved symptoms and enhanced immune function. Notably, patients usually did not experience drug resistance even after long term use and the side effects were also rather mild [19-23].

In conclusion, LTRAs could effectively relieve symptoms such as dyspnea, cough, and wheezing in pediatric bronchial asthma patients. LTRAs could also improve patient's pulmonary function and immune function with significant short-term and long-term efficacy and low relapse rate. Therefore, LTRAs are highly recommended in clinical practice treating pediatric bronchial asthma patients. However, the single centered small sample size is a limitation of this study. The conclusions of this study are to be confirmed by the results of a multicenter randomized controlled trial with a larger sample size.

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Disclosure of conflict of interest

None.

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References

[1] Bissler JJ, Franz DN, Frost MD, Belousova E, Bebin EM, Sparagana S, Berkowitz N, Ridolfi A and Kingswood JC. The effect of everolimus on renal angiomyolipoma in pediatric patients with tuberous sclerosis being treated for subependymal giant cell astrocytoma. Pediatr Nephrol 2018; 33: 101-109.

[2] Said MM and Bosland MC. The anti-inflammatory effect of montelukast, a cysteinyl leukotriene receptor-1 antagonist, against estradiol-induced nonbacterial inflammation in the rat prostate. Naunyn Schmiedebergs Arch Pharmacol 2017; 390: 197-205.

[3] Subspecialty Group of Respiratory Diseases, Society of Pediatrics, Chinese Medical Association; Editorial Board, Chinese Journal of Pediatrics. Guideline for the diagnosis and optimal management of asthma in children (2016). Zhonghua Er Ke Za Zhi 2016; 54: 167-181.

[4] Chaudhury A, Gaude GS and Hattiholi J. Effects of oral montelukast on airway function in acute asthma: a randomized trial. Lung India 2017; 34: 349-354.

[5] Que LG, Yang Z, Lugogo NL, Katial RK, Shoemaker SA, Troha JM, Rodman DM, Tighe RM and Kraft M. Effect of the S-nitrosoglutathione reductase inhibitor N6022 on bronchial hyperreactivity in asthma. Immun Inflamm Dis 2018; 6: 322-331.

[6] Hoxha M, Rovati GE and Cavanillas AB. The leukotriene receptor antagonist montelukast and its possible role in the cardiovascular field. Eur J Clin Pharmacol 2017; 73: 799-809.

[7] Altawalbeh SM, Thorpe CT, Zgibor JC, Kane-Gill S, Kang Y and Thorpe JM. Economic burden associated with receiving inhaled corticosteroids with leukotriene receptor antagonists or long-acting beta agonists as combination therapy in older adults. J Manag Care Spec Pharm 2018; 24: 478-486.

[8] Suknuntha K, Yubolphan R, Krueaprasertkul K, Srihirun S, Sibmooh N and Vivithanaporn P. Leukotriene receptor antagonists inhibit mitogenic activity in triple negative breast cancer cells. Asian Pac J Cancer Prev 2018; 19: 833-837.

[9] Butler CT, Reynolds AL, Tosetto M, Dillon ET, Guiry PJ, Cagney G, O'Sullivan J and Kennedy BN. A quininib analogue and cysteinyl leukotriene receptor antagonist inhibits vascular endothelial growth factor (VEGF)-independent angiogenesis and exerts an additive antiangiogenic response with bevacizumab. J Biol Chem 2017; 292: 3552-3567.

[10] Morina N, Haliti A, Iljazi A, Islami D, Bexheti S, Bozalija A and Islami H. Comparison of effect of leukotriene biosynthesis blockers and inhibitors of phosphodiesterase enzyme in patients with bronchial hyperreactivity. Open Access Maced J Med Sci 2018; 6: 777-781.

[11] Okubo K, Hashiguchi K, Takeda T, Baba K, Kitagoh H, Miho H, Tomomatsu H, Yamaguchi S, Odani M and Yamamotoya H. A randomized controlled phase II clinical trial comparing ONO-4053, a novel DP1 antagonist, with a leukotriene receptor antagonist pranlukast in patients with seasonal allergic rhinitis. Allergy 2017; 72: 1565-1575.

[12] Hançerli Törün S, Acar EM, Somer A, Erköse G, Şatana D, Bayramoğlu Z, Çalışkan E and Kılıçaslan Z. Management and treatment difficulties of multi-drug resistant pulmonary tuberculosis in a pediatric case. Mikrobiyol Bul 2018; 52: 89-95.

[13] Wang S, Tu J and Song Y. Evaluation of pulmonary reexpansion in a porcine model of bronchial foreign body. Pediatr Pulmonol 2018; 53: 278-283.

[14] Shi Y, Fu X, Cao Q, Mao Z, Chen Y, Sun Y, Liu Z and Zhang Q. Overexpression of miR-155-5p inhibits the proliferation and migration of IL-13-induced human bronchial smooth muscle cells by suppressing TGF-beta-activated kinase

1/MAP3K7-binding protein 2. Allergy Asthma Immunol Res 2018; 10: 260-267.
[15] Chen XH and He HM. Effects of moxibustion at "Feishu" (BL 13) and "Shenshu" (BL 23) on peripheral blood T cells and serum interleukin in asthmatic rats. Zhen Ci Yan Jiu 2017; 42: 159-162.
[16] Kurowski M, Jurczyk J, Moskwa S, Jarzebska M, Krysztofiak H and Kowalski ML. Winter ambient training conditions are associated with increased bronchial hyperreactivity and with shifts in serum innate immunity proteins in young competitive speed skaters. Arch Med Sci 2018; 14: 60-68.
[17] Victoria T, Srinivasan AS, Pogoriler J, Kreiger PA, Laje P, Oliver ER, Danzer E, Johnson AM, Moldenhauer JS, Peranteau WH and Adzick NS. The rare solid fetal lung lesion with T2-hypointense components: prenatal imaging findings with postnatal pathological correlation. Pediatr Radiol 2018; 48: 1556-1566.
[18] Kainuma K, Kobayashi T, D'Alessandro-Gabazza CN, Toda M, Yasuma T, Nishihama K, Fujimoto H, Kuwabara Y, Hosoki K, Nagao M, Fujisawa T and Gabazza EC. β2 adrenergic agonist suppresses eosinophil-induced epithelial-to-mesenchymal transition of bronchial epithelial cells. Respir Res 2017; 18: 79.
[19] Michalik M, Wójcik-Pszczoła K, Paw M, Wnuk D, Koczurkiewicz P, Sanak M, Pekala E and Madeja Z. Fibroblast-to-myofibroblast transtion in bronchial asthma. Cell Mol Life Sci 2018; 75: 3943-3961.
[20] Bisyuk Y, Kurchenko A, Dubovyi A and Dubuske L. The efficacy of fluticasone proprionate versus montelukast in different genotypes of ASP-299GLY TLR-4 polymosphisms in adult asthmatics. J Allergy Clin Immunol 2018; 141: AB210.
[21] Seo HJ, Lee PH, Kim BG, Lee SH, Park JS, Lee J, Park SW, Kim DJ, Park CS and Jang AS. Methacholine bronchial provocation test in patients with asthma: serial measurements and clinical significance. Korean J Intern Med 2018; 33: 807-814.
[22] Liu M, Zhang J and Liu C. Clinical efficacy of recombinant human latrophilin 3 antibody in the treatment of pediatric asthma. Exp Ther Med 2018; 15: 539-547.
[23] Skowasch D, Klein J, Homsi R and Pizarro C. A 60-year-old patient with asthma and dyspnoea after bronchial thermoplasty. Dtsch Med Wochenschr 2018; 143: 381.