Int J Clin Exp Med 2020;13(3):1872-1877
www.ijcem.com /ISSN:1940-5901/IJCEM0103086

Original Article

Montelukast combined with loratadine treats allergic rhinitis by lowering the levels of serum trace elements, sIgE and ECP

Wenliang Zhou[1*], Kuiguang Han[2*], Chengchao Cui[3], Mingxuan Wang[4], Xianding Fang[5], Tao Li[1], Lei Lu[1], Shuang Xie[1], Shijun Pi[6]

[1]Department of Otolaryngology, Zibo City Linzi District People's Hospital, Zibo, Shandong Province, China; [2]Department of Otolaryngology, Lanling People's Hospital, Linyi, Shandong Province, China; [3]Department of Otolaryngology, Laoling People's Hospital, Dezhou, Shandong Province, China; [4]Department of Ophthalmology and Otorhinolaryngology, Weixian Hospital of Traditional Chinese Medicine, Handan, Hebei Province, China; [5]Department of Otolaryngology, Zhoushan Guang'an Hospital, Zhoushan, Zhejiang Province, China; [6]Department of Otolaryngology, Zaozhuang Municipal Hospital, Zaozhuang, Shandong Province, China. [*]Equal contributors and co-first authors.

Received October 2, 2019; Accepted December 10, 2019; Epub March 15, 2020; Published March 30, 2020

Abstract: Objective: To explore the efficacy of leukotriene receptor antagonist montelukast, combined with histamine receptor antagonist loratadine, in the treatment of patients with allergic rhinitis, and their effects on the levels of serum trace elements, specific immunoglobulin E (sIgE) and eosinophil cationic protein (ECP). Methods: A total of 104 patients with allergic rhinitis were divided into two groups using the computer-based random number method, namely a leukotriene receptor antagonist treatment group (Group M, n=52), and a leukotriene receptor antagonist combined with histamine receptor antagonist treatment group (Group A, n=52). The patients were compared in rhinitis score after treatment, levels of sIgE and ECP during treatment, related complications, and satisfaction. Results: After treatment, Group A got lower rhinitis score than Group M, and showed lower levels of serum sIgE and ECP, but higher satisfaction than Group M (all $P<0.05$), and Group A was not different from Group M in the incidence of complications ($P>0.05$). Conclusion: Leukotriene receptor antagonist combined with histamine receptor antagonist is more effective than leukotriene receptor antagonist alone for patients with allergic rhinitis, which may take effects by lowering the levels of serum trace elements, sIgE and ECP. It indicates that such a combination use of them is worthy of further promotion in clinical practice.

Keywords: Allergic rhinitis, leukotriene receptor antagonist, histamine receptor antagonist

Introduction

Allergic rhinitis (AR), a common clinical rhinitis, is an inflammatory disease occurring after nasal mucosa is exposed to allergens [1, 2], which manifests as rhinostegnosis, unendurable itching of the nose, continuous clear nasal discharge, sneezing fit and others. It may compromise patients' life and work, so it should be paid attention to [3, 4].

Montelukast is a new leukotriene receptor antagonist (LTRA), which is relatively safe and effective in treating AR [5, 6], and loratadine belongs to histamine receptor antagonists (H1RAs), which has long been the first choice for the treatment of AR [7, 8]. Although separate use of the two drugs can take effects in treatment, but it usually cannot completely control the symptoms, showing a relatively high inefficiency rate. Therefore, combination use of them may be a new clinical treatment method, but there are few reports on it. Specific immunoglobulin E (sIgE), one of important indexes for the diagnosis of allergy, plays an important role in reflecting persistent allergy and desensitization [9]. AR is an allergic reaction for the exposure to allergens, and the level of sIgE can reflect the severity of AR. Eosinophil cationic protein (ECP) can induce basophilic cells and

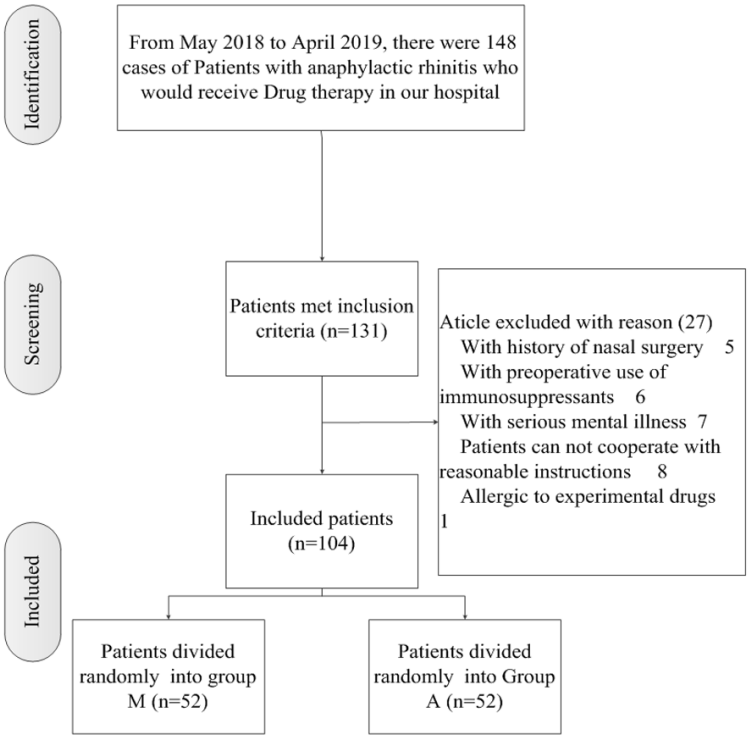

Figure 1. CONSORT flow chart.

macrophages to release histamines, and histamine can cause allergic reactions, so the level of serum ECP can objectively and directly reflect the severity of airway inflammation [10]. AR is a hyper responsiveness variant disease in airway, so ECP can reflect the severity of its inflammation.

This study aimed to explore the efficacy of H1RAs combined with LTRA in the treatment of AR patients, and its effects on the levels of serum trace elements (sIgE and ECP) to confirm the efficacy of the combination use of them, and find out the possible mechanism of its effects, so as to further popularize it in clinic practice.

Materials and methods

General data

A total of 148 AR patients treated in the Department of Otolaryngology, Zaozhuang Municipal Hospital from May 2018 to April 2019 were selected for this study according to inclusion and exclusion criteria, and 104 of which were enrolled based on screening (**Figure 1**). The enrolled patients were divided into Group M (treated with montelukast) and Group A (treated with montelukast and loratadine) using the computer-based random number method, 52 patients in each group. This study was approved by the Ethics Committee of Department of Otolaryngology, Zaozhuang Municipal Hospital.

The inclusion criteria were as follows: (1) patients suffering from AR [11]; (2) patients willing to receive the treatment of montelukast and loratadine; (3) patients between 18 years old and 80 years old; (4) patients with a course of disease ≥4 weeks; (5) patients who had not received any treatment of related drugs; (6) patients with normal communication ability and the ability of successfully participating in the whole experiment; (7) patients who agreed to participate in the study, and provided their own signature.

The exclusion criteria were as follows: (1) patients who had received nasal cavity surgery; (2) patients who were using immunosuppressive drugs (ISD); (3) patients suffering from serious mental diseases or patients unable to cooperate with reasonable instructions; (4) patients suffering from upper respiratory tract infection, variant asthma, gastroesophageal reflux or lower respiratory tract diseases; (5) patients allergic to drugs used in this study; (6) patients with severe function damage in important organs.

Methods

Patients in Group A were treated with oral administration of montelukast (Hangzhou Merck Sharp & Dohme Pharmaceutical Co., Ltd.) at 10 mg/time, once a day, and were also treated with oral administration of loratadine (Jiangsu Yabang Aipusen Pharmaceutical Co., Ltd.) at 10 mg/time, once a day. In contrast, patients in Group M were treated with oral administration of montelukast at 10 mg/time, once a day, and treated with oral administra-

Table 1. The rhinitis scores

Rhinitis scores	0	1	2	3
Rhinocnesmus	None	occasional but tolerable	obvious formication but tolerable	severe formication and intolerable
Nasal obstruction	None	occasionally	obviously	almost completely oral breathing
Sneeze (numbers/time)	None	3-9	10-14	≥15
Rhinorrhea (times of blowing nose)	None	≤4 times/day	5~9 times/day	≥10 times/day

Table 2. Comparison of basic data of two groups of patients

	Number of cases	Age (years)	Gender		BMI (kg/m^2)	Duration of disease (weeks)
			Male	Female		
Group M	52	42.31±8.22	32	20	27.83±6.92	12.06±2.85
Group A	52	43.29±7.67	35	17	28.22±5.86	11.96±3.12
t/X^2		-0.629	0.378		-0.310	0.171
P		0.531	0.539		0.757	0.865

Note: BMI: Body Mass Index.

tion of placebo (starch) at 10 mg/time, once a day. The two groups were treated with 2 courses, and one course covered 14 days. The drugs were handed to medical personnel after being placed in envelops, and the medical staff and patients did not know the grouping.

Observation indexes

Primary indexes: The rhinitis score of the two groups before and after treatment (**Table 1**) and effective treatment rate of them were analyzed and recorded [11]. The severity of rhinitis symptoms was positively correlated to rhinitis score. The effective rate reflected rhinitis score, and effective rate = (the number of cases with marked effect + the number of cases with effect)/the total number of cases ×100%. Efficacy index reflected the treatment efficacy, and efficacy index = (score before treatment - score after treatment)/score before treatment ×100%. An effective index larger than 50% stood for marked effect, index larger than 20% but smaller than 50% for effect, and index smaller than 20% for no effect. The levels of serum sIgE and ECP in the patients were determined using the enzyme-linked immuno-sorbent assay (ELISA). Secondary indexes: The complications and satisfaction of the patients after treatment were analyzed and recorded.

Satisfaction score: This study followed the patients who had been treated for three days to understand their satisfaction with the treatment based on a satisfaction questionnaire developed by our hospital. The questionnaire covered the discomfort after treatment, efficacy of treatment, adverse events after treatment and physical recovery, etc. With a full score of 100 points, it indicated a high satisfaction of the patient to the treatment with a score larger than 80 points, a satisfaction of the patient to the treatment with a score larger than 60 points and lower than 80 points, and a dissatisfaction to the treatment with a score less than or equal to 60 points. The satisfaction of the patients was calculated as follows: patient satisfaction = (the number of cases highly satisfied with the treatment + the number of cases satisfied with the treatment)/the total number of cases ×100%.

Statistical analysis

Data were statistically analyzed using SPSS 22.0, and measurement data were expressed as the mean ± standard deviation (Mean ± SD). Comparison of the same group before and after treatment was carried out using the paired t test, and comparison between groups was carried out using the independent-samples T test, on which measurement data of the two groups were analyzed. The number of cases/ratio (N/%) was used to represent enumeration data, and the Chi-square test or Fisher's exact probability test was used for statistical analysis. $P<0.05$ indicated a significant difference.

Results

Both two groups successfully participated in the whole experiment, without irreversible damage or withdrawal, and there were no differences between them in basic data including age, sex, body mass index (BMI), and course of disease (all $P>0.05$) (**Table 2**).

Rhinitis score and treatment efficacy

Before treatment, the two groups had no obvious difference in rhinitis score ($P=0.822$), while

Table 3. Comparison of rhinitis score and treatment efficacy of two groups of patients

	Rhinitis score		Treatment efficacy			
	Before treatment	After treatment	No effective	Effective	Marked effective	Effective rate
Group M (n=52)	9.84±3.01	2.75±0.83***	10	11	31	80.77%
Group A (n=52)	9.71±2.88	6.62±1.54***	0	17	35	100%
t/X^2	0.225	-15.952				11.528
P	0.822	0.000				0.003

Note: ***indicates compared to before treatment, P<0.001.

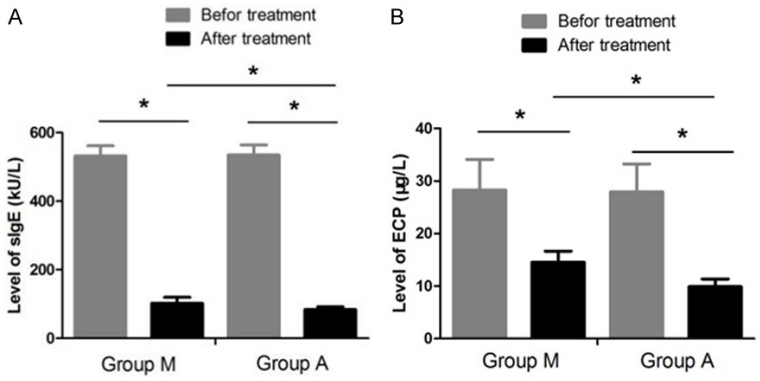

Figure 2. Comparison of serum trace elements levels between two groups of patients. A: Comparison of serum sIgE levels. B: Comparison of serum ECP levels. * indicates compared with each other, P<0.05.

after treatment, both groups got a significantly lower rhinitis score (P<0.001), and Group A got a significantly lower score than Group M (P<0.001) (**Table 3**). Marked effect, effect, and no effect were observed in 35 patients, 17 patients, and 0 patients, respectively, in Group A, which were not significantly different from those in Group M (P=0.003).

Serum sIgE and ECP

Before treatment, the two groups had no significant difference in levels of serum sIgE and ECP (P=0.640 and P=0.750), while after treatment, the two groups showed significantly decreased levels of serum sIgE and ECP (both P<0.05), and the levels of serum sIgE and ECP in Group A ((83.69±8.78) kU/L and (9.89±1.45) μg/L) were significantly lower than those in Group M (All P<0.05) (**Figure 2**).

Adverse reactions

The adverse reactions in Group A were as follows: nausea in 1 patient, vomiting in 2 patients, sleepiness in 7 patients, dry mouth in 3 patients, cough in 3 patients, abdominal pain in 2 patients, and hypodynamia in 8 patients, which were not significantly different from those in Group M (P>0.05) (**Table 4**).

Satisfaction

Investigation and statistics of patients' satisfaction with the treatment revealed that there was a significant difference between Group A and Group M in satisfaction (88.5% vs. 67.3%, P=0.034) (**Table 5**).

Discussion

AR is a hyper responsiveness variant disease in airway caused by the contact with various allergens or weather changes [12, 13], which may be accompanied by some variant inflammations of the upper respiratory tract, and others [14]. At present, glucocorticoid for partial nasal mucosa is a typical method for the treatment of AR [15]. Although it can take effects to a certain extent, it needs a long term to play its role, and long-term use of a hormone may cause central obesity, skin roughness, blood pressure or blood glucose increase, bone mineral density decrease, femoral head necrosis or others [16]. Therefore, it is urgent to explore other effective and safe non-hormone treatment methods.

Montelukast down regulates the secretion of adhesion molecules by specifically affecting cysteinyl-leukotrienes (Cys-LTs) and suppresses accumulation and chemotaxis of eosinophil (EO), thus playing an antiallergic role [17, 18]. H1RA, loratadine, inhibits the release of histamines from lymphocyte (LYM), but does not hinder the release of spontaneous histamines [17, 19], and it controls the synthesis and release of platelet activating factor (PAF) and leukotriene,

Table 4. Comparison of adverse reactions of two groups of patients

	Group M (n=52)	Group A (n=52)	χ^2	P
Nausea	2	1	0.707	0.400
Vomit	1	2	0.343	0.558
Sleepiness	5	7	1.321	0.251
Dry mouth	2	3	0.210	0.647
Cough	3	3	0.000	1.000
Abdominal pain	1	2	0.343	0.558
Hypodynamia	6	8	0.330	0.566
Total incidence rate	38.5%	50.0%	0.644	0.057

Table 5. Comparison of satisfaction degree of treatment effect between two groups of patients

Group	Very satisfied	Somewhat satisfied	Dissatisfied	Satisfaction degree
Group M (n=52)	28	7	17	67.3%
Group A (n=52)	37	9	6	88.5%
χ^2				6.757
P				0.034

thus further suppressing allergic reaction [20, 21]. This study confirmed that montelukast combined with loratadine was more effective in treating AR, which may be exactly due to the synergistic effect of the above treatment mechanism.

A study confirmed that montelukast alone was effective for AR [22], and this study also revealed that both separate use of montelukast and combination use of it and loratadine could lower the levels of serum sIgE and ECP in patients, but combination use was more powerful. It may be due to the following reasons: montelukast can suppress the release of sIgE and ECP by inducing Th cells differentiate into Th1 cells, and control the differentiation and maturation of them [23, 24], and loratadine can down regulate the expression of adhesion molecules by inhibiting cytokines or inflammatory mediators, sIgE and ECP [8, 25], so their combination can more effectively lower the levels of sIgE and ECP, thus exerting a better therapeutic effect.

In addition, this study confirmed that there were no significant differences in adverse reactions between patients treated with montelukast and loratadine and those treated with montelukast alone, which indicated that combination use of the two drugs caused dosage increase but did not bring more adverse reactions. Furthermore, patients were much more satisfied with the combination use, which may be due to the fact that patients felt a better effect from the combination use, and their clinical symptoms from rhinitis and daily life were changed positively. However, the total sample size of this study is small, and the short-term follow-up may cause relatively large errors, so it is necessary to carry out more accurate related randomized control trials.

In conclusion, the efficacy of montelukast combined with loratadine in AR patients may be achieved by lowering the levels of sIgE and ECP, and this study proves that combination use of them is more effective than separate use. Therefore, the combination use is worthy of further promotion in clinical practice.

Disclosure of conflict of interest

None.

Address correspondence to: Shijun Pi, Department of Otolaryngology, Zaozhuang Municipal Hospital, No. 41 Longtou Road, Shizhong District, Zaozhuang 277100, Shandong Province, China. Tel: +86-0632-3224228; Fax: +86-0632-3224228; E-mail: pishijun2d8g@163.com

References

[1] Bozek A. Pharmacological management of allergic rhinitis in the elderly. Drugs Aging 2017; 34: 21-28.

[2] Okubo K, Kurono Y, Ichimura K, Enomoto T, Okamoto Y, Kawauchi H, Suzaki H, Fujieda S and Masuyama K; Japanese Society of Allergology. Japanese guidelines for allergic rhinitis 2017. Allergol Int 2017; 66: 205-219.

[3] Masuda S. Epidemiology and clinical feature of allergic rhinitis in children. Arerugi 2016; 65: 990-993.

[4] Eifan AO and Durham SR. Pathogenesis of rhinitis. Clin Exp Allergy 2016; 46: 1139-1151.

[5] Wei C. The efficacy and safety of H1-antihistamine versus montelukast for allergic rhinitis: a systematic review and meta-analysis. Biomed Pharmacother 2016; 83: 989-997.

[6] May JR and Dolen WK. Management of allergic rhinitis: a review for the community pharmacist. Clin Ther 2017; 39: 2410-2419.

[7] Bjermer L, Westman M, Holmstrom M and Wickman MC. The complex pathophysiology of allergic rhinitis: scientific rationale for the development of an alternative treatment option. Allergy Asthma Clin Immunol 2019; 15: 24.
[8] Kim DH, Kim BY, Shin JH, Kim SW and Kim SW. Intranasal azelastine and mometasone exhibit a synergistic effect on a murine model of allergic rhinitis. Am J Otolaryngol 2017; 38: 198-203.
[9] Savage J, Sicherer S and Wood R. The natural history of food allergy. J Allergy Clin Immunol Pract 2016; 4: 196-203.
[10] Jagasia M, Scheid C, Socie G, Ayuk FA, Tischer J, Donato ML, Bátai Á, Chen H, Chen SC, Chin T, Boodée H, Mitri G and Greinix HT. Randomized controlled study of ECP with methoxsalen as first-line treatment of patients with moderate to severe cGVHD. Blood Adv 2019; 3: 2218-2229.
[11] Annesi-Maesano I, Didier A, Klossek M, Chanal I, Moreau D and Bousquet J. The score for allergic rhinitis (SFAR): a simple and valid assessment method in population studies. Allergy 2002; 57: 107-114.
[12] Meldrum K, Guo C, Marczylo EL, Gant TW, Smith R and Leonard MO. Mechanistic insight into the impact of nanomaterials on asthma and allergic airway disease. Part Fibre Toxicol 2017; 14: 45.
[13] Agrawal S, Burton WB, Manwani D, Rastogi D and De A. A physicians survey assessing management of pulmonary airway involvement in sickle cell disease. Pediatr Pulmonol 2019; 54: 993-1001.
[14] Rapiejko P, Jurkiewicz D, Pietruszewska W, Zielnik-Jurkiewicz B, Woroń J and Lipiec A. Treatment strategy of allergic rhinitis in the face of modern world threats. Otolaryngol Pol 2018; 72: 1-12.
[15] Jung M, Lee JY, Ryu G, Lee KE, Hong SD, Choi J, Kim S, Ahn K, Dhong HJ, Chung SK, Kim J and Kim HY. Beneficial effect of nasal saline irrigation in children with allergic rhinitis and asthma: a randomized clinical trial. Asian Pac J Allergy Immunol 2019; [Epub ahead of print].
[16] Balasubramanian A, Wade SW, Adler RA, Lin CJF, Maricic M, O'Malley CD, Saag K and Curtis JR. Glucocorticoid exposure and fracture risk in patients with new-onset rheumatoid arthritis. Osteoporos Int 2016; 27: 3239-3249.
[17] Tamada T and Ichinose M. Leukotriene receptor antagonists and antiallergy drugs. Handb Exp Pharmacol 2017; 237: 153-169.
[18] Amorim J, Borges MC, Fabro AT, Contini SHT, Valdevite M, Pereira AMS and Carmona F. The ethanolic extract from erythrina mulungu benth. flowers attenuates allergic airway inflammation and hyperresponsiveness in a murine model of asthma. J Ethnopharmacol 2019; 242: 111467.
[19] Yamauchi K and Ogasawara M. The role of histamine in the pathophysiology of asthma and the clinical efficacy of antihistamines in asthma therapy. Int J Mol Sci 2019; 20.
[20] Lipworth B, Newton J, Ram B, Small I and Schwarze J. An algorithm recommendation for the pharmacological management of allergic rhinitis in the UK: a consensus statement from an expert panel. NPJ Prim Care Respir Med 2017; 27: 3.
[21] Cortese F, Fransvea P, Saputelli A, Ballardini M, Baldini D, Gioffre A, Marcello R and Sganga G. Streptococcus pneumoniae primary peritonitis mimicking acute appendicitis in an immunocompetent patient: a case report and review of the literature. J Med Case Rep 2019; 13: 126.
[22] Noguchi T, Nakagome K, Kobayashi T, Ueda Y, Uchida Y, Soma T, Nakamoto H and Nagata M. Effect of LTRA on IP-10-induced eosinophil adhesion to ICAM-1. Allergol Int 2016; 65 Suppl: S62-64.
[23] Tang Y, Wei Y, Ye Z and Qin C. Th1, Th17, CXCL16 and homocysteine elevated after intracranial and cervical stent implantation. Int J Neurosci 2017; 127: 701-708.
[24] Munthe-Kaas MC, Gerritsen J, Carlsen KH, Undlien D, Egeland T, Skinningsrud B, Torres T and Carlsen KL. Eosinophil cationic protein (ECP) polymorphisms and association with asthma, s-ECP levels and related phenotypes. Allergy 2007; 62: 429-436.
[25] Liu SC, Lin CS, Chen SG, Chu YH, Lee FP, Lu HH and Wang HW. Effect of budesonide and azelastine on histamine signaling regulation in human nasal epithelial cells. Eur Arch Otorhinolaryngol 2017; 274: 845-853.