

REVIEW ARTICLE

IgE-mediated allergy: a rare cause of chronic spontaneous urticarial with allergen-specific immunotherapy as treatment option – a systematic review with meta-analysis from China

C.-R. Shi,[†] Y.-P. Li,^{‡,§} Y.-J. Luo,[¶] C.-B. Shi,^{††} X. Yan,^{†,*} K.-H. Yang,^{§,##} K. Yi^{§,##}

[†]First Hospital of Lanzhou University, Lanzhou, Gansu province, China

[‡]Chinese Evidence-Based Medicine Center, West China Hospital, Sichuan University, Chengdu, Sichuan province, China

[§]Evidence-Based Medicine Center, School of Basic Medical Sciences, Lanzhou University, Lanzhou, Gansu province, China

[¶]School of Public Health of Lanzhou University, Lanzhou, Gansu province, China

^{††}An-nine Branch of the General Hospital of Lanzhou Military Region, Lanzhou, Gansu province, China

^{##}The First Clinical Medicine College of Lanzhou University, Lanzhou, Gansu province, China

*Correspondence: X. Yan. E-mail: yanxiang528@sina.com

Abstract

Background Allergen-specific immunotherapy (SIT) has long been a controversial treatment for chronic urticaria (CU), although SIT has been used in patients with allergic diseases for more than 90 years.

Objectives To evaluate the efficacy and safety of SIT vs. conventional treatment (CT) in the treatment of CU.

Methods Systematic searches were conducted without language restrictions in MEDLINE, EMBASE, the Cochrane Library, ISI Web of Knowledge, China National Knowledge Infrastructure, and Chinese Scientific Journals Full Text Database. The primary outcomes were efficacy and quality of life (QOL) and the secondary outcomes were relapse rate and adverse events (AEs).

Results Fourteen studies (1838 patients) were included. None of them was double-blind placebo controlled. Our study demonstrated that SIT seemed to show more clinical efficacy rate (OR 2.39; 95% CI, 1.73–3.30; $I^2 = 55\%$, $P = 0.008$), more complete recovery rate (OR 2.13; 95% CI, 1.55–2.91; $I^2 = 61\%$, $P = 0.008$) and less relapse rate 2 weeks after treatment (OR 0.38; 95% CI, 0.24–0.61; $I^2 = 36\%$, $P = 0.20$) than CT. Only one study reported improved QOL and no study reported serious AEs after SIT.

Conclusions Current evidence indicates that IgE-mediated allergy may be causative in a small number of CU patients and specific immunotherapy with these allergens may be beneficial in those patients. However, the number of included studies was small and those qualities were low. So, available evidence is not adequate to draw an affirmative conclusion and larger studies of high quality are needed to provide increasingly convincing data and cases.

Received: 15 July 2011; Accepted: 23 September 2011

Conflict of interest

None.

Funding sources

No sponsorship from institutions or pharmaceutical industry.

Disclosures

None.

Introduction

Up to one in four people suffer from urticaria in their lifetime, and 0.5–1.0% of the population suffer from chronic urticaria (CU).¹ The CU is defined as spontaneous weals lasting longer than

6 weeks and is accompanied by angioedema in 40% of patients, which is therefore labelled as ‘chronic spontaneous urticaria’.² The CU can induce misery, embarrassment and cause severe quality of life (QOL) impairment,^{3,4} and its destructiveness can rival severe

coronary artery disease.⁵ There are high direct and indirect health care costs of this disease due to the large socioeconomic implications of a 20–30% reduction in performance.⁶ The mainstay of treatments for CU remains non-sedating H1-antihistamines alone or in combination.⁷ Although antihistamines can alleviate some symptoms, factors such as capricious course, intermittent attack, poor responsiveness to treatment and ongoing recurrence trouble both clinicians and patients. Thus, the treatment for CU is still a formidable challenge.⁸ Type I allergy seems to be a rare cause of CU, but it must be considered in patients with intermittent symptoms.

Allergen-specific immunotherapy (SIT), also known as allergen immunotherapy (AIT), desensitization therapy, specific-allergen immunotherapy, or allergy vaccine therapy, is recognized by the World Health Organization as the only treatment for allergic diseases⁹ and has been used clinically for 90 years. The main short-term objective of SIT is to reduce the responses to allergic triggers and alleviate symptoms. The long-term objective of SIT is to decrease inflammatory responses and prevent the development of persistent disease.¹⁰ The SIT represents a validated aetiological treatment of allergic disorders and is capable of alleviating symptoms and modifying the natural course of allergy.¹¹ Recent studies have shown that SIT was a relatively safe and effective treatment for allergic rhinitis,¹² conjunctivitis,¹³ asthma,¹⁴ stinging insect hypersensitivity,¹⁵ and even atopic dermatitis.¹⁶ However, the role of SIT for CU is unclear.

The ideal result of CU treatment should be both symptomatic relief and recurrence prevention. Long-term strategies such as preventive measures and immunomodulatory treatments could play important roles. Is SIT for CU effective or not? The results of previous studies were inconsistent and controversial.^{8,10} Therefore, assessing the effectiveness and safety of SIT in patients with CU is valuable. For this reason, we conducted this systemic review to investigate the efficacy and safety of SIT for CU patients.

Methods

Search strategy and selection criteria

Randomized controlled trials (RCTs) were searched in the Cochrane Library (Issue 1, 2011), MEDLINE (1966–2011), EMBASE (1974–2011), ISI Web of Knowledge (1948–2011), China National Knowledge Infrastructure (CNKI) (1994–2011), and Chinese Scientific Journals Full Text Database (CSJD) (1989–2011) up to January 2011. Bibliographies of relevant reviews and potential studies were also manually searched for additional citations. Searches were conducted by two independent authors (Chun-Rui Shi, Ya-Jie Luo). The main search subjects were the following Medical Subject Headings, full text and keywords: ‘(chronic) urticaria’, ‘hives’, ‘immunotherapy’, ‘desensitization’, ‘desensitisation’, ‘hyposensitization’, ‘hyposensitisation’, or ‘allergy vaccine therapy’.

The specific inclusion criteria were as follows: (i) children (age <18 years) and adults (age ≥18 years), without gender or race restrictions, with symptoms of CU in which the causal allergen was identified,¹⁷ without any other allergic diseases and previous treatment; (ii) sublingual or subcutaneous injections of SIT with all appropriate allergens considered at all doses and all durations of treatment, with or without combined conventional medicine; (iii) RCTs, without language restrictions. Other desensitization intervention measures, such as Chinese medicine desensitization therapy, were excluded. Acute urticaria (<6 weeks duration), physical urticaria and other urticaria types such as contact urticaria were also excluded. The primary outcomes were the efficacy (clinical efficacy rate and clinical complete recovery rate) and QOL; the secondary outcomes were the relapse rate and adverse events (AEs).

Data abstraction and assessment of bias risk

This systematic review was performed according to the Cochrane Handbook version 5.0.¹⁸ Two reviewers (Chun-Rui Shi, Ya-Jie Luo) independently selected studies based on screening titles, abstracts and included studies after scanning full-texts. Data regarding the characteristics of included patients, interventions and course of treatment were extracted. Further information was obtained from the study authors when needed. Risk of bias was assessed according to the Cochrane Collaboration tool, which consists¹⁸: sequence generations, concealment of allocation, blinding of study participants and investigators, incomplete outcome data addressed, selective outcome reporting and other sources of bias. We contacted the first author for more details if necessary. Two authors (Chun-Rui Shi and Ya-Jie Luo) independently involved in data extraction and quality assessment. All disagreements during study selecting, data extracting and quality assessing were resolved by group consensus or discussions with the third author (Xiang Yan).

Data analysis

For continuous outcomes, the standardized mean difference (SMD) or mean difference (MD) and the 95% confidence interval (CI) were calculated. Binary outcomes were pooled by using the odds ratio (OR) and 95% CI. Heterogeneity was measured with the I^2 test, where $I^2 > 50$ indicates a substantial or considerable heterogeneity across studies. In the absence of any statistically significant heterogeneity across studies, we reported a pooled effect derived from the fixed-effect model. A random-effect meta-analysis and subgroup analysis was performed in the presence of statistically significant heterogeneity. To investigate the resources of heterogeneity, subgroup analysis was conducted according to the methods of endpoint measurement and the evaluated subjects. Meta-analysis was performed with the available software (Review Manager 5.0.21; Copenhagen, Denmark) (The Nordic Cochrane Centre, The Cochrane Collaboration, 2009).

Results

Search results

Finally, fourteen RCTs (1838 cases) were included (Fig. 1).^{19–32} All of them were single-centred studies in China, however, none of them was double-blind placebo controlled. Allergens were identified with skin prick tests (SPTs) except two studies^{29,31} and SIT was performed with subcutaneous injections in all studies. The other characteristics of the included studies are listed in Table 1.

The methodological quality of the included studies is summarized in Table 2. Three studies reported the generation of random sequence based on the order of the patient's hospital visit^{26,32} and a randomized block design.²⁸ The other studies only mentioned 'randomization', but did not specify their method of generating random sequences. All studies did not report concealed allocation and blinding. We contacted the first author of the studies by e-mails and correspondences when necessary, but got no reply.

Results of meta-analysis

Children For children, SIT seemed to show more clinical efficacy rate than CT^{23,27} (OR 4.49; 95% CI, 1.69–11.91; $P = 0.003$) with no heterogeneity ($I^2 = 0\%$, $P = 0.89$). However, there was no statistically significant difference between these two groups in complete recovery rate^{23,27} (OR 2.20; 95% CI, 0.86–5.59; $P = 0.10$) with no heterogeneity ($I^2 = 0\%$, $P = 0.97$). No study reported relapse rate at any time (Fig. 2).

Adult Allergen-specific immunotherapy seemed to show more clinical efficacy rate than CT^{21,28–32} (OR 3.16; 95% CI, 1.80–5.55; $P < 0.0001$) in adult patients. However, the heterogeneity across studies was 54% according I^2 test ($P = 0.05$). Subgroup analysis

showed that SIT seemed to show more clinical efficacy rate than CT in studies using non-UAS (OR 4.56; 95% CI, 2.00–10.39; $P = 0.0003$) with low heterogeneity ($I^2 = 45\%$, $P = 0.16$), and there was no statistically significant difference between these two groups in studies using UAS (OR 2.14; 95% CI, 0.96–4.74; $P = 0.06$) with substantial heterogeneity ($I^2 = 62\%$, $P = 0.07$) (Fig. 3). After sensitivity analysis, we removed studies that were conducted by Tang,²⁸ the pooled results of studies using USA did not change (OR 1.13; 95% CI, 0.44–2.94; $P = 0.80$) with low heterogeneity ($I^2 = 4\%$, $P = 0.31$).

For adult patients, SIT seemed to show more complete recovery rate than CT^{29,31,32} (OR 2.84; 95% CI, 1.65–4.90; $P = 0.0002$) with substantial heterogeneity ($I^2 = 60\%$, $P = 0.08$). Subgroup analysis showed that SIT seemed to show more complete recovery rate than CT in a study using non-USA (OR 6.80; 95% CI, 2.33–19.80; $P = 0.0004$) and in studies using UAS (OR 2.06; 95% CI, 1.08–3.94; $P = 0.03$) with low heterogeneity ($I^2 = 29\%$, $P = 0.23$) (Fig. 4).

Allergen-specific immunotherapy seemed to decrease relapse rate (2 weeks after treatment) than CT^{31,32} (OR 0.34; 95% CI, 0.17–0.66; $P = 0.002$) in adult patients. However, the heterogeneity across studies was 70% according to I^2 test ($P = 0.07$). Subgroup analysis showed that SIT seemed to decrease relapse rate than CT in the study using non-UAS³¹ (OR 0.13; 95% CI, 0.04–0.46; $P = 0.001$) and there was no statistically significant difference between these two groups in the study using UAS³² (OR 0.54; 95% CI, 0.23–1.26; $P = 0.16$) (Fig. 5).

Quality of life (QOL) was only reported in one study.²⁹ Song assessed the QOL of patients pre- and post-SIT with the dermatology life quality index questionnaire. Improvement of QOL was observed in patients treated with SIT ($n = 60$) and CT ($n = 30$) ($P = 0.000$). Furthermore, the QOL of the German SIT reagent group was more than that of the CT group ($P = 0.003$).

Unclassified populations Allergen-specific immunotherapy seemed to show more clinical efficacy rate than CT^{19,20,22,25,26} (OR 1.75; 95% CI, 1.13–2.72; $P = 0.01$) in unclassified populations. However, the heterogeneity across studies was 70% according to the I^2 test ($P = 0.009$). Subgroup analysis showed that SIT seemed to show more clinical efficacy rate than CT in studies using non-UAS^{20,22,25} (OR 1.96; 95% CI, 1.12–3.43; $P = 0.03$) with substantial heterogeneity ($I^2 = 70\%$, $P = 0.04$) and there was no statistically significant difference between these two groups in studies using UAS^{19,26} (OR 1.48; 95% CI, 0.73–2.99; $P = 0.27$) with substantial heterogeneity ($I^2 = 84\%$, $P = 0.01$) (Fig. 6). After removing a study conducted by Wei,²² the pooled results of studies using non-UAS criteria did not change (OR 3.30; 95% CI, 1.61–6.76; $P = 0.001$) with low heterogeneity ($I^2 = 0\%$, $P = 0.42$).

Allergen-specific immunotherapy seemed to show more complete recovery rate than CT^{19,22,24,25} (OR 1.77; 95% CI, 1.16–2.70; $P = 0.008$). However, the heterogeneity across studies was 78% according to I^2 test ($P = 0.003$). Subgroup analysis showed that

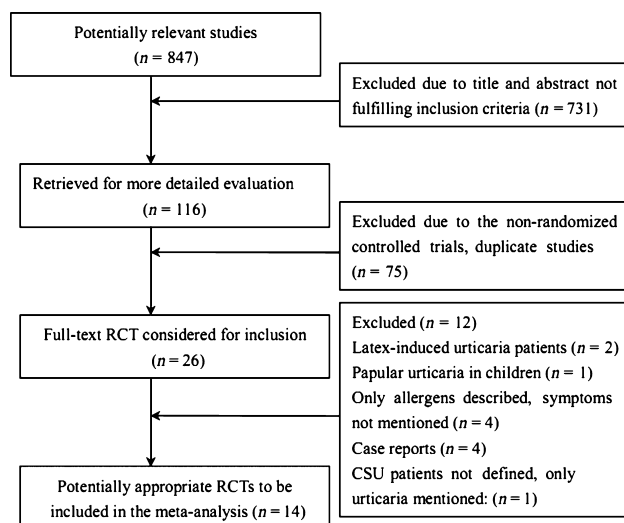


Figure 1 Flowchart for the identification of studies.

Table 1 Characteristics of included trials

Source	No. of patients	Age, mean (range), year	Allergen detection	Intervention	Course of treatment	Assess disease activity and determine the efficacy of standard	Time of follow-up
Wu <i>et al.</i> ¹⁹	T: 40 C: 40	11–56	16 species of inhaled allergens and 27 species of food allergens	T: SIT if symptoms onset combine chlorphenamine po qd-tid in the first 12 weeks C: Cetirizine 10 mg qd and chlorphenamine 4 mg qn	T: 24 week C: 6 weeks	According to reduce UAS before and after treatment, SSRI < 25% was considered as no effect	2 weeks
Cao <i>et al.</i> ²⁰	T: 78 C: 78	6–62	Results of detection not mentioned	T: SIT C: chlorphenamine 4 mg tid and Diphenhydramine 25 mg qn, if the severe patient plus 2 mg cyproheptadine qn	3 months	Disease activity was not assessed, no change during the treatment was considered as no effect	6 months
Ren <i>et al.</i> ²¹	T: 32 C: 13	5–56	21 species of inhaled allergens	T: SIT if symptoms onset combine corticosteroid and antihistamine po C: corticosteroid and antihistamines po	8–12 months	Not described	2 year
Wei <i>et al.</i> ²²	T1: 356 T2: 79 C: 38	3–71	15 species of inhaled allergens and 11 species of food allergens	T1: SIT T2: SIT combine application of ketotifen 1 mg po tid, famotidine 20 mg po bid C: ketotifen 1 mg po tid, famotidine 20 mg po bid	T: 6 months C: 1 months	Disease activity was not assessed, no change during the treatment was considered as no effect	Not mentioned
Gao <i>et al.</i> ²³	T: 37 C: 25	3–14	17 species of inhaled allergens	T: SIT combine Loratadine 5 mg qd and Chlor-trimeton 2–4 mg bid as symptom onset C: Application of Loratadine 5 mg qd and Chlor-trimeton 2–4 mg bid as symptom onset	8–12 months	According to reduce UAS before and after treatment, SSRI < 25% was considered as no effect	2 years
E <i>et al.</i> ²⁴	T: 46 C: 43	9–71	18 species of food allergens	T: SIT, dexamethasone iv gtt as symptom acute onset C: antihistamine po, dexamethasone iv gtt as symptom acute onset	12 weeks	Symptom recurrent onset in 2 years was considered as no effect	Not described
Su <i>et al.</i> ²⁵	T: 96 C: 30	5–68	19 species of inhaled and food allergens	T: SIT, antihistamine po as symptom onset C: antihistamine po as symptom onset	8–12 months	Not described	12 months
Wen <i>et al.</i> ²⁶	T: 162 C: 140	T: 33 (15–50) C: 31 (12–50)	Results of detection not mentioned	T: SIT combine Loratadine 10 mg po qd as symptom onset in initial stage C: Loratadine 10 mg po qd, ketotifen 100 mg po qd, Vitamin C 200 mg po qd, and topical corticosteroid ointment	12 months	According to reduce UAS before and after treatment, SSRI ≤ 20% was considered as no effect	12 months

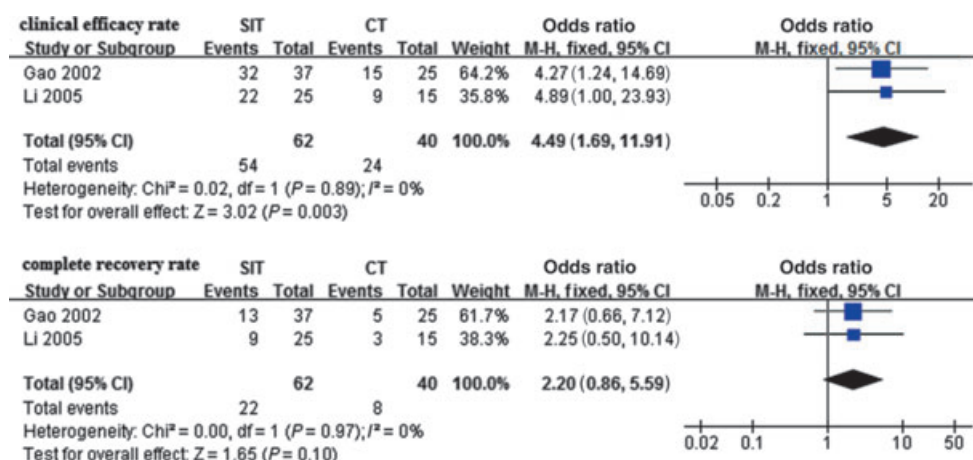
Table 1 Continued

Source	No. of patients	Age, mean (range), year	Allergen detection	Intervention	Course of treatment	Assess disease activity and determine the efficacy of standard	Time of follow-up
Li <i>et al.</i> ²⁷	T: 25 C: 15	4–14	18 species of inhaled allergens	T: SIT combine ketotifen 0.5 mg bid (weight ≤14 kg) or ketotifen 1 mg bid (weight >14 kg) as symptom onset C: ketotifen 0.5 mg bid (weight ≤14 kg) or ketotifen 1 mg bid (weight >14 kg) as symptom onset	8–12 months	According to reduce UAS before and after treatment, SSRI <25% was considered as no effect	2 years
Tang <i>et al.</i> ²⁸	T: 32 C: 32	36.9 (18–61) 38.8 (20–60)	Dermatophagoides farinae	T: SIT combine mizolastine 10 mg qd as symptom onset C: mizolastine 10 mg qd as symptom onset	24 weeks	According to reduce UAS before and after treatment, SSRI ≤ 20% was considered as no effect	24 weeks
Song <i>et al.</i> ²⁹	T1: 30 T2: 30 C: 30	T1: 38.81 ± 11.99 T2: 39.12 ± 12.23 C: 38.49 ± 12.3	5 species of inhaled allergens were detected by levels of allergen-specific IgE antibody	T1: SIT (Reagents produced by German company) T2: SIT (Reagents produced by Chinese hospital) C: ketotifen 1 mg po tid, famotidine 20 mg po bid	12 months	According to reduce UAS before and after treatment, SSRI < 20% was considered as no effect	Not described
Guo <i>et al.</i> ³⁰	T: 75 C: 72	T: 32.14 ± 3.22(16–45) C: 33.36 ± 3.15(17–43)	Results of detection not mentioned	T: SIT C: corticosteroid, calcium and antihistamines po	2 years	Disease activity was not assessed, no change during the treatment was considered as no effect	Not described
Wang <i>et al.</i> ³¹	T: 34 C: 34	18–55	Results of detection not mentioned; allergens were detected by SPT and levels of allergen-specific IgE antibody	T: SIT combine loratadine 10 mg po qd and BCG Polysaccharide and Nucleic Acid Preparation, 0.5~1.0 mg im. qod C: loratadine 10 mg po qd and BCG Polysaccharide and Nucleic Acid Preparation, 0.5~1.0 mg im. qod	T: SIT 12 months medications 3 months C: 3 months	Disease activity was not assessed, no change during the treatment or reduce <30% was considered as no effect	12 months
Huang <i>et al.</i> ³²	T: 51 C: 45	18–63 T: 35.82 ± 14.37 C: 35.13 ± 9.58	Dermatophagoides farinae	T: SIT combine desloratadine 5 mg qd and cimetidine 200 mg tid C: desloratadine 5 mg qd and cimetidine 200 mg tid	T: SIT 20 weeks medications 4 weeks C: 4 weeks	According to reduce UAS before and after treatment, SSRI < 20% was considered as no effect	20 weeks

C: conventional treatment group; SIT, Allergen-specific immunotherapy; SPT, skin prick testing; SSRI, symptom score reduction index; T, Allergen-specific immunotherapy group; UAS, urticaria activity score.

Table 2 Methodological quality of included trials

Source	Sequence generation	Allocation concealment	Blinding of participants, personnel and outcome assessors	Incomplete outcome data (ITT analysis)	Selective outcome reporting	Other sources of bias
Wu <i>et al.</i> ¹⁹	Unclear	Unclear	No (open label)	Unclear	Unclear	Unclear
Cao <i>et al.</i> ²⁰	Unclear	Unclear	No (open label)	Unclear	Unclear	Unclear
Ren <i>et al.</i> ²¹	Unclear	Unclear	No (open label)	Unclear	Unclear	Unclear
Wei <i>et al.</i> ²²	Unclear	Unclear	No (open label)	Unclear	Unclear	Unclear
Gao <i>et al.</i> ²³	Unclear	Unclear	No (open label)	Unclear	Unclear	Unclear
E <i>et al.</i> ²⁴	Unclear	Unclear	No (open label)	Unclear	Unclear	Unclear
Su <i>et al.</i> ²⁵	Unclear	Unclear	No (open label)	Unclear	Unclear	Unclear
Wen <i>et al.</i> ²⁶	Sequence according to the patient visiting hospital	Unclear	No (open label)	Unclear	Unclear	Unclear
Li <i>et al.</i> ²⁷	Unclear	Unclear	No (open label)	Unclear	Unclear	Unclear
Tang <i>et al.</i> ²⁸	YES (randomized block design)	Unclear	No (open label)	Yes (lost 2 cases to follow-up in the control group)	Unclear	Unclear
Song <i>et al.</i> ²⁹	Unclear	Unclear	No (open label)	Yes (lost 3 cases in the allergen-specific immunotherapy group and 3 cases in the control group to follow-up)	Unclear	Unclear
Guo <i>et al.</i> ³⁰	Unclear	Unclear	No (open label)	No	Unclear	Unclear
Wang <i>et al.</i> ³¹	Unclear	Unclear	No (open label)	No	Unclear	Unclear
Huang <i>et al.</i> ³²	Random order by visiting hospital	Unclear	No (open label)	Yes (lost 4 cases to follow-up and 2 cases discontinue treatment in the control group)	Unclear	Unclear

**Figure 2** Clinical efficacy rate and complete recovery rate for children.

SIT seemed to show more clinical efficacy rate than CT in studies using non-UAS^{22,24,25} (OR 2.18; 95% CI, 1.34–3.53; $P = 0.03$) with substantial heterogeneity ($I^2 = 81\%$, $P = 0.005$) and there was no statistically significant difference between these two groups in studies using UAS¹⁹ (OR 0.80; 95% CI, 0.31–2.03; $P = 0.63$) (Fig. 7). After removing study conducted by Wei,²² the pooled results of studies using non-UAS did not change (OR 4.30; 95% CI, 2.28–8.12; $P < 0.00001$) with low heterogeneity ($I^2 = 0\%$, $P = 0.50$).

For unclassified populations, SIT seemed to decrease relapse rate (2 weeks after treatment) than CT^{19,25} (OR 0.43; 95% CI, 0.23–

0.83; $P = 0.002$) with low heterogeneity ($I^2 = 12\%$; $P = 0.12$). Subgroup analysis showed that SIT seemed to decrease relapse rate than CT in the study using non-UAS²⁵ (OR 0.29; 95% CI, 0.12–0.75; $P = 0.001$) and there was no statistically significant difference between these two groups in study using UAS¹⁹ (OR 0.60; 95% CI, 0.24–1.46; $P = 0.26$) (Fig. 5).

The pooled results of all studies

Combined all studies, SIT seemed to show more clinical efficacy rate^{19–23,25–32} (OR 2.39; 95% CI, 1.73–3.30; $P < 0.00001$;

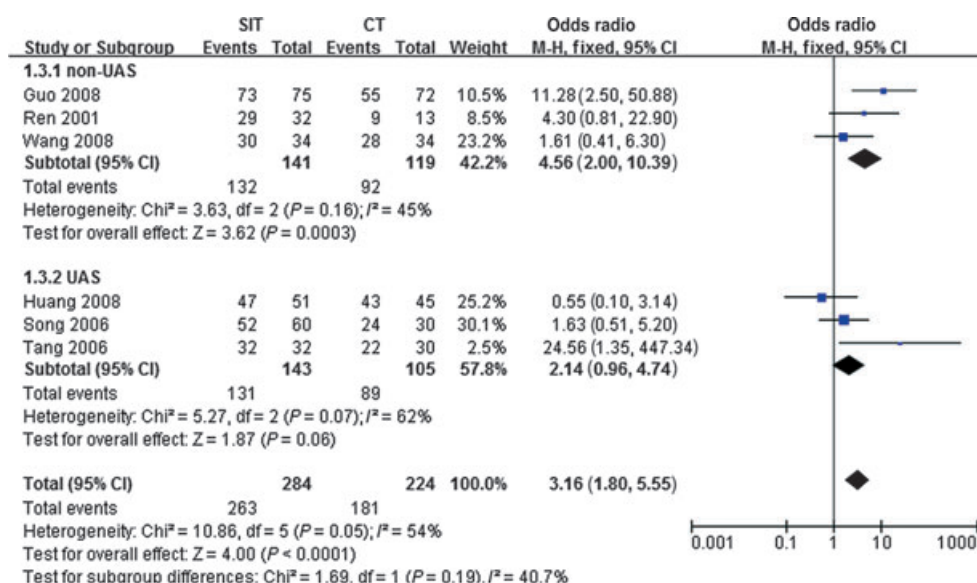


Figure 3 Clinical efficacy rate for adult.

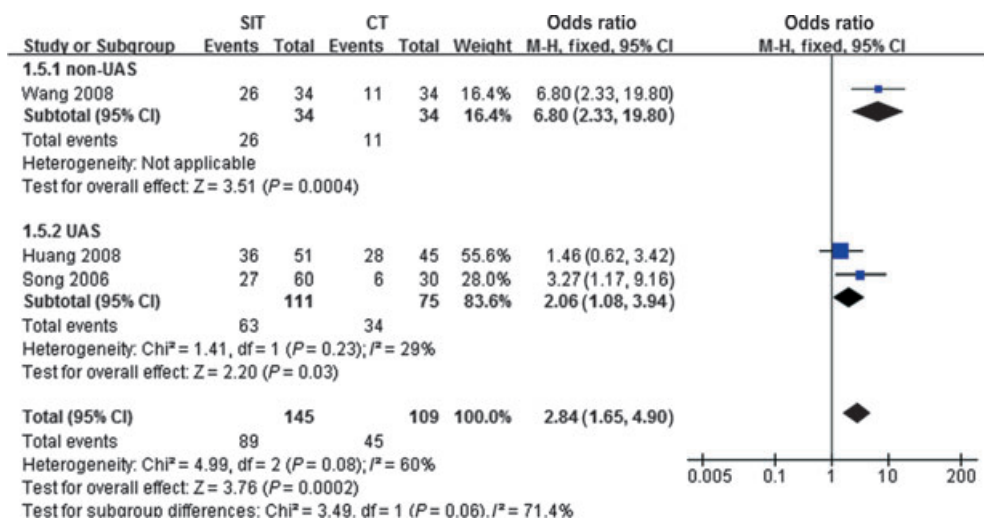


Figure 4 Complete recovery rate for adult.

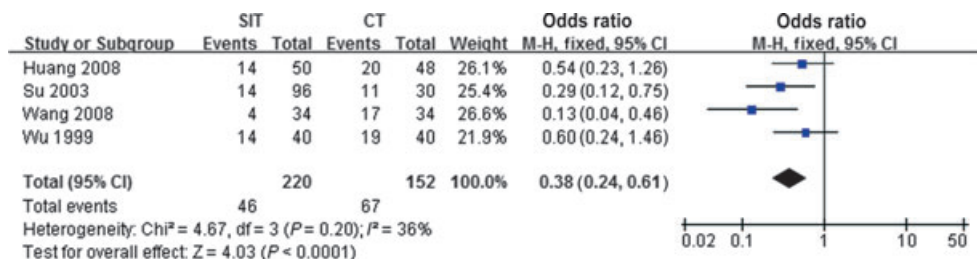


Figure 5 The relapse rate (all studies).

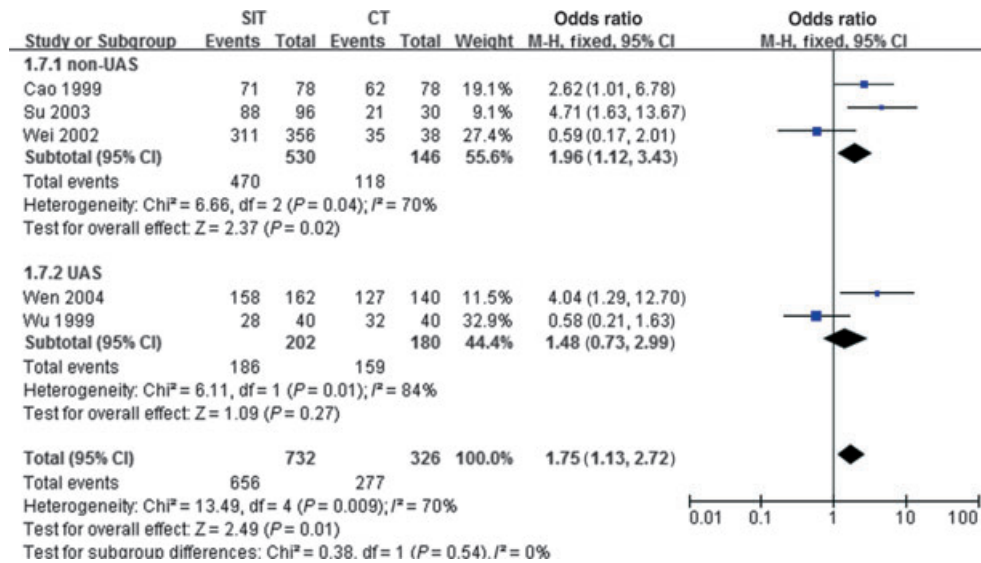


Figure 6 Clinical efficacy rate for unclassified populations.

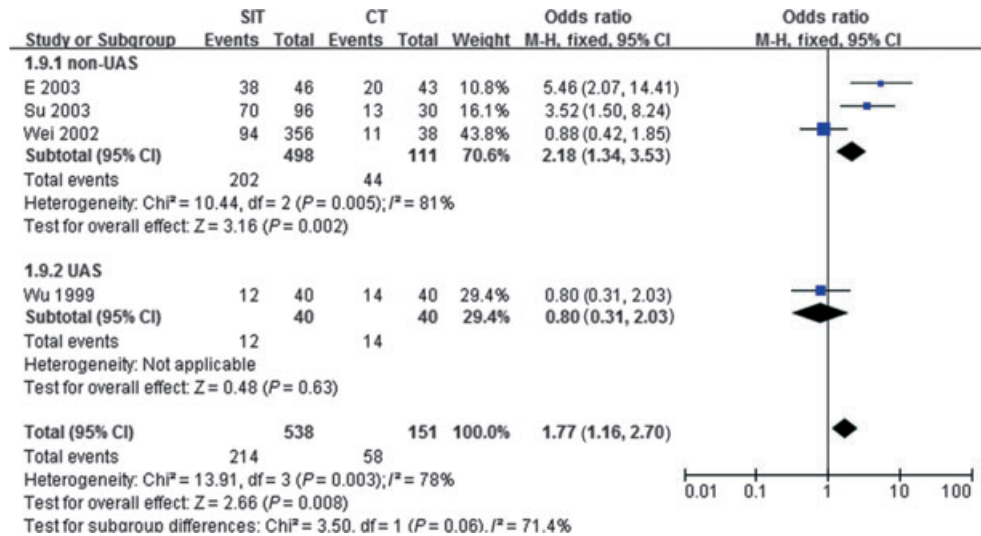


Figure 7 Complete recovery rate for unclassified populations.

$I^2 = 55\%$, $P = 0.008$) (Fig. 8) and complete recovery rate^{19,22–25,27,29,31,32} (OR 2.13; 95% CI, 1.55–2.91; $P < 0.00001$; $I^2 = 61\%$, $P = 0.008$) (Fig. 9) than CT. The SIT seemed to decrease relapse rate^{19,25,31,32} (OR 0.38; 95% CI, 0.24–0.61; $P < 0.0001$; $I^2 = 36\%$, $P = 0.20$) than CT after pooling all studies (Fig. 5).

None of the studies reported serious AEs during SIT. Minor side-effects such as local flushing and mild itching were reported and tolerated (Table 3). We cannot calculate total AEs data as not all studies reported AEs. A total of 82 AEs were reported; 23 were in the SIT group and 59 in the CT group.

Discussion

Summary of evidence

Our study included fourteen trials (1838 participants) regarding the efficacy of treatment with SIT and CT for CU. The pooled results showed that SIT seemed to show more clinical efficacy rate, complete recovery rate and lower relapse rate than CT. Only one study reported that SIT improved patients' QOL, although QOL was considered important and was recommended to assess disease activity in CU patients.² In our study, we noticed an interesting thing. The pooled results of studies using UAS were different from

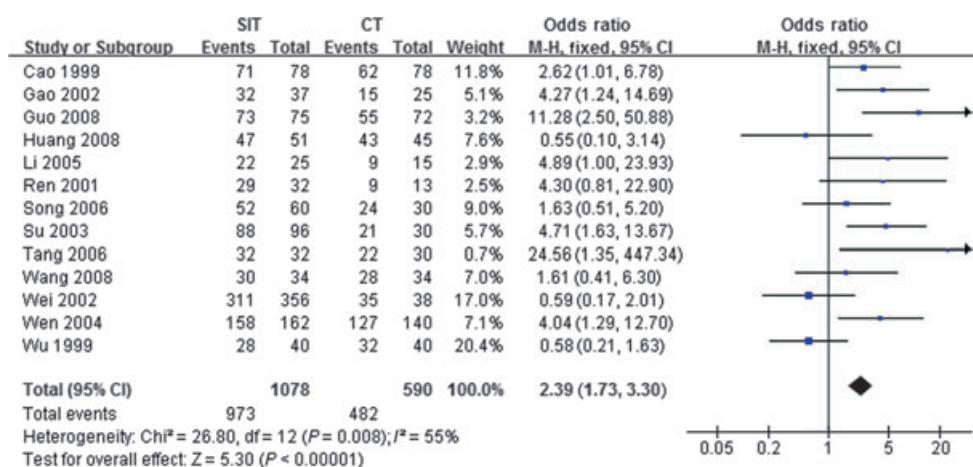


Figure 8 Clinical efficacy rate (all studies).

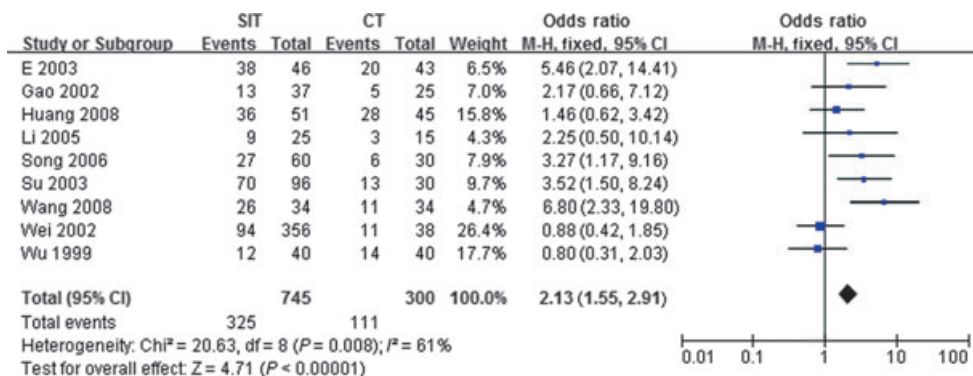


Figure 9 Complete recovery rate (all studies).

those of studies using non-UAS, especially in clinical efficacy and relapse rates for adult and unclassified patients. This showed that the pooled results for clinical efficacy and relapse rates were not adequate to draw a positive conclusion. So, in the future we strongly suggest that studies about CU should use UAS to assess disease activity according to EAACI/GA²LEN/EDF/WAO guideline.²

The effectiveness of SIT for CU is controversial and CU has not been identified as a common skin disease until now. The aetiology of CU is unknown in 80–90% of patients.³³ Possible reasons for CU include medications, food, infections and autoimmunity.³⁴ To date, no reliable test exists to identify whether or not a patient's CU is autoimmune or nonautoimmune.³⁵ Because the clinical relevance of allergy hypersensitivity as the aetiology of CU is unknown, SIT was considered ineffective.¹⁰ The effectiveness of SIT for CU has been questioned. Some dermatologists advocate eliminating SIT as a therapeutic option for CU because the risks might outweigh the benefits. There is still no sufficient evidence to confirm that SIT is ineffective for CU. None of the studies reported serious AEs after using SIT, in our review.

Although four of fourteen studies did not mention adverse events, we did not exclude the possibility of inadequate reporting of AEs.

Some recent studies showed that aeroallergens were a possible aetiology of CU.³⁶ The prevalence of positive SPTs among patients with CU was 47.7%.³⁷ Because the symptoms of CU are similar to that of allergen-induced skin reactions, the concept of IgE-mediated cutaneous mast cell and basophil activation in CU is possible.³⁸ Two RCTs confirmed the efficacy of sublingual immunotherapy (SLIT) in patients with latex-induced urticaria (studies investigating other types of urticaria were excluded).^{39,40} Sweat extract immunotherapy has successfully treated cholinergic urticaria.⁴¹ Dust mite allergies have been hypothesized as an important pathogenic factor in CU, and 27 patients have benefited from SIT.⁴² Allergies were resolved with immunotherapy in two patients with a history of respiratory house dust mite allergy and chronic urticaria.⁴³ Abdo reported a 93% alleviation in clinical symptoms using SIT with Giardia's antigen preparation.⁴⁴ A single report⁴⁵ described a case of urticaria due to grass pollinosis treated successfully with desensitization. CU occurring during the grass

Table 3 Adverse events of included trials reported

Source	Allergen-specific immunotherapy group	Conventional treatment group
Wu <i>et al.</i> ¹⁹	Not described	Mild dry mouth and fatigue in 3 patients
Cao <i>et al.</i> ²⁰	No case	Sleepiness, fatigue, mouth dry, but the number of cases are not described
Ren <i>et al.</i> ²¹	No case	Not described
Wei <i>et al.</i> ²²	Not described	Not described
Gao <i>et al.</i> ²³	one patient local redness at the injection	No case
E <i>et al.</i> ²⁴	No case	Not described
Su <i>et al.</i> ²⁵	No case	Not described
Wenet <i>et al.</i> ²⁶	10 patients have local reaction, three patients have systemic reaction, two patients with fever, one patient feel sick	29 patients feel sleepiness, 22 patients feel mouth dry, one patient feel sick
Li <i>et al.</i> ²⁷	No case	Not described
Tang <i>et al.</i> ²⁸	five patients exacerbations, one patient feel sleepiness	one patients exacerbations, three patients feel sleepiness
Song <i>et al.</i> ²⁹	Not described	Not described
Guo <i>et al.</i> ³⁰	Not described	Not described
Wang <i>et al.</i> ³¹	Not described	Not described
Huang <i>et al.</i> ³²	Mild drowsiness, headache, dizziness, dry mouth, gastrointestinal discomfort but the number of cases are not described	Mild drowsiness, headache, dizziness, dry mouth, gastrointestinal discomfort but the number of cases are not described

season was resolved after the patient achieved a maintenance dose of Timothy grass.⁴⁶

Our results showed that SIT might have a positive role in CU patients. The SIT may modulate mast cell and basophil homeostasis and reduce the cutaneous sensitivity to allergens.⁴⁷ Interestingly, during the course of SIT, the cutaneous reactivity reduction occurs not only towards the specific allergen, but also to the non-specific mast cell stimuli and histamine.⁴⁸ Therefore, in urticarial patients, SIT could influence the mast cell activity, thereby also improving the sensitivity threshold to the non-specific stimuli. Pharmacological therapies focus on symptom management, whereas immunotherapy concentrates on the potential correction of the pathological immune response. This may explain why SIT can reduce the recurrence of CU.

Strength and limitations of our study

This review was performed according to the Cochrane collaboration for systematic reviews.¹⁸ This is the first systematic review that evaluated the efficacy of SIT vs. CT for CU patients. However, our meta-analysis presented several potential limitations. Overall, the qualities of the included studies were low. The included studies of this systematic review had the following limitations, which influenced the strength of the evidence:

- (i) All studies were conducted in China. Despite careful searching in MEDLINE, the Cochrane library, EMBASE and ISI Knowledge of Web, studies in other countries and regions were not found. Our findings are more applicable to China, which could give some directions to the treatments of CU in other countries and regions.
- (ii) A similar baseline between the treatment and control groups was important, but the details were not mentioned.
- (iii) The methodological qualities of included studies were low.

Most of the studies mentioned 'randomization', but the process was not described in detail. The results could have been exaggerated if the concealed allocation was not implemented sufficiently. Unfortunately, no study described the details of concealed allocation; therefore, selection bias is highly possible. All included studies were open label; none of them was double-blind placebo controlled; thus the possibility of detection bias was high. At the same time, only three studies analyzed data using intention-to-treat (ITT) method. (iv) The standard of measuring outcomes and assessing disease activity was not unified in the included studies. Seven of 14 studies^{20,24,27,28–30,33} used UAS to assess CU disease activity, which was proposed in the new guidelines,² and only 2 studies^{29,30} reported the raw data of UAS. Thus, these might be the reasons for considerable heterogeneity across included studies. (v) QOL was assessed as an important outcome, but it was only reported in one study. (vi) The follow-up time must be sufficient as CU is a chronic disease. None of the studies mentioned long-term safety profiles of the treatments, and prolonging the follow-up time was necessary. (vii) There was no distinct age group of subjects in some studies. It was unknown whether or not SIT had a different effect on adults and children.

Implications for research and practice

As the number and the sample sizes of included studies were small and the methodological qualities of included studies were low. Even though, the pooled results of all studies showed that SIT demonstrated better clinical efficacy than CT for CU patients, we should be cautious when we apply these results to clinical practice. Our results were needed to be tested in future large studies with rigor methodological ways. Future RCTs need to consider the following aspects: (i) enrolled patients should be diagnosed

according to the guideline standard, have a distinct age group, and be screened with strict inclusion and exclusion criteria; (ii) the treatment group and control group should have a similar baseline described completely; (iii) UAS and QOL should be used as proposed in the new guidelines, and raw data should be reported completely for convenient analysis; (iv) there should be adequate follow-up time to observe AEs; (v) multi-centred high-quality RCTs should be reported based on the CONSORT statement 2010.

Conclusion

Current evidence indicates that IgE-mediated allergy may be causative in a small number of CU patients and specific immunotherapy with these allergens may be beneficial in those patients. However, the methodological qualities of included studies were low and all of them were conducted in China. So, there is a great need for further studies to collect more evidence.

Acknowledgement

We thank Dr. Yali Liu and Dr. Weixin Li for their help for the methodology and Yingtai Chen, Hao Chen, Zhicheng Luo, and Yongjun Teng for their guidances with the language.

References

- Maurer M, Weller K, Bindslev-Jensen C *et al*. Unmet clinical needs in chronic spontaneous urticaria. A GA2LEN task force report. *Allergy* 2011; **66**: 317–330.
- Zuberbier T, Asero R, Bindslev-Jensen C *et al*. EAACI/GA²LEN/EDF guideline: definition, classification and diagnosis of urticaria. *Allergy* 2009; **64**: 1417–1426.
- O'Donnell BF, Lawlor F, Simpson J, Morgan M, Greaves MW. The impact of chronic urticaria on quality of life. *Br J Dermatol* 1997; **136**: 197–201.
- Maurer M, Ortonne JP, Zuberbier T. Chronic urticaria: an internet survey of health behaviours, symptom patterns and treatment needs in European adult patients. *Br J Dermatol* 2009; **160**: 633–641.
- Baiardini I, Giardini A, Pasquali M *et al*. Quality of life and patients' satisfaction in chronic urticaria and respiratory allergy. *Allergy* 2003; **58**: 621–623.
- Delong LK, Culler SD, Saini SS, Beck LA, Chen SC. Annual direct and indirect health care costs of chronic idiopathic urticaria: a cost analysis of 50 nonimmunosuppressed patients. *Arch Dermatol* 2008; **144**: 35–39.
- Zuberbier T, Asero R, Bindslev-Jensen C *et al*. EAACI/GA2LEN/EDF guideline: management of urticaria. *Allergy* 2009; **64**: 1427–1443.
- Morgan M, Khan DA. Therapeutic alternatives for chronic urticaria: an evidence-based review, part 1. *Ann Allergy Asthma Immunol* 2008; **5**: 403–412.
- Bousquet J, Lockey RF, Malling HJ. WHO position paper. Allergen immunotherapy: therapeutic vaccines for allergic disease. *J Allergy Clin Immunol* 1998; **102**: 558–562.
- Huggins JL, Looney RJ. Allergen immunotherapy. *Am Fam Physician* 2004; **70**: 689–696.
- Frew AJ. 25. Immunotherapy of allergic disease. *J Allergy Clin Immunol* 2003; **111**: S712–S719.
- Compalati E, Penagos M, Tarantini F, Passalacqua G, Canonica GW. Specific immunotherapy for respiratory allergy: state of the art according to current meta-analyses. *Ann Allergy Asthma Immunol* 2009; **1**: 22–28.
- Skoner D, Gentile D, Bush R, Fasano MB, McLaughlin A, Esch RE. Sublingual immunotherapy in patients with allergic rhinoconjunctivitis caused by ragweed pollen. *J Allergy Clin Immunol* 2010; **125**: 660–666.
- Abramson MJ, Puy RM, Weiner JM. Injection allergen immunotherapy for asthma. *Cochrane Database Syst Rev* 2010; **8**: CD001186.
- Severino MG, Cortellini G, Bonadonna P *et al*. Sublingual immunotherapy for large local reactions caused by honeybee sting: a double-blind, placebo-controlled trial. *J Allergy Clin Immunol* 2008; **122**: 44–48.
- Niebuhr M, Kapp A, Werfel T. Specific immunotherapy in the treatment of atopic dermatitis [in German]. *Hautarzt* 2007; **58**: 232–236.
- Wilson DR, Torres Lima M, Durham SR. Sublingual immunotherapy for allergic rhinitis: systematic review and meta-analysis. *Allergy* 2005; **60**: 4–12.
- Higgins JPT, Altman DG. Chapter 8: assessing risk of bias in included studies. In: Higgins JPT, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions, Version 5.0.1. The Cochrane Collaboration; Updated September 2008*. Available at: <http://www.cochrane-handbook.org> (last accessed October 16 2010).
- Wu JH, Han CL, Wu ML, Liao XY, Tang YX. Observation of allergen skin tests and desensitizing therapy in 80 cases of chronic urticaria [in Chinese]. *J Clin Dermatol* 1999; **28**: 359–360.
- Cao CF, Song SL, Zhu SH. Desensitization therapy vs antiallergenic medicine in the treatment of chronic urticaria [in Chinese]. *Chin J Dermatovenereol* 1999; **13**: 94.
- Ren JY. Clinical observation of therapeutic effect of desensitization in the treatment of chronic urticaria [in Chinese]. *J Clin Dermatol* 2001; **30**: 246.
- Wei YM, Xu HB, Xu ZX. Allergen detection and immunotherapy of chronic urticaria [in Chinese]. *Guangxi Med* 2002; **24**: 474–475.
- Gao Y, Li YC, Chen XB. The efficacy of desensitization treatment in children with chronic urticaria [in Chinese]. *J Wenzhou Med Coll* 2002; **32**: 200–201.
- E YA, Guo Y. Desensitization treatment of 89 cases of chronic urticaria patients [in Chinese]. *Qinghai Med J* 2003; **33**: 38.
- Su TL, Zhang JZ, Luo YS. Allergen detection and desensitization of chronic urticaria [in Chinese]. *Modern Med J* 2003; **31**: 204.
- Wen H, Ke CM, Tao L. Immunotherapy vs conventional drug therapy in 302 cases with chronic urticaria [in Chinese]. *J Clin Med Chin* 2004; **121**: 12760–12762.
- Li SM, Li SJ, Wang W. The efficacy of specific desensitization therapy in children with chronic urticaria [in Chinese]. *Chin J Child Health Care* 2005; **13**: 199.
- Tang H, Zheng ZZ, Xu JH, Hu Y. Researches on CC chemokines in the pathogenesis of chronic urticaria and the Clinical and Laboratory study on specific immunotherapy for treatment of chronic urticaria [in Chinese]. PhD thesis. Fudan University, 2006; 1–78.
- Song B, Wei LH, Zheng LX, Fang SN, Du XH, Xiong F. Clinical study in allergen immunotherapy of chronic urticaria [in Chinese]. *Chin Med* 2006; **19**: 419–422.
- Guo JM. Efficacy of specific prevention and care in chronic urticaria [in Chinese]. *Chin J Practical Med* 2008; **3**: 130–131.
- Wang ZX, Li WY, Liu GH. Effect study of SIT to chronic urticaria [in Chinese]. *J China Hosp Pharm* 2008; **28**: 1771–1773.
- Huang C, Gen CF, Jiang W, Xue W, Chen QH, Zhang LP. Clinical observation of carid desensitizing therapy combined with antihistamine drug in the treatment of chronic urticaria [in Chinese]. *Chin J Derm Venereol* 2008; **22**: 597–598.
- Nichols KM, Cook-Bolden FE. Allergic skin disease: major highlights and recent advances. *Med Clin North Am* 2009; **93**: 1211–1224.
- Kaplan AP, Greaves M. Pathogenesis of chronic urticaria. *Clin Exp Allergy* 2009; **39**: 777–787.
- Philpott H, Kette F, Hissaria P, Gillis D, Smith W. Chronic urticaria: the autoimmune paradigm. *J Intern Med* 2008; **38**: 852–857.
- Refaat MM, Ossman EN, Farres MN, El-Khodeery MM, Arafa NA, Attia MY. Assessment of the role of aeroallergens in patients with chronic urticaria. *Revue française d'allergologie* 2010; **50**: 394–397.

- 37 Kulthanan K, Jiamton S, Rutnin NO, Insawang M, Pinkaew S. Prevalence and relevance of the positivity of skin prick testing in patients with chronic urticaria. *J Dermatol* 2008; **35**: 330–335.
- 38 Vonakis BM, Saini SS. New concepts in chronic urticaria. *Curr Opin Immunol* 2008; **20**: 709–716.
- 39 Nettis E, Di Leo E, Calogiuri G *et al.* The safety of a novel sublingual rush induction phase for latex desensitization. *Curr Med Res Opin* 2010; **26**: 1855–1859.
- 40 Nettis E, Colanardi MC, Soccio AL *et al.* Double-blind, placebo-controlled study of sublingual immunotherapy in patients with latex-induced urticaria: a 12-month study. *Br J Dermatol* 2007; **156**: 674–681.
- 41 Tanaka T, Ishii K, Suzuki H, Kameyoshi Y, Hide M. Cholinergic urticaria successfully treated by immunotherapy with partially purified sweat antigen [in Japanese]. *Arerugi* 2007; **56**: 54–57.
- 42 Lodi A, Di Berardino L, Chiarelli G *et al.* Chronic urticaria and allergy to Acari. Experience with a specific desensitization therapy [in Italian]. *G Ital Dermatol Venereol* 1990; **125**: 187–189.
- 43 Kasperska-Zajac A, Brzoza Z. Remission of chronic urticaria in the course of house dust mite immunotherapy – mere coincidence or something more to it? *Vaccine* 2009; **27**: 7240–7241.
- 44 Abdo Rodriguez A, Espino Anton P, Zaldivar Estevez JC. Immunotherapy using *Giardia lamblia* extract in recurrent chronic sensitized urticaria [in Spanish]. *Rev Alerg* 1991; **38**: 113–116.
- 45 August PJ, O'Driscoll J. Urticaria successfully treated by desensitization with grass pollen extract. *Br J Dermatol* 1989; **120**: 409–410.
- 46 Morgan M, Khan D A. Therapeutic alternatives for chronic urticaria: an evidence-based review, Part 2. *Ann Allergy Asthma Immunol* 2008; **6**: 517–526.
- 47 Akdis M, Akdis CA. Mechanisms of allergen-specific immunotherapy. *J Allergy Clin Immunol* 2007; **119**: 780–791.
- 48 Garcia NM, Lynch NR, Di Prisco MC, Lopez RI. Nonspecific changes in immunotherapy with house dust extract. *J Invest Allergol Clin Immunol* 1995; **5**: 18–24.