American Journal of Medicine and Medical Sciences 2019, 9(3): 125-129
DOI: 10.5923/j.ajmms.20190903.10

Learning Efficiency and Possibility of Anti-Leukotriene Preparations for Children with a Bronchial Asthma in Uzbekistan Conditions

Mirrahimova Maktuba Habibullayevna[1], Khalmatova Barno Turdihadjayevna[2], Tashmatova Gulnoza Aloyevna[3,*]

[1]Associate Professor of the Department of Children's Diseases №1, Tashkent Medical Academy, Uzbekistan
[2]Professor, Head of the Department of Children's Diseases №1, Tashkent Medical Academy, Uzbekistan
[3]Assistant of the Department of Children's Diseases №1, Tashkent Medical Academy, Uzbekistan

Abstract The article presents data from a clinical trial to study the efficacy and tolerability of local production montelukast drugs. The clinical efficacy of the drugs was evaluated in points to improve clinical and laboratory data. The study showed positive dynamics of clinical and laboratory parameters in all children who received Montelukast drugs. Studies have shown that taking montelukast drugs leads to a decrease in the level of cys-LT, IgE in children with bronchial asthma.

Keywords Children, Allergies, Atopy, Bronchial asthma, Montelukast, Randomized clinical trial

1. Introduction

All over the world, including in Uzbekistan, childhood asthma is a chronic allergic disease that requires special attention. Epidemiological studies show that almost 1/3 of sick children suffer 5 or more wheezing episodes per year (which is considered as the equivalent of an attack in adults). According to the WHO, the prevalence of BA has reached 5% of the average adult and 10% among the world's children [1, 4, 8, 10, 12]. Bronchial asthma often develops among children of preschool age (80%), often the first attacks occur in the first year of life. Despite certain successes achieved in developing new approaches to the prevention and treatment of this pathology, the prognosis of asthma is not comforting, its further growth is expected, especially among children, an increase in the number of severe forms and fatal cases, which is associated with a continuing negative effect on the human body pollutants, ozone and aeroallergens with genetic prerequisites [2, 5, 9, 15].

Important mediators involved in the pathogenesis of the ABA are cysteinyl leukotrienes (Cys-LT) (LTC4, LTD4, LTE4), which have pronounced pro-inflammatory and bronchoconstrictor properties and are formed as a result of arachidonic acid exchange via the 5-lipoxygenase (5-LO) pathway from phospholipid hypophospholipid hypophospholipid phosphate gland in the phospholipid hypophospholipid gland by the action of phospholipase A2. The increase in their concentration in the blood causes bronchospasm, increased secretion of bronchial glands, increased vascular permeability [7, 9, 11, 14]. Therefore, the use of pharmacological drugs - antagonists of cis-LT1 receptors has been approved for a long time in many countries of the world and well-proven pharmacotherapy of BA and AR in adults and children [3, 4, 6, 9, 13].

In the pharmaceutical market of the Republic of Uzbekistan today there are several names of Montelukast drugs (Singlon, Gedeon Rixter, Hungary; Montular, Kusum, India; Miteka, India; Brizezi, India, etc.).

2. Purpose of the Study

Evaluation of the clinical efficacy and tolerability of montelukast preparations Uzbekistan, in comparison with the drug Singlon, produced by Gedeon Richter (Hungary).

3. Materials and Methods

The study was conducted in accordance with the Hel ¬ Sync Declaration (adopted in June 1964 (Hel - sinki, Finland) and revised in October 2000 (Edinburgh, Scotland)) and in

* Corresponding author:
Tashmatovagulnoza@gmail.com (Tashmatova Gulnoza Aloyevna)
Published online at http://journal.sapub.org/ajmms

accordance with the Law of the Republic of Uzbekistan "On Drugs and Pharmaceutical Activities "," The National Standard of Uzbekistan - GSR - Good Clinical Practice ", taking into account the GSR rules applied in international practice, the Regulation" On the procedure for conducting clinical trials and the examination of clinical research materials medicines and medicines" (Appendix 1 to the Order of the Ministry of Health of the Republic of Uzbekistan No. 40 of January 26, 2015). From parents of patients obtained informed consent.

The clinical trial was limited, comparative, open, controlled, randomized with four parallel groups. Studies have been conducted in patients who are hospitalized in the departments of pulmonology, allergology at the Department of Children's Diseases No.1 of the Tashkent Medical Academy.

The study involved 150 children aged 2 to 14 years with a diagnosis of intermittent, mild and moderate persistent bronchial asthma. All children were divided into 4 groups: 1st group - children who received Astanol (Remedy Group, Uzbekistan) n=30; Group 2 - children who received the Neoclast (OOO Nobel) n=30; Group 3, children who received Montex (Nika Pharm, Uzbekistan) n=20; Group 4 (control) children who received the drug Singlon (Gedeon Rixter, Hungary) n=60. The average age of children was 6.8 ± 2.1 years. The number of boys and girls included in the study was comparable. Children from 2 to 5 years were prescribed montelukast in a dose of 4 mg (chewable tablets), children from 6 to 14 years old 5 mg (chewable tablets) once a day, for the night, for 1 month.

All children underwent a general clinical examination (collection of allergological anamnesis, examination, physical) examination, complete blood count, determination of total IgE, determination of cys-LT in the urine, chest X-ray, spirometry or peak flowmetry and after the study.

Urine samples for the determination of cys-LT in an amount of 5 ml were collected in the morning. The quantitative determination of the final metabolite cys-LT (LTC4/D4/E4) in the urine (reagent from Neogen, Ukraine) was performed by enzyme immunoassay. Measurement range: 0.04-8 ng / ml. Sensitivity: 0.04 ng/ml. Statistical processing of the results was performed using the Statistica 10.0 software package. Data are presented as arithmetic means with an average error. The difference of values was considered significant at $p < 0.05$.

4. Results and Discussion

Criteria for inclusion in the test were:

- patients of both sexes aged from 2 to 14 years;
- diagnosis – intermittent, mild and moderately severe persistent bronchial asthma;
- availability of informed written consent of the patient's parents (guardians) for the child's participation in the clinical trial.

The criteria for non-inclusion were:

- age of patients younger than 2 years and older than 14 years;
- the presence of contraindications for the appointment of Montelukast;
- severe bronchial asthma constant flow (because monotherapy is not recommended). - Patient participation in other clinical studies in the past 30 days;
- lack of informed written consent of the patient to participate in a clinical study.

The effectiveness of the drugs was evaluated by the following criteria:

- clinical improvement of the patient's condition (taking into account the dynamics of characteristic manifestations);
- reduction of manifestations and intensity of shortness of breath, cough, sputum.- Improving laboratory data.

Evaluation of the effectiveness of the studied drug was carried out on the basis of the above criteria in points according to the following scale:

3 points	High efficiency	A significant improvement in clinical examination data is the absence of allergy symptoms (dyspnea intensity, cough, asthma attacks - a score of 0-2). Reducing the number of leukotrienes by 51-100%.
2 points	Moderate efficiency	A moderate improvement in clinical examination data is a reduction in the severity of allergy symptoms by the end of the course of treatment (dyspnea, coughing, asthma intensity - 3-5 points). Reducing the number of leukotrienes C4 / D4 / E4 to 26-50%.
1 points	Low efficiency	A slight improvement in clinical examination data - the degree of allergy symptoms by the end of the course of treatment (dyspnea, coughing, asthma intensity - 6-8 points). Reduction in the number of leukotrienes C4 / D4 / E4 by 10-25%.
0 points	No effect	No changes or deterioration of clinical examination data - severity of allergy symptoms by the end of the course of treatment (intensity of dyspnea, cough, asthma attacks - total points > 8. The number of leukotrienes C4 / D4 / E4 is unchanged.

Tolerability of the drug was evaluated on the basis of subjective symptoms and sensations, which the patient or his parents reported independently and taking into account the objective data obtained by the doctor. Taking into account the dynamics of laboratory parameters, as well as the frequency of occurrence and the nature of adverse reactions. Assessment of the tolerability of the studied drug was carried out on the basis of the above criteria in points on a scale from 0 to 4 points.

4 points	An objective examination and / or laboratory tests did not reveal any pathological changes or clinically significant abnormalities and / or the patient does not report adverse reactions.
3 points	An objective examination and / or laboratory studies in the dynamics reveal minor changes that are transient in nature and do not require a change in the treatment regimen of the investigational drugs and / or the patient notes manifestations of minor adverse reactions that do not cause serious problems.
2 points	An objective examination and / or laboratory studies in the dynamics reveal significant changes that do not require additional measures and / or the patient notes manifestations of an adverse reaction that has a negative effect on his condition, but does not require discontinuation of the drug.
1 points	During an objective examination and / or laboratory tests, significant changes are detected in the dynamics, and / or the patient notes manifestations of an adverse reaction that has a negative effect on his condition and requiring discontinuation of the drug.
0 points	An objective examination and / or laboratory tests in the dynamics revealed significant changes, and / or the patient notes manifestations of an adverse reaction that require discontinuation of the drug and additional medical measures.

A simple randomization method was used to distribute the subjects into groups. The original table of patient distribution by groups was formed on the basis of random numbers obtained using the MSExcel random number generation function.

The distribution by groups was carried out on the basis of sealed envelopes provided by the sponsors. After the patient was included in the study and assigned a serial number, the envelope corresponding to that number was opened, and the treatment attached to this envelope was prescribed.

The starting point of the beginning of participation of the patient in the study: the day of the first dose of the study drug or the reference drug.

Treatment was described in detail in all patients included in the study.

Any therapy associated with concomitant diseases was registered in the history of the disease and individual registration form.

All patient examination data was recorded in the patient's history, outpatient card and individual patient registration form.

Table 1. Dynamics of clinical manifestations of allergy in patients

Symptoms	Montex n =20		Neoclast n =30		Astanol n =30		Singlon n =70	
	after	before	after	before	after	before	after	before
Cough	2,83±0,03	0,5±0,01	2,23±0,04	0,4±0,01	2,76±0,02	0,73±0,03	2,9±0,04	0,1±0,01
Dyspnea	2.8±0,07	0,2±0,05	3,0±0,05	0,5±0,08	3.0±0,07	0,7±0,09	2,9±0,09	0,3±0,04
Choking attacks	2.1±0,05	0,06±0,002	2,1±0,08	0,08±0,003	2.1±0,07	0,1±0,005	2,7±0,09	0,04±0,001
p	*<0,001*		*<0,001*		*<0,001*			

The severity of symptoms was expressed in points:

0 - no sign 2 - moderately pronounced
1 - mild 3 - pronounced

This table shows that after the use of montelukast drugs, both domestically produced and Singlelon, the clinical manifestations of allergy decreased. Only such a symptom of the disease as cough was observed in 20-30% of children, in the form of coughing.

Table 2. The dynamics of the content of eosinophils in the blood (in%)

Drugs	**General blood analysis**	
	Eosinophils %	
	Before treatment	After treatment
«MONTEX» n =30	5,9±0,20	2,3±0,2
«NEOCLAST» n =30	6,1±0,20	2,9±0,3
«ASTANOL» n =30	5,6±0,20	3,1±0,12
«SINGLON» n =60	6,2±0,20	2,1±0,2

In all patients, a significant decrease in peripheral blood eosinophil content was observed at the 4th week of therapy.

The study of the content of IgE in the blood of patients, as the main indicator of the allergological profile, also revealed a significant improvement in the results of the treatment with the tested drugs ($p < 0.001$).

Table 3. Dynamics of the level of total immunoglobulin E in the blood (M ± m)

Drugs	**IgE (ed/l)**	**IgE(ed/l)**
Montex n =28	481.2±5,5	245.3±4,11
Neoclast n =30	512.2±5.8	196.4±3,7
Astanol n =18	381.6±4.5	236.4±4,07
Singlon n =52	502.7±5,6	185,7±3,09

As can be seen from the data of table 3, all children showed a decrease in the level of total IgE in the blood one month after taking the drugs. The greatest decrease was observed in children who received Singlon and Neoclast ($p < 0.001$).

Numerous clinical studies indicate the key role of cys-LT in the pathogenesis of bronchial obstruction in bronchial asthma. Patients with bronchial asthma showed statistically

significantly higher levels of cys-LT in the urine compared with healthy children.

During the study, we studied the state of the level of cys-LT in the urine in 52 patients.

Table 4. Dynamics of cys-LT in the urine (nm/l)

Drugs	$C_4D_4E_4$	$C_4D_4E_4$
Montex n =30	4.15±0.18	2.89±0.09
Singlon n =22	4.23±0.2	1.92±0.06

Studies have shown that taking montelukast drugs leads to a decrease in the level of cys-LT in the urine. At the same time, in children who received Singlelon, a more significant decrease in the level of cys-LT was observed than in children who received the domestic drug Montex ($p < 0.05$). But this fact does not in any way reduce the effectiveness of the drug Montex.

In children older than 5 years of age, we conducted a study of peak expiratory flow rate by conducting peak flowmetry. A study of the PEF1 index (in%) did not reveal any significant changes during the entire study in all groups. But it should be noted that all children had positive changes in the value of this indicator (table 5).

Table 5. Dynamics of changes in PEF1 (in%) of children 5 years and older

Drugs	PEF_1 initial data	PEF_1 after treatment
Montex n =12	60,2±1,06	79,1±1,11
Neoclast n =17	64,3±1,01	75,1±1,03
Astanol n =14	65,2±1,12	73,7±1,01
Sinlon n =22	58,2±1,12	77,7±1,09

Summarizing the obtained results of the research, and having carried out their analysis, the values of the indicators of efficacy and tolerability of drugs, which indicate the equivalence of their action on the examined patients, are derived.

Table 6. Efficacy and tolerability in points

Indicator	Efficacy	Tolerability
Montex	2,8±0,1	4,0±0
Neoclast	2,8±0,05	4,0±0
Astanol	2,9±0,01	3,9±0,06
Sinlon	3,0±0,00	4,0±0

5. Conclusions

In accordance with the results of clinical studies and recommendations of international documents (GINA, 2015) [4], montelukast recommendation for use in asthma mild to moderate severity as an alternative to inhaled corticosteroids or as an adjunctive therapy. The use of montelukast in pediatric practice will ensure the stability of the state of children with bronchial asthma, and allows to reduce the dose of IGS.

The data obtained allow us to conclude that the drugs of monteukast production Uzbekistan (Montex, Astanol, Neoclast) are effective drugs for the treatment of children with intermittent and persistent form of asthma (mild and moderate). With a light course of bronchial therapy in children from 2 to 5 years of age, monotelukast monotherapy can be used.

REFERENCES

[1] Anandan C, Nurmatov U, van Schayck OCP, Sheikh A. Is the prevalence of asthma declining? Systematic review of epidemiological studies. Allergy, 2010, 65: 152-167.

[2] Federal clinical guidelines for the diagnosis and treatment of bronchial asthma, 2016 revision [electronic resource] http://spulmo.ru/obshchestvo/news/news-812 (circulation date 24.08.2017).

[3] From the Global Strategy for Asthma Management and Prevention (2015 Update). Available from: http://www.ginasthma.org.

[4] GINA 2015. www.ginasthma.org.

[5] Ledford DK, Wenzel SE, Lockey RF. Aspirin or other nonsteroidal inflammatory agent exacerbated asthma. J Allergy Clin Immunol Pract, 2014, 2(6): 653657.

[6] Miligkos M, Bannuru RR, Alkofide H, Kher SR, Schmid CH, Balk EM. Leukotriene-receptor antagonists versus placebo in the treatment of asthma in adults and adolescents, a systematic review and meta-analysis. Ann Intern Med, 2015, 163(10): 756-767. doi: 10.7326/M15-1059.

[7] Nenasheva N.V. The role of anti-leukotriene drugs in achieving control of bronchial asthma - Medical Council – 2018 №18- c.44-55.

[8] Peng WS, Chen X, Yang XY, Liu EM. Systematic review of montelukast's efficacy for preventing post-bronchiolitis wheezing. Pediatr Allergy Immunol, 2014, 25(2): 143-150.

[9] Romanova I.S., Kozhanova I.N., Gavrilenko L.N. et al. The role of Montelukast anti-leukotriene in the treatment of children with bronchial asthma. - Medical News – 2012 №2 - c.62-69.

[10] Selimzyanova S.R., Vishneva E.A., Promyslova E.A. Principles of diagnosis and treatment of bronchial asthma in children at the present stage: review of updates GINA 2014–2015.

[11] Sidorenko I.V., Zakharzhevskaya T.V. The efficacy and safety of montelukast in the treatment of bronchial asthma and allergic rhinitis in routine clinical practice: results of a prospective multicenter observational program. RAJ, 2016, 2: 44-53.

[12] Thomas AE. Platts-Mills. The Allergy Epidemics:

1870–2010. J Allergy ClinImmunol, 2015, 136(1): 3-13.

[13] URL: http://www.who.int/mediacentre/factsheets/fs307/en/.

[14] White A, Ta V. Survey-defined patient experiences with aspirin-exacerbated respiratory disease (AERD). J Allergy Clin Immunol Pract, 2015, 3: 711-718.

[15] Ye YM, Kim SH, Hur GY, Kim JH, Park JW, Shim JJ, Jung KS, Lee HY, Park HS, PRANA Group Addition of Montelukast to Low-dose inhaled corticosteroid leads to fewer exacerbations in older patients than medium-dose inhaled corticosteroid Monotherapy. Allergy, Asthma Immunol Res, 2015, 7(5): 440-448.
doi: 10.4168/aair.2015.7.5.440.