

Clinical research of sublingual immunotherapy on refractory atopic dermatitis with dermatophagoides farina drops.

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Abstract

Objective: To evaluate the efficacy and safety of the treatment of refractory atopic dermatitis with dust mite allergen vaccine through sublingual immunotherapy.

Methods: To adopt the self control research, compare the eczema area and severity index (EASI), percentage of skin damage area (BSA%) and change in pruritus scoring and drug use scoring of 35 patients with dust mite allergen and refractory atopic dermatitis after receiving the treatment with dust mite allergen vaccine and sublingual immunotherapy for 1 year, and observe recurrence.

Results: 31 patients insist in completing the course of treatment for 1 year and 4 patients quit. Eczema area and severity index (EASI), percentage of skin damage area (BSA%) and change in pruritus scoring and drug use scoring after treatment obviously reduce (P mean<0.01) compared with those before treatment. The effective rate is 77.41%. Adverse reactions related to treatment do not obviously occur. The recurrence rate is 9.67% after 1-year follow-up.

Conclusion: The sublingual allergen immunotherapy is an effective method with good safety to treat refractory atopic dermatitis caused by dust mite.

Keywords: Atopic dermatitis, Dust mite, Sublingual immunotherapy, Dermatophagoides farina, Safety.

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Introduction

Atopic dermatitis (AD) is a chronic and recurrent skin disease with inflammation. It attacks children in most cases. Its clinical manifestations are shown in parts with high incidence at different age stages, such as eczema, skin dryness and severe itching [1,2]. The disease is with complex causes and can last for many years. Genetic allergic constitution and various allergen stimulations in the living environment are important factors to cause the disease, especially few patients suffer bad efficacy of traditional therapeutic methods for many years. We get used to calling it "refractory atopic dermatitis" [3,4]. We apply dust mite allergen vaccine sublingual immunization to part of patients with refractory atopic dermatitis based on detected positive dust mite allergen, obtain good efficacy, and make the following report now.

Data and Methods

Case selection

The selected patients saw a doctor in the outpatient of our Allergy department from January 2014 to December 2015. We confirm the following inclusion criteria [5,6]: 1. The patients were diagnosed with moderate and severe atopic dermatitis, had more than 10% of skin damage body surface area, and received standardized treatment from specialist doctors for at least equal or greater than 2 years and obtained bad efficacy; 2.

The detected dust mite specificity IgE level based on allergen external serum was equal or greater than 3; 3. The age varied from 5 to 55; 4. The sex was not limited; 5. The patients agreed to sign an informed consent letter. Exclusion criteria: 1. The patients were infectious with atopic dermatitis and with skin damage; 2. In addition to dust mite, other allergen specificity serum IgE level was equal or greater than 3; 3. During the treatment, the patients needed to systematically use glucocorticoid hormone equivalent to 2 mg prednisone each day; 4. The patients had received or were receiving phototherapy (such as UVB and PUVA); 5. The patients used immunosuppressive agents or systematically applied glucocorticoid hormone within the past 1 month; 6. The patients suffered from chronic diseases (such as diabetes, high blood pressure, and severe liver and kidney dysfunction) and were not suitable for specificity immunotherapy; 7. The patients were with pregnancy or lactation; 8. The patients suffered from immunosuppressive diseases (such as malignant tumor, malignant tumor history or HIV infection history); 9. The patients simultaneously suffered from severe asthma. Exclusion criteria: 1. The patients asked to withdraw from the treatment; 2. The patients violated the therapeutic scheme; 3. The patients lost follow-up; 4. The patients were pregnant women.

Methods

Serum allergen specificity IgE detection: Swedish Pharmacia CAP detection system was adopted to diagnose the patients with one of positive dermatophagoides pteronyssinus and dermatophagoides farinae as positive dust mite, when sIgE is greater than 0.35 kU/L and make classification according to sIgE content [7].

Therapeutic methods: The drug washout period (that is, anti allergic and anti inflammatory Chinese and western medicine with immunosuppressive action in addition to all therapeutic methods are stopped in this period) covers the first 3 weeks before sublingual immunotherapy begins. Only oral loratadine, cetirizine and external mometasone furoate cream can be used during the cleaning period and the follow-up treatment period. The selected patients keep standardized dermatophagoides farina drops (Chanllergen-Df, produced by Wowu Biotechnology Co., Ltd located in Zhejiang, China) below the tongue according to the treatment sequence. The methods are as shown: to keep dermatophagoides farina drops below the tongue for 2 min and swallow them (1 time/d). No.1 is for the first week (the total protein concentration of 1 µg/mL); No. 2 is for the second week (10 µg/mL); No. 3 is for the third week (100 µg/mL); the doses within 7 days a week are respectively 1, 2, 3, 4, 6, 8, and 10 drops for No. 1~3; No. 4 (333 µg/mL) is for the fourth ~ fifth week, that is, 3 drops a time; No. 5 is used for maintenance after the sixth week, that is, 2 drops a week. No. 4 is used to treat the patients of less than 14. The course of treatment is all 1 year. The patients' symptoms and signs before the treatment (baseline) and at the end of the 12th month after the treatment are respectively observed and compared with the baseline. The patients who and have follow-up record including medication situation within the previous 1 week and receive the course of treatment of less than 12 months just participate in safety evaluation rather than are listed in efficacy observation.

Efficacy observation index and decision criterion main efficacy index: Eczema area and severity index (EASI) consulted the methods by Hanifin [8], that is, the sum of skin damage severity score, skin damage area, and coefficient product for four parts of the whole body. Erythema, infiltration/papule/edema, scratch/exfoliation, and moss hyalinosis on head, trunk, and upper and lower limbs are respectively graded in each follow-up. The average severity is showed through 0~3 scores: nothing for zero score; mild for 1 score; moderate for 2 scores; severe for 3 scores. The most serious situation of the part is recorded, based on which skin damage area score is calculated in order to obtain the sum of EASI score. Efficacy criteria: efficacy index = (baseline EASI score – EASI score before treatment)/baseline EASI score. Recovery means that efficacy index is equal or greater than 0.90. Excellent efficacy means that the efficacy index varies from 0.60 to 0.89. Progress means that efficacy index varies from 0.20 to 0.59. Invalid means that efficacy index is less than 0.20. Recovery plus excellent efficacy is effective rate. Minor efficacy index: 1. the percentage of skin damage area (BSA%, the percentage of body surface area); 2. VAS (visual analogue

scale) evaluation: 0 cm is without pruritus; 3. drug scoring: The volume doses of drugs applied to the patients before treatment (baseline) and within 1 week at the end of 12 months after treatment are compared. Among them, each 5 mg loratadine or cetirizine represents 1 score and each 2.5 g mometasone furoate cream represents 1 score (Table 1).

Table 1: The scores comparison before and after treatment in pre- and post-treatment (Mean ± SD).

Subjects	Pre-treatment	Post-treatment	t	P
EASI	32.48 ± 1.87	5.93 ± 0.74	84.27	0
BSA (%)	35.03% ± 0.17%	7.31% ± 0.21%	54.51	0
Pruritus	8.47 ± 0.49	2.04 ± 0.41	54.6	0
Pharmacological	25.63 ± 7.61	1.79 ± 0.87	19.23	0

Safety evaluation: The evaluation criteria formulated based on ARIA (2008) is applied to grade systemic adverse reactions [9]. Level 0: no symptoms or non specificity symptoms; Level 1: mild systemic reaction symptoms, local urticaria, rhinitis, or mild asthma (peak flow rate reduces less than 20% since baseline); Level II: moderate systemic reaction symptoms, slowly-occurred systemic urticaria and (or) moderate asthma (peak flow rate reduces less than 40% since baseline); Level III: severe (non-fatal) systemic reaction symptoms, rapidly-occurred (<15 min) and systemic urticaria, vascular edema or severe asthma (peak flow rate reduces greater than 40% since baseline); Level IV: allergic shock symptoms, rapidly-occurred itching, flushing, erythema, systemic urticaria, vascular edema, rapidly-occurred asthma or hypotension or others.

Statistical methods: To compare the patients' symptoms and signs before and after treatment, itching and meditation scores based on SPSS22.0 statistical software and make the pairing t test. P<0.05 represents difference with statistical significance.

Results

General data: The outpatient screens 42 patients that meet the conditions according to the order. Among them, 35 patients meet the inclusion and exclusion criteria and agree to follow the therapeutic scheme. Among them, there are 18 male patients and 17 female patients; they are 7~25 years old, an average age of (14.05 ± 7.36) and average course of disease of (16.04 ± 7.41) years. Among them, 25 patients were with mild and moderate allergic rhinitis and asthma history and needed to take orally and use externally drugs to control above diseases according to the course of disease. Now they just suffer from mild rhinitis symptoms and do not need drugs to control the symptoms. The remaining 10 patients ever suffered from pure allergic rhinitis and needed drugs to control the disease. But at present, the symptoms disappear or become mild. In other words, the drugs are unnecessary. The above patients mainly suffer from skin diseases now.

Therapeutic results: 31 patients complete 1 year of course of disease. The remaining 4 patients quit treatment due to adverse

reactions or bad efficacy. After 1 year of sublingual immunotherapy, 31 patients improve skin symptoms and signs in different degrees after treatment. EASI score, BSA%, itching VAS score, drug score obviously reduce after treatment. The specific situation is as shown in Figure 1. Among them, 21 patients (67.74%) recover; 3 patients (9.67%) are with excellent efficacy; 7 patients (22.58%) improve; there are no invalid patients. During the treatment period of September through December, 17 patients completely stop taking orally antihistamine. Among them, 9 patients intermittently apply glucocorticoid hormone ointment. The remaining patients obviously reduce oral drugs and drugs for external use after treatment. In addition, the patients improve nasal and respiratory symptoms to some extent based on self-evaluation after treatment. There are no serious patients.

Safety evaluation: 4 patients fail to complete the course of treatment; 3 patients (9.67%) suffer from lip or sublingual swelling, oral itching, pruritus or dryness after the first week of the treatment; 1 patient (3.23%) suffers from urticaria during the local maintenance period and has no above adverse reactions mentioned in Level II. The total number of drug administration is 13291 and the occurrence rate of bad adverse reaction is 0.75%. The patients who suffer from systemic adverse reactions have rapidly relieved the symptoms after they receive conservative treatment or allergen vaccine reduction and (or) drug treatment.

Follow-up: 31 patients who complete the course of treatment receive follow-up for 1 year. 3 patients (9.67%) recur in 6~12 months after ending the course of treatment, but they obviously reduce after treatment. After applying glucocorticoid hormone ointment or receiving the additional doses of the original ointment, the remaining patients do not suffer from skin damage and special change in disease conditions.

Discussion

AD incidence rate gradually increases year by year and has great impact on the patients' growth, life and work. Generally specifically, the standardized and recommended therapeutic method is to take drugs for oral and external use based on patients' specific disease conditions. The method is effective for most patients. Its disadvantage is that patients need to always rely on drugs and suffer from recurred diseases once they stop taking drugs. Few patients with refractory atopic dermatitis receive several courses of standardized treatment for many years, but they suffer from the efficacy that is still not ideal. So it is very meaningful to explore a method with more ideal and lasting efficacy and reducing or stopping the use of drugs.

In this research, we take the patients clinically diagnosed with moderate and severe atopic dermatitis and refractory patients who receive standardized treatment for at least 2 years and obtained poor efficacy as the research object and hope to seek a method that can effectively solve the problems of diseases from the patients' heart. The incidence of AD is closely related to the patients' genetic allergic constitution and environment.

Among them, the allergen in the environment is an important factor. In the research, we take the strong positive patients tested through dust mite allergen as the research object and dust mite as the most important and common allergen which is very difficult to completely avoid contact in real life. In view of the therapeutic value of allergen specific immunotherapy (SIT) in allergic reaction diseases such as asthma and allergic rhinitis [10-13], we test and treat the research objects base on the method and select the more convenient sublingual immunotherapy (SLIT) in order to improve the patients' compliance. According to research results, we find that after the patients with positive specific atopic dermatitis detected through dust mite allergen receive immunotherapy for 1 year, they obviously reduce various efficacy indexes after treatment, with the recovery rate of 67.74% and the effective rate of 77.41%.

In addition, in the follow-up 1 year, the recurrence rate is only 9.67%. It shows that the method is with good efficacy. This is similar to similar research results by other scholars. In this research, during the treatment, the patients suffer from the incidence rate of 12.90% in poor reactions and 0.75% in systemic poor reactions. This also hints that the method is with good safety and verified by other similar data. We think that the method is worthy being recommended to the positive patients with refractory atopic dermatitis through dust mite detection. In addition, the interesting finding is that the selected patients suffer from allergic rhinitis combination or non combined asthma in some different degrees in the course of disease, and control the severity of disease through drugs. However, when skin disease becomes a main symptom, rhinitis or asthma symptoms basically can voluntarily relieve or disappear. And after we conduct 1 year of specific immunotherapy, the above symptoms are also further improved. This hints that there is internal relationship between the patients' skin disease and respiratory disease. Dust mite is an important factor in the occurrence of both diseases. The patients show different disease conditions at the different stage of allergic disease. However, we need to further verify how both specially evolve and what internal connection both have through the research in the future.

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