Research Paper

Clinical Efficacy of Sublingual Specific Immunotherapy in Children with Allergic Rhinitis and its Impact on their Inflammatory Factors and Immune Function

PING DONG, S. M. TANG*, L. SU, XIN JIA AND W. SHEN

Department of Otorhinolaryngology, Zhoushan Women's and Children's Hospital, Zhoushan, Zhejiang 316000, China

The main objective of this study is to analyze the effects of sublingual specific immunotherapy and conventional drug therapy on inflammatory factors and immune function in children with allergic rhinitis. The research subjects were divided into three groups, group A received sublingual administration of dust mite drops, group B received routine treatment such as passive intervention with topical hormones, antihistamines and nasal irrigation and group C received sublingual administration of dust mite drops and on the basis of drop therapy, conventional treatments such as topical and systemic use of corticosteroids, antihistamines and anti-leukotriene's are combined. Comparison was done among the three different sets of indicators. After treatment, the allergic rhinitis symptom score, visual analog scale score and inflammatory factor index levels in the three groups were calculated. The score was lower in group A than in group B and lower in group C than in group A. Adverse reactions were lowest in group A and highest in group C. After treatment, the levels of whole blood cluster of differentiation 4^+, cluster of differentiation 4^+/cluster of differentiation 8^+ cells and serum immunoglobulin E were lower in group C than group A, and lower in group B than group A. The cluster of differentiation 8^+ index was highest in group C and lowest in group B. Sublingual specific immunotherapy is effective and safe for children with allergic rhinitis.

Key words: Sublingual specific immunotherapy, dust mite drops, anti-histamine agents, allergic rhinitis

Allergic Rhinitis (AR) is a type I hypersensitivity inflammation of the nasal mucosa that is mediated by Immunoglobulin E (IgE) and characterized by paroxysmal sneezing, runny nose, nasal congestion and itching after a sensitized individual is re exposed to an allergen[1]. In recent decades, with the aggravation of environmental pollution, AR and the incidence rate of concurrent diseases have shown a rapid growth trend[2]. 10 %-40 % of the world's population has suffered from it. It is conservatively estimated that the number of patients with AR worldwide exceeds 500 million and the prevalence rate in children is as high as 19.9 %-50.1 %. Children with AR can also develop multiple allergic and related diseases at the same time, such as allergic conjunctivitis, allergic asthma, eustachian tube dysfunction, otitis media, sinusitis, nasal polyps and other diseases. Especially for children of low age, recurrent episodes can lead to low immune function, poor night sleep quality and long-term chronic hypoxia, which may even lead to severe impairment of children's learning status and cognitive function, affecting children's growth and intellectual development[3], causing great harm to their families. Actively treating AR is necessary to prevent the occurrence and development of allergic asthma which is very challenging in current research[4].

Specific Immunotherapy (SIT) refers to the goal of achieving tolerance to allergen stimulation by continuously stimulating specific allergens. SIT is divided into injection and sublingual administration schemes. Sublingual Immunotherapy (SLIT) involves taking dust mite drops under the tongue, which improves allergy sensitivity by regulating the immune response of the body to dust mite allergens. Due to its advantages such as good efficacy, safe and convenient medication, SLIT has more than 10 y of experience in clinical medication in China and it is widely used as a first-line clinical treatment regimen for AR. Traditional drugs are mainly divided into hormone and antihistamine drugs, whose main role is to inhibit and prevent the occurrence of allergic

***Address for correspondence**
E-mail: tangshiminggood@163.com

reactions, which require long-term medication, which is prone to relapse after withdrawal and there are too many adverse reactions. This study was conducted on 93 children with AR to analyze the efficacy of three different medication regimens, including SLIT, local hormone and antihistamine regimens, SLIT combined with hormone and antihistamine regimens, on children with AR and their effects on inflammatory factors and immune function.

MATERIALS AND METHODS

Data source:

According to the inclusion and exclusion criteria, a total of 93 children with AR aged 3-5 y who were admitted to Zhoushan Women's and Children's Hospital in Zhejiang Province, China from January 2021 to December 2021 were selected. The researchers divided the children into three groups according to the random number table method, including 31 patients in each group. Group A (AR without a history of asthma) received sublingual administration of dust mite drops, Group B (AR without a history of asthma) received conventional treatment such as passive intervention, topical use of hormones, antihistamines and nasal irrigation and Group C (AR with a history of asthma) were treated with sublingual administration of dust mite drops in combination with topical and systemic use of hormones as well as conventional treatment such as antihistamines and anti-leukotriene's. There was no statistically significant difference in the basic data of children in groups A, B and C before treatment ($p>0.05$).

Inclusion criteria:

All children met the AR diagnostic criteria in the "Guidelines for the Diagnosis and Treatment of Allergic Rhinitis in Children"; the course of disease exceeds 30 d; age should be 3-5 y old; no history of treatment with acaroid mite drops; no long-term and standardized history of systemic or local drug use; patients with allergic asthma who have no history of acute attack within the past 1 mo of remission; before immunotherapy, the forced expiratory vital capacity in the first second measured by pulmonary function was above 80 %; parents of the children agreed to participate in this study and signed an informed consent form; serum allergen testing was performed in all children before admission, indicating an increase in total IgE values and the use of dust mites as a single allergen; the allergen skin prick test showed that all dust mites were positive (+++ or +++ above).

Exclusion criteria:

Patients with immune deficiency diseases; patients with acute asthma attacks and chronic obstructive pulmonary disease before admission; patients with other airway diseases; patients with respiratory tract infection (acute); patients with parenchymal organ dysfunction diseases; children's family members do not cooperate and those who cannot undergo long-term follow-up.

Research methods:

All 93 children received symptomatic basic treatment for AR and instructing them to take more rest, stay away from allergens, develop a reasonable diet and improve immune function.

Group A (AR without a history of asthma): Dust mite vaccine drops were produced by Zhejiang Yiwu Biotechnology Co., Ltd. (GYZZ S20060012). Dust mite vaccine drops were administered under the tongue containing 1-3 min before swallowing, once a day at a fixed time period. After taking the drug for 10 min, normal drinking and eating were resumed. If there are too many drops at a time, it can be taken multiple times. Children with AR are generally advised to have their medication administered with the help of their parents or under their supervision. The sublingual treatment with dust mite drops is divided into two stages: A dose increasing stage and a maintenance stage. From the 1st w to the 3rd w of treatment, there is an incremental period. For the 1st w, a total protein concentration of 1 mg/l is used, for the 2nd w, a total protein concentration of 10 mg/l is used and for the 3rd w, a total protein concentration of 100 mg/l is used. The doses for the 2nd d and 3rd d per week are 1, 2, 3, 4, 6, 8 and 10 drops, respectively. From the 4th w of treatment to the end of the course of treatment, the maintenance period is to use a total protein concentration of 333 mg/l and 3 drops each time.

Group B (AR without asthma history): The local antihistamine levocabastine nasal spray (GYZZ (2001) No. J-42, Janssen Pharmaceutical Company, Belgium) was used twice a day, twice a time per nostril; nasal glucocorticoid mometasone furoate nasal spray (Mercadon, Belgium, imported drug registration number: H20130182): 1 press per nostril

(50 μg per press) Once a day (total of 100 μg). The 2.3 % hypertonic seawater nasal spray (GSYJXZ 2011 No. 2661844 of Gerolymatos International Co., Ltd., Greece) was selected as the nasal cleaning before each local application of nasal cavity. According to clinical symptoms and signs, weekly reexamination was done to reduce the number, type of medication use and the continuous duration of medication should not exceed 2 mo.

Group C (AR with a history of asthma): Based on the treatment regimen of group A and group B, systemic treatment was added. The anti-leukotriene drug montelukast sodium chewable tablet (Belgian MSD GYZZ J20130047) was taken 4 mg once a night, with continuous medication duration of not more than 2 mo.

After 3, 6, 9 and 12 mo of treatment, the three groups of children were evaluated for relevant indicators.

Research indicators:

Treatment: Compare the symptoms, signs and Visual Analog Scale (VAS) scores of AR in the three groups before and after treatment for 3, 6, 9 and 12 mo. The score of AR was evaluated using the scoring criteria for AR symptoms developed by the Otolaryngology Head and Neck Surgery Branch of the Chinese Medical Association (Tianjin, 2015). The total score is 3 points and the higher the score, the more severe the symptoms of rhinitis (Table 1). Physical sign score of AR: 1 point indicates mild swelling of the inferior turbinate, visible in the nasal septum and middle turbinate; 2 points indicates that the inferior turbinate is close to the nasal septum or the bottom of the nose, but there are still small gaps; 3 points indicates that the lower turbinate is close to the nasal septum and the middle turbinate is not visible. The VAS is a scale of 0-10 cm, operated by the patient to subjectively evaluate the severity of their illness. 0 cm represents no distress while 10 cm represents the most serious distress imaginable. The patient marks the severity of their illness on the VAS scale and the doctor converts the scale (cm value) into a score. The total score of VAS is 10 points and the higher the total score, the more severe the discomfort symptoms of the patient.

Inflammatory factors and immune function: Peripheral venous blood samples were taken from the children before treatment, 6 mo and 12 mo after treatment. Enzyme-linked immunosorbent assay was used to detect serum inflammatory factors and immune function related indicators, including Interleukin (IL)-2, IL-4, IL-10, Interferon gamma (IFN-γ), Whole blood Cluster of Differentiation 4^+ ($CD4^+$), Cluster of Differentiation 8^+ ($CD8^+$), $CD4^+$/$CD8^+$, serum IgE, etc.

Evaluation of adverse drug reactions: After 12 mo of medication, adverse reactions of different medication regimens were evaluated and divided into 4 levels for evaluation (Table 2).

Statistical analysis:

Statistical Package for the Social Sciences (SPSS) 16.0 statistical software was used to process the data in the study, t-test was used to compare the two groups and $p<0.05$ was regarded as a difference with statistical significance.

TABLE 1: SCORING CRITERIA FOR AR SYMPTOMS

Graded scoring	AR symptoms			
	Sneezing (consecutive times at a time)	Runny nose (number of times per day)	Nasal obstruction	Nasal itch
1 point	3-5	≤4	Feel when consciously inhaling	Occasionally
2 point	6-10	5-9	Intermittent or interactive	A sense of ant crawling behavior that can be tolerated
3 point	≥11	≥10	Breathe through the mouth almost all day	A sense of ant crawling behavior that cannot be tolerated

TABLE 2: EVALUATION CRITERIA FOR ADVERSE DRUG REACTIONS

Grade	Degree	Symptom
Level 1	Mild systemic reactions	Local urticaria, rhinitis or mild asthma (Peak Expiratory Flow (PEF) decreased by <20 % from baseline)
Level 2	Moderate systemic reaction	Slow onset (>15 min), generalized urticaria and/or moderate asthma (PEF decreased by <40 % from baseline)
Level 3	Severe (non-fatal) systemic reactions	Rapid onset (<15 min) with systemic urticaria, vascular edema or severe asthma (PEF rate decreased by >40 % from baseline)
Level 4	Anaphylactic shock	Rapid onset of itching, flushing, erythema, systemic urticaria, wheezing, asthma, hypotension, etc.

RESULTS AND DISCUSSION

Comparison of symptoms and scores of AR among three groups of patients before and after medication was shown in Table 3. Before medication, there was no significant difference in the symptom scores of AR among the three groups. After 3, 6, 9 and 12 mo of medication, group C had the lowest score, followed by group A and group B which had the highest score. This indicates that group C has the best medication effect. With the passage of medication time, the score gap between group A and group C is continuously narrowing. After 12 mo of medication, the scores between the two groups were almost the same. This indicates that over the time, the effectiveness of SLIT is not worse than that of SLIT combined with hormones and antihistamines.

Comparison of physical sign scores of AR among three groups of patients before and after medication was shown in Table 4. Before medication, there was no significant difference in the physical signs of AR among the three groups. After 3, 6, 9 and 12 mo of medication, group B had the highest score, followed by group A and group C had the lowest score. There was no significant difference between group A and group C, before and after 12 mo treatment.

Comparison of VAS scores between three groups of patients before and after medication was shown in Table 5. Before medication, there was no significant difference in VAS scores among the three groups of patients. After medication, the VAS scores of patients in all three groups decreased, but the range of group B was the lowest and group C was the highest. After 12 mo of medication, there was no significant difference in VAS scores between group A and group C.

Comparison of inflammatory factors among three groups of patients before and after medication was shown in Table 6. There was no significant difference in inflammatory factors among the three groups of patients before medication. After 6 mo and 12 mo of continuous medication, all indicators in the three groups changed, with group C having the largest change range and group A taking the second place.

Comparison of immune function among three groups of patients before and after medication was shown in Table 7. Before medication, there was no significant difference in immune function among the three groups of patients. After medication, the amplitude change in group C was the largest, while the amplitude change in group B was the smallest.

Comparison of adverse drug reactions among the three groups was shown in Table 8. The three groups of patients were treated for 12 mo, during which the adverse drug reactions in the three groups A, B and C were 0, 5 and 6 respectively. This indicates that group A has a high safety of medication.

AR is a serious systemic allergic disease induced by environmental allergic reactions. When patients are exposed to allergens, their bodies are prone to secrete IgE, a histamine-mediated transmitter and trigger non-infectious inflammatory reactions in the nasal mucosa by cytokines and immunoactive cells within the body[5]. Dust mite allergens are considered to be the main substance inducing AR, which are widely present in the daily living environment of humans. Currently, SLIT is widely recognized as a clinical treatment scheme in various hospitals. The principle is to naturally purify dust mite allergens into protein based biological agents and continuously stimulate the human immune system through small doses of allergens through sublingual administration, thereby improving the body's ability to adapt to allergens and achieving immune tolerance[6].

TABLE 3: COMPARISON OF SYMPTOM SCORES OF PATIENTS WITH AR IN DIFFERENT MEDICATIONS AND DIFFERENT STAGES (x̄±s)

Group	Before medication	Medication for 3 mo	Medication for 6 mo	Medication for 9 mo	Medication for 12 mo
A (n=31)	2.42±0.28	2.02±0.24	1.62±0.17	1.21±0.13	0.99±0.11
B (n=31)	2.42±0.27	2.22±0.23	2.01±0.19	1.88±0.18	1.76±0.18
C (n=31)	2.41±0.28	1.99±0.22	1.59±0.15	1.19±0.12	0.98±0.11

Note: Comparison among the three groups before medication was p>0.05; at different times after treatment, the comparison between group A and group B was p<0.05, group B and group C was p>0.05 and group A and group C was p>0.05

TABLE 4: COMPARISON OF PHYSICAL SIGN SCORES OF PATIENTS WITH AR AT DIFFERENT STAGES OF MEDICATION (x̄±s)

Group	Before medication	Medication for 3 mo	Medication for 6 mo	Medication for 9 mo	Medication for 12 mo
A (n=31)	2.51±0.22	2.19±0.21	1.82±0.18	1.41±0.16	1.08±0.11
B (n=31)	2.51±0.21	2.31±0.19	2.09±0.2	1.92±0.18	1.79±0.14
C (n=31)	2.52±0.22	2.16±0.2	1.78±0.19	1.32±0.15	1.06±0.11

Note: Comparison among the three groups before medication was p>0.05; at different times after treatment, the comparison between group A and group B was p<0.05, group B and group C was p>0.05 and group A and group C was p>0.05

TABLE 5: COMPARISON OF VAS SCORES OF THREE GROUPS OF PATIENTS AT DIFFERENT STAGES BEFORE AND AFTER MEDICATION (x̄±s)

Group	Before medication	Medication for 3 mo	Medication for 6 mo	Medication for 9 mo	Medication for 12 mo
A (n=31)	5.12±0.52	4.32±0.49	3.28±0.29	2.92±0.19	2.14±0.18
B (n=31)	5.14±0.51	4.99±0.5	4.72±0.33	4.41±0.25	4.11±0.21
C (n=31)	5.09±0.51	4.21±0.49	3.18±0.28	2.85±0.21	2.12±0.19

Note: Comparison among the three groups before medication was p>0.05; at different times after treatment, the comparison between group A and group B was p<0.05, group B and group C was p>0.05 and group A and group C was p>0.05

TABLE 6: COMPARISON OF INFLAMMATORY FACTORS IN DIFFERENT STAGES OF THREE GROUPS OF PATIENTS BEFORE AND AFTER MEDICATION (x̄±s, ng/l)

Index	Group A			Group B			Group C		
	Before medication	Medication for 6 mo	Medication for 12 mo	Before medication	Medication for 6 mo	Medication for 12 mo	Before medication	Medication for 6 mo	Medication for 12 mo
IL-2	36.82±3.42	68.24±5.81	80.12±7.66	36.76±3.41	42.56±4.58	56.36±5.92	36.8±3.43	70.26±7.29	84.92±8.37
IL-4	112.36±10.72	92.48±9.16	78.64±8.14	111.98±10.75	101.62±9.92	92.18±8.78	112.42±10.76	90.08±8.79	76.28±8.06
IL-10	108.62±9.48	82.65±8.53	64.46±7.16	108.48±9.42	96.76±9.26	84.38±8.26	108.64±9.47	78.63±8.15	62.21±7.24
IFN-γ	66.41±6.25	92.56±8.84	129.62±9.68	66.36±6.22	78.69±8.28	92.49±8.92	66.38±6.24	98.49±8.86	131.72±10.24

Note: Comparison among the three groups before medication was p>0.05; at different times after treatment, the comparison between group A and group B was p<0.05, group B and group C was p>0.05 and group A and group C was p>0.05

TABLE 7: COMPARISON OF IMMUNE FUNCTION BETWEEN THREE GROUPS BEFORE AND AFTER MEDICATION (x̄±s)

Index	Group A			Group B			Group C		
	Before medication	Medication for 6 mo	Medication for 12 mo	Before medication	Medication for 6 mo	Medication for 12 mo	Before medication	Medication for 6 mo	Medication for 12 mo
CD4+ (%)	47.86±2.12	42.26±1.98	37.74±1.86	47.84±2.13	44.32±2.01	42.25±1.92	47.85±2.14	41.18±1.97	37.28±1.85
CD8+ (%)	25.28±2..29	27.42±2.28	29.23±2.45	25.27±2.28	26.12±2.13	26.94±2.32	25.29±2.28	27.54±2.31	29.46±2.43
CD4+/CD8+	1.88±0.11	1.52±0.11	1.31±0.11	1.88±0.12	1.76±0.12	1.54±0.11	1.89±0.11	1.49±0.11	1.29±0.09
IgE (U/ml)	466.68±42.72	228.38±22.75	108.24±11.25	465.52±42.56	362.45±32.12	282.54±22.86	467.58±42.82	212.36±21.58	102.84±10.95

Note: Comparison among the three groups before medication was $p>0.05$; at different times after treatment, the comparison between group A and group B was $p<0.05$, group B and group C was $p>0.05$ and group A and group C was $p>0.05$

TABLE 8: COMPARISON OF ADVERSE DRUG REACTIONS AMONG THREE GROUPS OF PATIENTS (CASES (%))

Group	Adverse drug reaction				Total (%)
	Level 1	Level 2	Level 3	Level 4	
Group A	0	0	0	0	0
Group B	3	2	0	0	5 (16.13 %)
Group C	4	2	0	0	6 (19.35 %)

Note: Comparison of adverse drug reactions between groups B and C was $p>0.05$, group A and group B was $p<0.05$ and group A and group C was $p<0.05$

Early studies suggest that the pathogenesis of AR is that the histamine plays a main role as an inflammatory mediator. Histamine can bind to H1 receptors and stimulate smooth muscle contraction and gland secretion, thereby expanding blood vessels and enhancing their permeability causing allergic reactions[7]. In this trend of research results, the use of antihistamines to treat AR has become the mainstream treatment for a period of time. This type of drug can form a competitive combination with H_1 allergy and block the binding channel of histamine, avoiding its biological effects, reducing the activity of allergic reactions and playing a soothing role in symptom relief. The disadvantage of this drug is that it can only block a portion of the allergic reaction and its effect is temporary. Once the drug action is stopped, it is easy to cause recurrence.

Immunotherapy is based on protein extracts derived from natural allergens, with the core of adapting the human body to allergens. Immunotherapy can simultaneously regulate the secretion of cytokines in T helper type 1 (Th1) cells and T helper type 2 (Th2) cells of immune responses in the same progression, keeping them in balance and thereby inhibiting the synthesis of IgE, interfering with the progression of AR and blocking the body's own allergic reaction[8]. The drug mechanism of immunotherapy mainly includes three aspects-Antibody response, effector cell response and T cell response. The antibody response is the activation of basophils in the serum after administration, which can inhibit allergens and IgE. There are two subclasses of Immunoglobulin G (IgG) cells, IgG_1 and IgG_4 which belong to blocking antibodies and have a neutralizing effect on the specificity of allergens in the body and their duration of action is long. On one hand, they block the pathway of allergens binding to IgE antibodies and on the other hand, they can avoid binding to antigen presenting cells, which can make Th1 and Th2 more balanced which in turn, promote the level of IgG_1 and IgG_4 to be increased, achieving a virtuous cycle which indicates the process of preventing allergic reactions[9]. The effector cell reaction is the rapid occurrence of drug action after medication, which will inhibit many effector cells such as eosinophils, basophils and mast cells present in the human nasal mucosa, reducing the vitality and aggregation of these cells[10]. T cell response is the formation of T

cells which can be induced after immunotherapy and then participate in allergic reactions. In this process, T cells inhibit the Th2 immune response process, regulate IL-10 and promote the Th1 immune response process[11].

Glucocorticoid receptor is a steroid hormone composed of soluble single chain polypeptides and phosphoproteins. Glucocorticoids are mainly distributed in epithelial cells, submucosal glands and inflammatory cells in the human nasal cavity. The use of glucocorticoids as a medication for AR has been controversial. The glucocorticoid drug, mometasone furoate nasal spray mainly controls nasal allergy by inhibiting the inflammatory mediators in the body and plays a vital role in alleviating the symptoms of nasal discomfort in patients. Moreover, mometasone furoate can also mediate the level of immune cells, prevent inflammation and promote the response of anti-inflammatory proteins. Montelukast is a class of leukotriene receptor antagonists, whose pharmacological action is to inhibit airway inflammation by blocking the pathway of leukotriene action. Some scholars have shown that using montelukast to treat rhinitis should simultaneously reduce the use of glucocorticoids and the incidence of adverse reactions[12]. The combination of glucocorticoid and montelukast has a rapid effect on inhibiting inflammation at the target site of AR, but it is prone to adverse reactions such as epistaxis of varying degrees.

In this study, different drugs used in groups A and C have significant effects on inhibiting inflammatory factors and improving the immune function of patients. IL-2 is an important anti-inflammatory factor. Once the body's inflammatory response is evident, it can neutralize pro-inflammatory factors, thereby reducing the inflammatory response. IL-4 is the core mediator in the IgE synthesis process and can facilitate the smooth completion of allergic reactions mediated by IgE. IL-10 is involved in the reaction process of T cells. IFN-γ can inhibit the synthesis of IgE and reduce the specific response to allergens, thereby alleviating the disease[13]. IL-2, IL-4, IL-10 and IFN-γ are considered to be important indicators of inflammatory factors. $CD4^+$, $CD8^+$, $CD4^+/CD8^+$ and IgE are widely used as important indicators to measure immune function. In this study, group A used dust mite vaccine drops for SLIT, with good results and no adverse reactions. It has a good effect on inhibiting inflammatory factors and improving immune function. In group B, the combination of antihistamines and hormone drugs was not effective and had many adverse reactions. The combination of group A and group B in group C had good efficacy, but there were many adverse reactions. Compared with group A, there was no significant difference in efficacy, inhibition of inflammatory factor and improvement of immunity. Therefore, SLIT with a single drug should be widely promoted as a clinical medication regimen for AR in children.

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Conflict of interests:

The authors declared no conflict of interest.

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