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Principles of Allergen Immunotherapy and Its Clinical Application in China: Contrasts and Comparisons with the USA

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Abstract

Allergen immunotherapy (AIT) for allergic rhinitis (AR), asthma, and other allergic diseases has developed quickly. House dust mite (HDM), *Artemisia* (wormwood), *Humulus japonicus* (Japanese hop), *Alternaria alternata*, and *Cladosporium herbarum* are the five most common inhalant allergens in China. AIT has been performed in China for over 60 years. With the support of the Chinese Medical Association (CMA) and the Chinese Medical Doctors Association (CMDA), the Chinese College of Allergy and Asthma (CCAA) was established in 2016 as a specialized branch of CDMA and is the main certification authority for AIT. Chinese allergists and scientists have made tremendous progress in the development of AIT. There have been many publications by Chinese allergists and scientists worldwide encompassing original research studies, systematic reviews, case studies, and clinical trials. Currently, conventional subcutaneous immunotherapy (SCIT) is the preferred AIT in China, but sublingual immunotherapy (SLIT) is beginning to gain recognition. An increasing number of clinical trials have been conducted to investigate the clinical efficacy and side effects of SLIT and SCIT. In China, HDM is the only commercial standardized allergen extracts in clinical use, whereas the others are crude allergen extracts. Besides standardized allergen extracts, other forms of hypoallergenic extracts are still being investigated and developed in China. Immunotherapy in China is similar to that in the USA in which allergen extracts can be mixed for SCIT. However, allergen extracts cannot be mixed for SCIT in Europe.

Keywords Allergen-specific immunotherapy · Sublingual immunotherapy · Subcutaneous immunotherapy · Allergic rhinitis

Abbreviations

AEs	Adverse events
AIT	Allergen immunotherapy
AR	Allergic rhinitis
AASS	Average Adjusted Symptom Score
CFDA	China Food and Drug Administration
CCAA	Chinese College of Allergy and Asthma
CMA	Chinese Medical Association
CMDA	Chinese Medical Doctors Association
CS	Chitosan
CPE	Complete peanut extract
CVA	Cough variant asthma

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DC	Dendritic cells
DCN	*Dermatophagoides* chitosan nanoparticle
Der f	*Dermatophagoides farinae*
EAACI	European Academy of Allergology and Clinical Immunology
HMSNs	Hollow mesoporous silica nanoparticles
HDM	House dust mite
LAB	Lactic acid bacteria
MSNs	Mesoporus silica nanoparticles
OVA	Ovalbumin
PUMCH	Peking Union Medical College Hospital
RQLQ	Rhinoconjunctivitis Quality of Life Questionnaire
RIT	Rush immunotherapy
SPT	Skin prick testing
SCIT	Subcutaneous immunotherapy
SLIT	Sublingual immunotherapy
TLR7	Toll-like receptor 7
TNSS	Total Nasal Symptom Scores
VAS	Visual analog scores

Introduction

Over the last four decades, the prevalence of asthma, allergic rhinitis (AR), and atopic dermatitis has been increasing worldwide, affecting patients' quality of life and generating a significant economic burden [1]. This is also the case in many regions and cities in China. The prevalence of adult AR in the 18 major cities of China was 17.6% in 2011 [2].

The editorial board of the *Chinese Journal of Otorhinolaryngology* was established in 1990 and has since introduced five updated Chinese guidelines for AR. The most recent Chinese guidelines for AR was published in English literature in *Allergy, Asthma & Immunology Research* in 2018 [3–5].

The current recommended treatment paradigm for AR mainly includes (a) allergen and irritant avoidance, (b) pharmaceuticals, (c) doctor–patient interaction and education, and (d) specific allergen immunotherapy (AIT) [1]. AIT is the only current medical intervention that can potentially affect the natural course of allergic diseases [6, 7]. In 1911, Leonard Noon and John Freeman first introduced AIT in their article on 'Prophylactic inoculation against hay fever' [8]. William Frankland et al. published the first randomized controlled trial in AIT on subcutaneous grass pollen immunotherapy [8]. In 2006, the European Academy of Allergology and Clinical Immunology (EAACI) noted that AIT was a cause-targeted treatment that changed the development of the disease process [6]. Through the years, AIT has been shown to be an effective therapeutic approach in patients with AR, allergic conjunctivitis, allergic asthma, and hymenoptera venom allergy [1].

In China, treatment of allergies with allergen immunotherapy began about 60 years ago. Since then, and paralleling the increasing number of patients with allergic disorders in China, AIT has become widely used and investigated. Ninety-six percent of Chinese ENT specialists believe that AIT is the preferred treatment for AR and allergic asthma [9]. Chinese guidelines for the use of AIT [10] as well as an expert consensus document on subcutaneous immunotherapy (SCIT) have been published [11]. Similar to international guidelines, Chinese doctors recommend earlier initiation of AIT for AR patients if appropriate resources are available, and are not limited to patients who fail drug treatment only [10, 11]. Many published studies of AIT in China are in the Chinese literature and written in Chinese, rendering them inaccessible or incomprehensible to international readers.

Geoepidemiology of Inhalant Allergens in China and Other Countries

AIT is an effective treatment for allergenic disorders due to inhalant allergens. Biological components from pollens, fungus, dust mites, insects, and animal hair are the most common environmental inhalant allergens. A multicenter study involving 14 countries in Europe reported that grass pollen, house dust mite, birch pollen, cat dander, olive pollen, mugwort, German cockroach, and the mold *Alternaria* are the most prevalent allergens in a majority of the subjects in these countries [12]. However, there is still great variation regarding which allergens are the most prevalent in each country.

Allergic rhinitis is a global health care issue that affects 23–30% of the European population [13, 14] and 12–30% of the US populations [15]. Data from a nationwide survey on the prevalence of allergic rhinitis in children of 6–13 years old in eight metropolitan cities (Shanghai, Guangzhou, Xian, Wuhan, Harbin, Chengdu, Hohhot, and Urumiqi) in China showed that the mean prevalence of childhood allergic rhinitis was 9.8%, ranging from 3.9% in Xian to 16.8% in Guangzhou [16]. Another study reported that the prevalence of allergic asthma in children 0–14 years old was 14.4, 20.42, and 7.83% in Beijing, Chongqing, and Guangzhou, respectively [17].

The prevalence of allergic rhinitis in Chinese adult populations is also highly variable. A nationwide study in 11 major cities across China reported that the prevalence of allergic rhinitis was 8.7% in Beijing, 11.2% in Changchum, 16.1% in Changsa, 14.1% in Guangzhou, 8.9% in Hangzhou, 13.3% in Nanjing, 13.6% in Shanghai, 15.7% in Shenyang, 19.3% in Wuhan, 9.1% in Xian, and 24.1% in Urumqi [18]. The spectra of inhaled allergens are similar to western countries, with pollen, dust mites, mugwort, fungus, animal dander, and cockroach being the most common ones [19]. Interestingly, sensitization to silk is identified as the strongest

predictor of rhinitis in Anqing population [20], while *Chenopodium* and *Humulus lupulus* are identified as an inhalant allergen in Changji. The prevalence of pollen-induced AR is extremely high in the grasslands of northern China due to high seasonal pollen exposure, largely influenced by local environmental and climate conditions. A recent study using interviewer-administered questionnaire and SPT on 6043 subjects from random sampling found that 32.4 and 18.5% of the subjects had epidemiologic AR and pollen-induced AR, respectively, in the inner Mongolia grasslands [21]. A retrospective study on the prevalence and trend of sensitization to aeroallegens in patients with allergic rhinitis in Guangzhou showed that while house dust mite is the most common allergen, there is an increasing trend of pet allergen sensitization from 2005 to 2014 [22].

Japanese cedar pollen is the most common allergen in Japan [23]. A study on 408 healthy infants in Japan found that 44/408 (10.7%) had IgE antibodies to one or more aeroallergens including house dust mites, cat fur, and Japanese cedar pollen. In addition, 8/408 (2.0%) had nasal eosinophils [24]. In another study, the mean age of onset of asthma in Japan was 2.3 ± 1.9 years [25]. A more recent study on 8815 children between 6 and 9 years old demonstrated that indicated 39% are sensitized to Japanese cedar pollen [26].

A 2017 study assessed the safety of allergen immunotherapy in the USA. Based on a national survey of allergists, there was one fatal reaction after every 2.5 million injection visits between the years 1990 and 2001, based on a national survey of allergists [27]. This equated to 3.4 fatal reactions per year. The study also found that the rate of systemic reactions with SCIT was about 0.1–0.2% for conventional buildup schedules. This rate increased with cluster IT and there were 11 cases of nonfatal anaphylaxis resulting from 1×10^9 sublingual immunotherapy (SLIT) doses.

In the USA, there are currently four FDA-approved sublingual therapies, which are for timothy grass, a grass mix, dust mite, and ragweed. A recent survey was conducted on the perception of sublingual immunotherapy in allergists in the USA [28]. This study revealed that there has been a marked increase in the use of sublingual immunotherapy over the past 5 years. In fact, 297 of 268 respondents (73.5%) from the USA have used sublingual immunotherapy, which is a significant increase over 5.9% in 2007 and 11.4% in 2011. The main limitation in sublingual therapy was that each approved therapy only treats a single allergen.

When prescribing AIT, health professionals should carefully consider the relevance of the allergens to individual patients and use allergen extracts with proven safety and efficacy. Since in many countries AIT is prescribed by primary care providers, updated training on the most current understanding of AIT and evidence-based primary care allergy guidelines are greatly needed for optimal treatment for allergy patients [29].

Distribution of Common Allergens in China

As in the rest of the world, house dust mite (HDM) is the most common indoor allergen in China (Figs. 1 and 2) [30]. In 2012, we summarized two hundred thousand allergen-specific immunoglobulin E (sIgE) results at Peking Union Medical College Hospital and found that HDM, *Artemisia* (wormwood), *Humulus japonicus* (Japanese Hop), *Alternaria alternata*, and *Cladosporium herbarum* were the most common inhalant allergens [31].

House Dust Mite

In China, the most important allergenic mites found in homes are *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus* and the storage mite *Blomia tropicalis* [32]. The seasonal distribution of each mite species may be variable. Our study analyzed 1798 separate mite and insect specimens in 345 dust samples in Beijing and reported that *D. farinae* was the predominant species, followed by *D. pteronyssinus* and *D. siboney* [33]. The seasonal density distribution of HDM showed the highest mite concentration in September through October, followed by May through July, and lowest in March and November [34]. However, in Wuhan, located in central China, the overall mite detection rates were 67.4% from April to July, 22.4% from August to October, and 10.2% from November to March [35]. In Xishuangbanna, a tropical rainforest in southwest China, the mite family *Pyroglyphidae*, including *D. farinae*, *D. pteronyssinus*, and *D. siboney*, are the most common species year round because of the relatively stable yearly temperature in the tropical rainforest climate [36].

Artemisia and Japanese Hop

The weed pollens from *Artemisia* (Fig. 3) and *Humulus japonicus (H. japonicus)* (Fig. 4) are two of the most important fall seasonal allergens in China. Common species of *Artemisia* found in China include *Artemisia annua*, *Artemisia capillaries*, and *Artemisia sieversiana*. *Artemisia* are biennial herbs and their pollen grains are either spherical or oblate spherical, ranging from 20 to 30 μm in diameter. Depending on the weather and region, they usually bloom from July to September with a 2-month flowering period. *Artemisia* species are present throughout the country, growing on wasteland, mountain slopes, and forest edges. Sensitization to *Artemisia* pollen increases with age, affecting 5.06% of children under and 15.45% above 5 years of age [37]. Two studies in Hubei Province showed that 10.5% (189/1800) of AR patients in Jingmen City [38] and 5.5% (12/216) asthmatic children in Wuhan City [39] are sensitized to *Artemisia*.

H. japonicus is an annotinous or perennial twining flowery herb characterized by creeping stems with spiny hair and

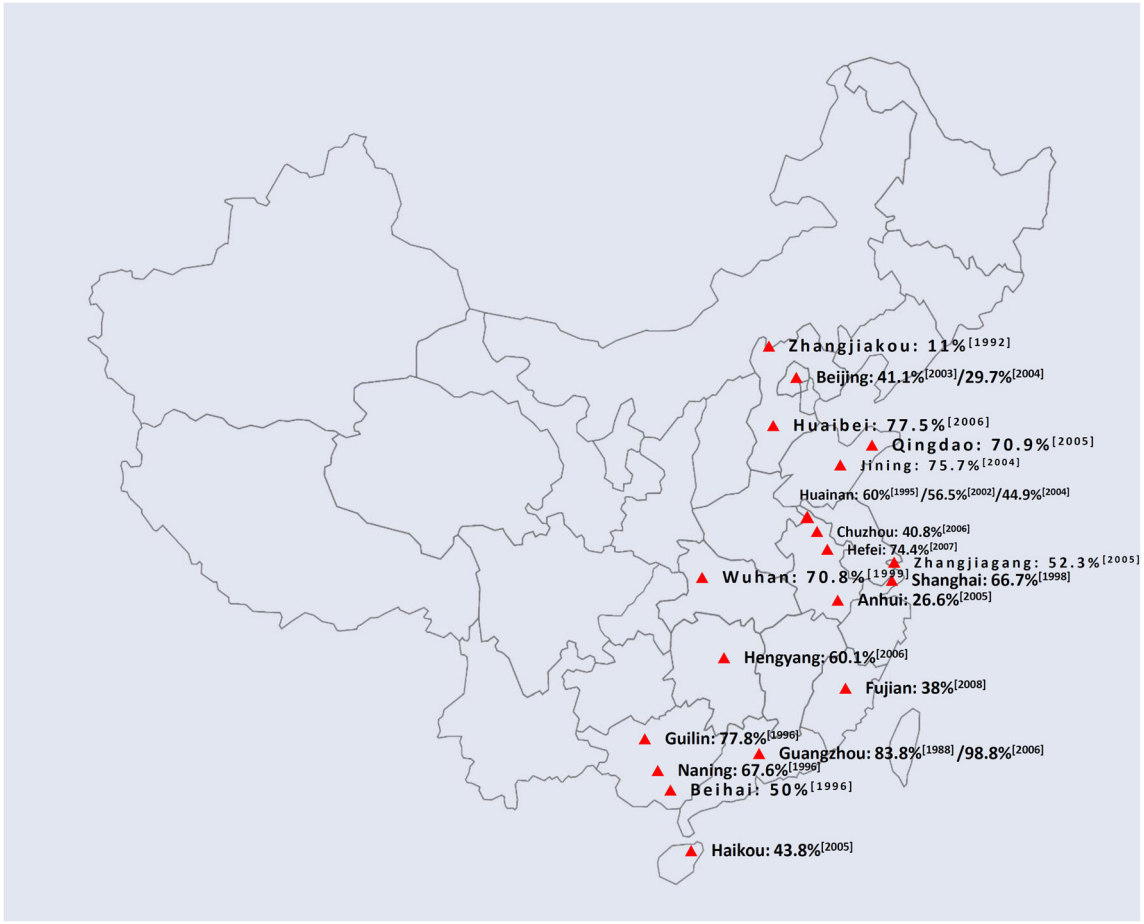

Fig. 1 Distribution of house dust mites in different regions in China

spherically shaped pollen grains of about 30 μm. It flowers from July through September. *H. japonicus* is found throughout nearly the entire country, except for Qinghai and Xinjiang provinces. It grows by gullies and the roadsides. It can also be found in other Asian countries, including Japan and Korea [40].

H. japonicus pollen is more commonly detected in northern China than southern China (Fig. 5) [37–39, 41–68]. Sensitization to *H. japonicus* is as high as 21.8% in the Shandong coastal area [46].

Alternaria alternata and *Cladosporium herbarum*

Molds are also important perennial allergens in China. Most in vivo and in vitro testing in China is done with a mixed mold extract. However, it is known that *A. alternata* and *C. herbarum* are widely distributed in China. In Guangdong Province, *A. alternata* sensitivity was present in 14.9% (59/397) of children with asthma [56] and in 44.9% (730/1625) of patients with allergic rhinitis [58], whereas *C. herbarum* was positive in 47.4% (771/1625) of patients with allergic rhinitis [58]. *C. herbarum* was positive in 3.6% (16/450) of children with asthma in Hainan, the southernmost province of China [60].

History of Allergen Immunotherapy in China

The first allergy department in China was established at the Peking Union Medical College Hospital (PUMCH) in 1956. The first generation of Chinese clinical allergists prepared allergen extracts from pollen, dust mites, fungi, animal dander, and insects for skin prick testing (SPT) and AIT [69]. During the first 40 years, only crude extracts were available for AIT, and SCIT was the only administration route. SLIT for *D. farinae* was later introduced in China in 2006. Intralymphatic immunotherapy has also been reported [70].

In China, almost half of the patients with autumn pollen AR develop seasonal allergic asthma within 9 years [71–73]. Currently, only three standardized allergen extracts of HDM have been approved by the China Food and Drug Administration (CFDA) for AIT use in China. Novo-Helisen-Depot (Allergopharma Joachim Ganzer KG, Germany) (CFDA approved in 1999) was the first of these to be approved. However, Alutard-SQ (ALK-Abelló,

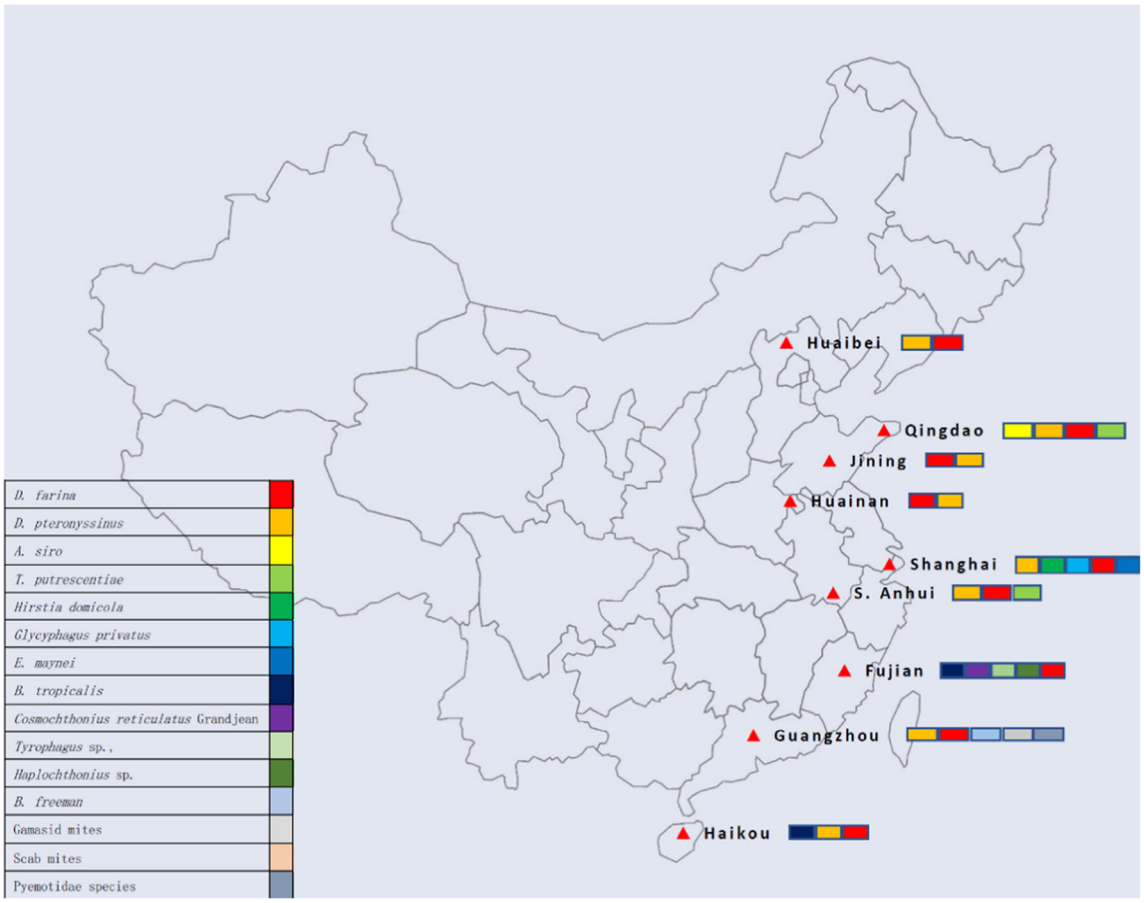

Fig. 2 Various kinds of house dust mites in China

Denmark) (CFDA approved in 2004) is now much more widely used for SCIT in China. Chanllergen-Df Drops (Wolwo Pharma, China) (CFDA approved in 2006) is the only SLIT product available in China. There are also many crude allergen extracts used in China. Compared to Western countries, AIT in China began much later but is becoming more available in many centers throughout China.

Fig. 3 *Artemisia sieversiana*

AIT in China

SCIT

SCIT with HDM Allergen Extracts

There have been several studies on the long-term therapeutic effects of SCIT with standardized HDM in AR or asthma patients in China [74–90], including double-blind placebo-

Fig. 4 *Humulus japonicus*

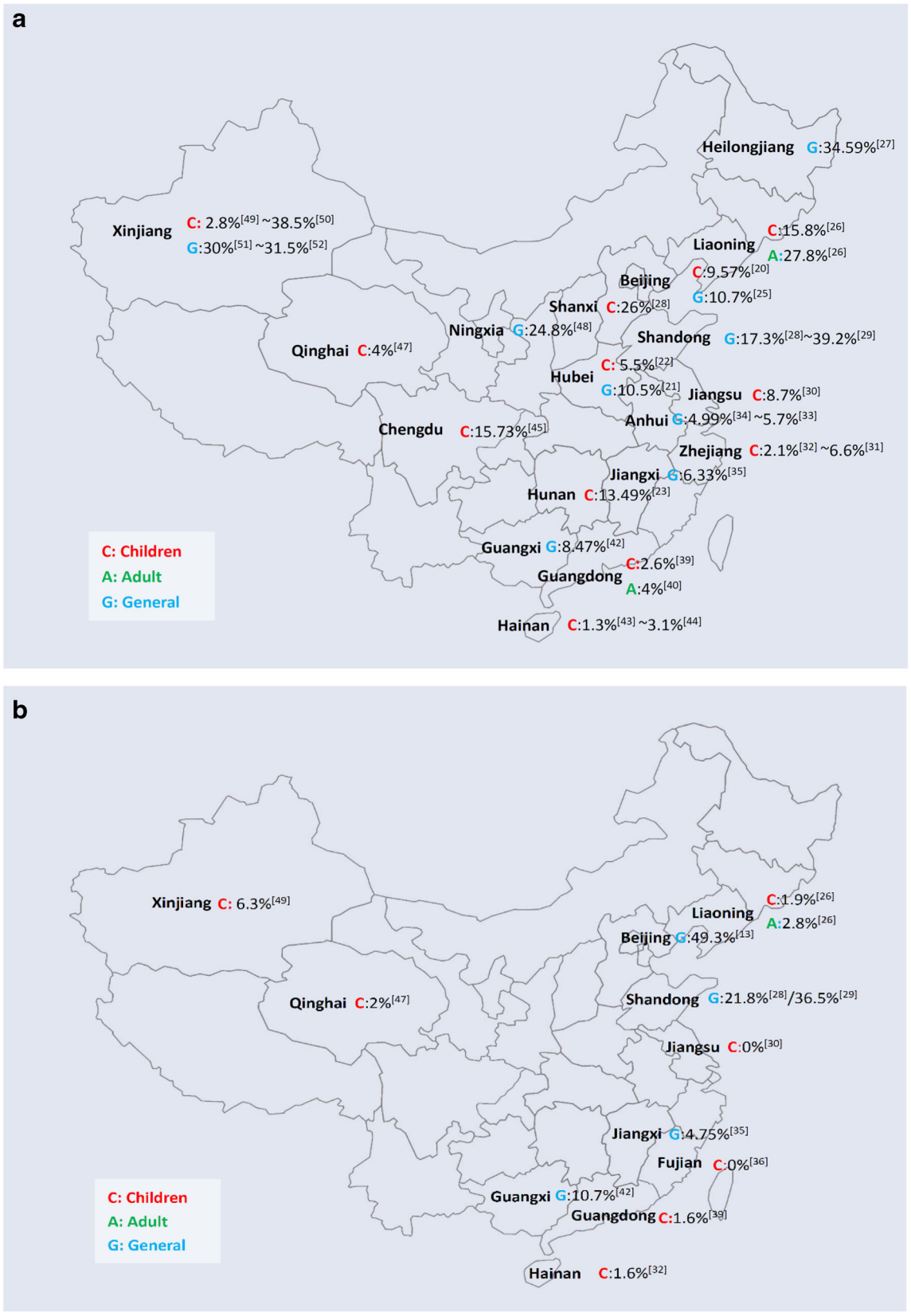

Fig. 5 Sensitization to *Artemisia* (**a**) and *Humulus japonicus* (**b**) in China

controlled studies [84]. Data from these studies indicate that SCIT is an effective and promising treatment of AR in Chinese patients. The following endpoints have been studied: (1) reduced or completely controlled allergy symptoms and improvement in quality of life, (2) reduced symptomatic treatment medication, (3) remodeling of the immune system, (4) preventing AR from developing into asthma, and (5) preventing new allergies.

A double-blind, placebo-controlled study involving 132 asthmatic subjects from three different regions of Mainland China was by far the largest randomized controlled trial in China to investigate the effect of SCIT with Alutard-SQ [84]. The symptom scores began to diverge at week 29 with the immunotherapy group showing a significantly lower score until week 48. In actively treated subjects, skin test response decreased but *Der p* sIgE remained unchanged. Another study used Total Nasal Symptoms Scores (TNSS) and Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) to assess nasal symptoms and quality of life in 47 AR patients and reported that the efficacy started and kept improving 3 months after treatment and remained relatively stable after 1 year [75].

A study on AR patients in Guangzhou City showed that there was no significant difference in the efficacy of SLIT between dust mite monosensitized and polysensitized patients [91]. Similarly, another study in Chongqing showed that asthma children with multi-allergen sensitization could be desensitized by a single HDM-SCIT, which could also help prevent the onset of new sensitization [85]. It should be noted that although standardized HDM vaccine can rapidly improve large airway function following the commencement of treatment, its effect on small airways can be delayed [86]. Moreover, patients with severe asthma tend to be responders rather than nonresponders [87, 89]. AIT was more effective in children compared to adults [76]. In HDM-induced atopic dermatitis patients, HDM-SCIT relieved clinical symptoms and altered levels of IL-10, TGF-beta1, s-IgG4, and IFN-γ [92].

SCIT with Other Allergen Extracts

Many nonstandardized crude extracts have been used in China for a long time. The advantages of nonstandardized allergen extracts include a wider variety of allergen extract, lower cost, and the ability to offer mixed allergen extracts. In 1987, Leng et al. [93] studied AIT with *Artemisia* pollen allergen extract in China. This was the earliest international report of AIT in China. *Humulus* pollen extract has been found to be effective and safe for use in AR with/without asthma [94]. Similarly, significant improvement in symptom scores, lung function, medication scores, eosinophil count, and SPT index has been reported after nonstandardized AIT with ragweed and/or mugwort extracts [95].

SLIT

SLIT with HDM Allergen Extracts

The long-term therapeutic effects of SLIT for HDM in AR or asthma were examined in various studies, [95–119] including five that were double-blind placebo controlled [96, 102, 103, 115, 120]. One meta-analysis evaluating 25 studies reported that SLIT provided significant relief in symptom and reduced the need for medications in persistent AR [121].

A double-blind placebo-controlled randomized clinical trial of 484 asthmatic adults showed that sublingual HDM allergen immunotherapy was well tolerated in adult asthmatics and effectively controlled disease in patients with moderate (but not mild) persistent asthma [96]. Another multicentered, randomized, double-blind, placebo-controlled study of SLIT on 120 HDM-induced AR patients showed that the total symptom and visual analog scores (VAS) in the SLIT group decreased significantly after week 14, and individual AR symptoms were significantly improved after week 22 [103]. Similarly, Yue et al. performed SLIT with *Der f* drops on patients with *Der f* allergic asthma and rhinitis and further confirmed the safety and effectiveness of SLIT [104]. The onset of the action can be observed as early as 3 months after initiation of treatment [122].

The efficacy and safety of SLIT in children, especially very young children, was also demonstrated [105, 123]. For patients with cough variant asthma (CVA) [106] and atopic dermatitis [116], similar therapeutic effectiveness of SLIT was noted. Longer duration of SLIT treatment over a 3-year course is more efficacious than a 1- or 2-year course [124].

SCIT Vs SLIT

SCIT and SLIT are both effective treatments for allergic diseases [125–129]. In general, SLIT appears to be associated with fewer and less severe adverse reactions than SCIT [130], while SCIT usually has higher efficacy and faster onset. After 2 years of AIT with standardized HDM extract for patients with persistent AR, no significant difference was found in the reduction of the total nasal symptoms between the SCIT and SLIT groups. However, there was a significant reduction of VAS score of nasal obstruction in the SCIT group compared with the SLIT group [112]. Similar findings on the effectiveness of SCIT and SLIT were reported in other studies [113, 131, 132]. However, Gui et al. [114] performed AIT in 248 AR patients and observed a significant difference of response rate between the SCIT and SLIT groups (92.19 vs. 49.46%).

AIT in Other Asian Countries

HDM

AIT with HDM is not only used to treat AR and asthma, but also AD. Nahm et al. [133] treated 251 AD patients with HDM extract using SCIT and observed a favorable clinical response rate of 73.6%. Moreover, the response rate of SCIT was significantly higher in patients with severe AD (90.6%) than patients with mild to moderate AD (63.7%) ($p < 0.001$). This study showed that early initiation of SCIT might lead to a favorable clinical outcome in patients with severe AD sensitized to HDM.

In 2016, a double-blind trial [134] in Japan assessed the efficacy of SLIT with 300 index of reactivity (IR), 500 IR, or placebo groups in 968 HDM-AR patients. The Average Adjusted Symptom Score (AASS) in the last 8 weeks of treatment was significantly improved in both the 300 IR and the 500 IR groups compared to that in the placebo group ($p < 0.001$). All four nasal symptoms significantly improved in both 300 IR and 500 IR groups. Furthermore, rescue medication use was reduced and the Japanese Rhinoconjunctivitis Quality of Life Questionnaire outcome was also improved in the 300 IR group. Furthermore, a prospective, randomized, controlled, open-labeled, three parallel group trial recruited 48 patients monosensitized to HDM [135] and demonstrated that a significant reduction of total rhinitis and asthma symptom score, total medication score, VAS, and skin reactivity to HDM, as well as serum-specific HDM-IgE, was shown in both SLIT and SCIT groups.

Pollen

Japanese cedar (*Cryptomeria japonica*) pollinosis is one of the most common causes of seasonal rhinitis in Japan [136]. In the 1970s, SCIT for cedar pollinosis was performed at university hospitals and medical clinics in Japan [137]. However, in the 1980s, the introduction of second-generation antihistamines and intranasal corticosteroids gradually decreased the use of SCIT. In 2004, a multicenter, double-blind, randomized, placebo-controlled, parallel group study of SLIT demonstrated the safety and beneficial effects of immunotherapy for cedar pollinosis rather than by pharmacotherapy alone [138, 139]. The mean of the daily total symptom scores and the QOL score were significantly lower in the SLIT group than in patients experiencing pollinosis symptom receiving symptomatic treatment [139]. More recent studies also support the effectiveness of AIT in improving nasal and ocular symptoms [140, 141]. Another study found that the efficacy of SLIT in patients with cedar pollinosis may be induced by apoptosis of $CD4^+$ T cells and basophils [142].

Side Effects of AIT

AIT can cause local or systemic reactions. Local reactions are more common and expected. Although systemic reactions are part of administering AIT, it is imperative that the clinicians take precautions to minimize the risk of systemic reactions by appropriate patient selection and dose adjustment. SCIT should only be administered by experienced allergists with the proper equipment and medications to treat anaphylaxis. The EAACI, AAAAI, and ACAAI all recommend at least 30 min of observation after each injection [143]. The incidence of long-term side effects is very low as long as the standard of care is followed. The risk of death from anaphylaxis during AIT is as low as one in 2.5 million injections.

Side Effects of SCIT

To examine the side effects of SCIT, Lan et al. [144] observed 166 patients who received 3087 injections of AIT (Alutard, ALK-ABELLO, Denmark). Systemic adverse reactions occurred 25 times in eight children which was 0.81% of the total injections. All the children with systemic adverse reactions manifested a strong positivity to SPT against HDM with rapid recovery after proper treatment (Table 1).

In a retrospective study on patients receiving SCIT with crude pollen allergen extracts over a 20-year period between December 1993 to September 2013, 70 systemic adverse reactions were observed in 35 patients during the observation period. Of these, 58.6% (41/70) were grade I reactions, 15.7% (11/70) were grade II reactions, 17.1% (12/70) were grade III reactions, and 8.6% (6/70) were grade IV reactions. The majority (97.1% (68/70)) of systemic reactions occurred during the maintenance phase. Risk factors included injections errors, pollen season, and increasing of dose despite previous large local reactions [145]. In contrast, Shen et al. reported that the systemic adverse reactions tend to happen during the initial treatment phase (Alutard, ALK-ABELLO, Denmark), and were mainly urticaria and angioedema [146].

Side Effects of SLIT

Shao et al. [110] enrolled 264 children aged 3–13 years old with *Der f*-induced AR who randomly received both SLIT and pharmacotherapy or pharmacotherapy only for 12 months. Some adverse events (AEs) were found during the study period (Table 2), but no severe systemic AEs were reported [147] (Fig. 6).

New Technology and Treatment Strategies

In spite of the advances with AIT, safer and more effective AIT strategies are needed. Novel approaches to improve AIT

Table 1 Reported systemic adverse reactions during HDM SCIT

	China [144]	Other East Asian countries [133]
Systemic adverse reactions	4.8% (8/166)	10.4% (26/251)
Grade 1	12% (3/25)	81% (21/26)
Grade 2	60% (15/25)	19% (5/26)
Grade 3	28% (7/25)	0 (0.0%)
Grade 4	0% (0.0%)	0 (0.0%)

SCIT = subcutaneous immunotherapy

include use of adjuvants, recombinant allergens, DNA vaccines, and alternate routes of administration. Novel vaccine development for future immunotherapy in China can be seen in Fig. 7.

Adjuvants

A potential therapeutic method on experimental allergic asthma is to target Toll-like receptor 7 (TLR7). A synthesized versatile Toll-like receptor 7 agonist was conjugated to recombinant Der f 1 and evaluated in a mouse model of HDM sensitization [149]. Both TLR7a–Der f 1 and Der f 1 treatment reduced IgE levels and increased IgG1 and IgG2 and with a Th2 → Th1 shift in splenocyte culture supernatant and bronchoalveolar lavage. TLR7a–Der f 1 treatment also induced a significant increase in IL-12 level, while Der f 1 only induced a slight increase in IL-12. More importantly, TLR7 agonist–Der f 1 (TLR7a–Derf 1) reduced airway responsiveness and airway inflammation and protected animals from anaphylaxis upon challenge. This data indicates the significance of TLR7 in airway responsiveness in a mouse model. The protective and suppressive potential of TLR7a–Der f 1 vaccine in dust mite allergic asthma remains to be determined in humans.

Chitosan (CS), a biodegradable material, has been reported to be a safe and effective method of allergen delivery. One study compared the efficacy between *Dermatophagoides farinae* (*Der f*) and *Dermatophagoides farinae*/chitosan nanoparticle vaccine (DCN) in an asthma mouse model. Compared with a control group, AHR and lung inflammation were greatly reduced in both the *Der f* group and the DCN group. The numbers of total cells and eosinophils in BALF from these two groups also were significantly lower than those of the control group. However, mice treated with sublingual DCN showed increased higher level of IFN-γ in the supernatant of splenocyte culture and bronchoalveolar lavage fluid and increased levels of IgG2a and IgA in the serum compared to mice treated by *Der f* only [150].

Mesoporous silica nanoparticles (MSNs) have also gained significant attention as potential delivery vehicles and for their use as adjuvants [151]. In 2018, Peng et al. used hollow mesoporous silica nanoparticles (HMSNs) as vehicles for HDM allergen in order to improve the efficacy of SIT. Spherical HMSNs (100 nm) with a pore diameter of 2.897 nm were successfully loaded with *Der f*2 protein with a loading capacity of 90 μg *Der f*2/1 mg HMSNs. Its preventive effects on allergic asthma were evaluated by subcutaneous administration of *Der f*2-loaded HMSNs in a mouse model of *Der f*2-induced allergic asthma. The *Der f*2 loaded on HMSNs released slowly in 72 h. Their data showed that treatment with *Der f*2-loaded HMSNs could efficiently decrease *Der f*2-specific IgE levels, inflammatory cell infiltration in lung tissue, and Th2 cytokine IL4 levels in BALF. In addition, *Der f*2-loaded HMSNs increased the *Der f*2-specific IgG levels, Th1 cytokine IFN-γ levels, and induced proliferation of splenocytes to *Der f*2 and increased IFN-γ levels. These results showed that *Der f*2-loaded HMSNs were efficient in preventing allergic inflammation, and HMSNs may be potential vehicles for SIT of HDM allergy [152].

Table 2 Reported adverse events during SLIT

	China [110]	Other East Asian countries [147]
Exacerbation of rhinitis	13 (24.1%)	16 (18.1%)
Exacerbation of asthma	8 (14.8%)	–
Local rashes	5 (9.3%)	4 (4.5%)
Itching sensation in the oral cavity or of the lip	1 (1.9%)	13 (14.8%)
Gastrointestinal disorders	2 (3.7%)	11 (12.6%)
Eye itching	1 (1.9%)	4 (4.5%)
Anaphylactic shock	0 (0.0%)	0 (0.0%)

SLIT = sublingual immunotherapy

Recombinant Allergens

Lactic acid bacteria (LAB) are food-grade bacteria with "GRAS" (generally regarded as safe) status, and their anti-allergic effects have already been recognized. Increasing studies have utilized the expression of various heterologous antigens in LAB as oral vaccines. Hu et al. successfully expressed the major peanut allergen Ara h 2.02 in the LAB expression system and evaluated its efficacy in an experimental animal model of peanut allergy. The goal is to develop a safe, effective, and convenient oral vaccine for peanut allergy. The results showed that systemic anaphylactic symptoms and Th2 responses (IgE antibody, MCP-1 level, histamine release, and IL-4 production) were significantly attenuated in the experimental groups when compared with the control group. Moreover, specific IgG2a antibody and the ratio of IFN-/IL-4 were intensely increased through pretreatment with the Ara h 2.02-expressing LAB [153]. These observations suggest that this peanut allergy recombinant LAB oral vaccine, utilizing a recombinant strain which expresses a hypoallergenic peanut allergen, is a viable treatment modality in food allergy.

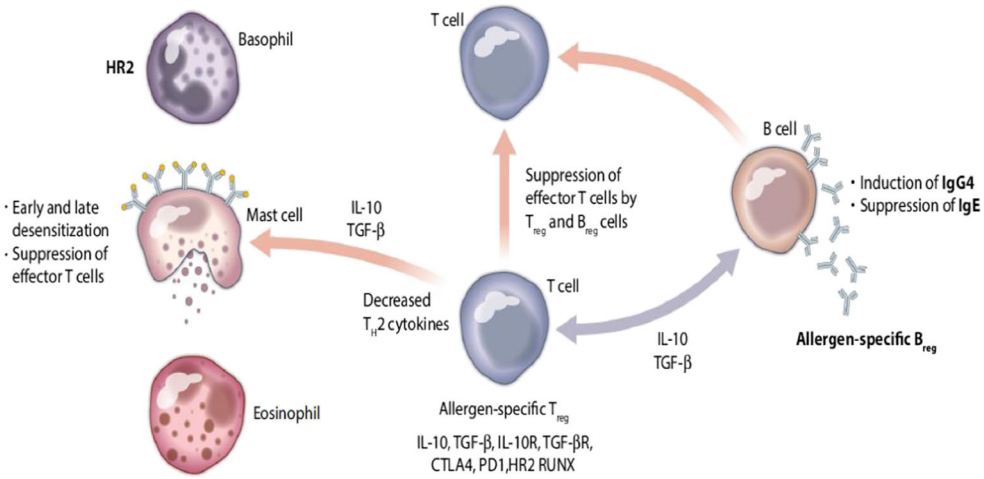

Fig. 6 Mechanisms of allergen-specific immunotherapy. Allergen-specific Treg cells generate and suppress other effector Th1 and Th2 cells, which directly or indirectly suppress mast cells and basophils, resulting in early and late desensitization of mast cells and basophils. Suppression of allergen-specific IgE and inducement of IgG4 by T cells and induction of allergen-specific IL-10^+ Breg cells also lead to the suppression of effector T cells [148]

Likewise, Zhang et al. have described another LAB expression system as an oral immunotherapy agent for Der p2 [154].

DNA Vaccines

Plasmid DNA vaccines expressing allergens have been investigated as an alternative immunotherapy approach in allergy. DNA vaccines delivered by dendritic cells are more efficient than plasmid DNA vaccines. By transferring *Der p* allergen genes into immature dendritic cells (DC), Wu et al. [155] successfully induced immune tolerance in mice with HDM asthma. The transfection of major allergens of house dust mite, *Der p*1, and *Der p*2 resulted in the increase of the secretion of IL-10, IL-12, and TGF-beta by DCs but did not induce the maturation of immature DCs. The Th2 responses decreased and Th1 responses increased when the asthmatic mouse $CD4^+$ T cells were cocultured with transfected DCs. The transfected DCs induced the increase of regulatory T cells, especially the IL-10-secreting regulatory T cells in asthmatic mice in vivo, and inhibited the inflammation and Th2 responses in a regulatory-dependent manner [155]. The results provided a novel concept that DCs may be an effective target for the clinical treatment of allergic asthma at the genetic level.

Rush and Cluster Immunotherapy Schedules

Rush and cluster immunotherapy schedules accelerate immunotherapy buildup. A cluster immunotherapy schedule involves the patient receiving several allergen injections (generally two to four injections) sequentially in a single day of treatment on

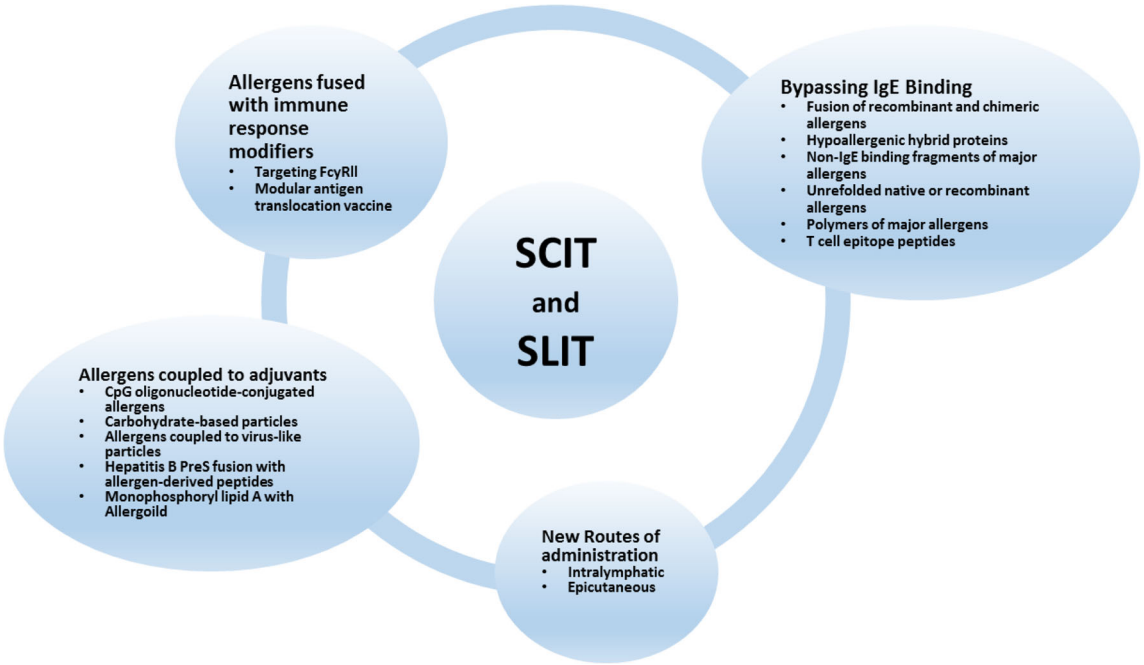

Fig. 7 Novel vaccine development for future immunotherapy

nonconsecutive days. The maintenance dose is generally reached in 4–8 weeks. In rush immunotherapy (RIT) protocols, higher doses are administered at 15- to 60-min intervals over a 1- to 3-day period until the maintenance dose is achieved [156]. RIT shows similar and even earlier onset of clinical efficacy compared to conventional AIT, and there is no evidence to support a difference in systemic adverse reactions [157]. Similarly, the cluster schedule reduced the time to reach maintenance dose and caused mild systemic adverse reactions with no differences compared to conventional schedules [158, 159].

Epicutaneous Immunotherapy

Studies of epicutaneous immunotherapy in murine models of allergy have generated substantial data to support its safety and efficacy. In a study by Li et al. [160], mice were first given five weekly treatments of 10–1000 μg complete peanut extract (CPE) or ovalbumin (OVA) on shaved back skin and subsequently with oral CPE or OVA plus cholera toxin skin for 5 weeks and monitored for hypersensitivity responses. While CPE or OVA to structurally intact skin did not lead to allergic sensitization to peanut or OVA, cutaneous allergen application blocked the subsequent induction of the oral sensitization including inhibiting oral sensitization-induced CPE-specific IgE, IgG1, and IgG2a production in a dose-dependent fashion. Such treatment also suppressed peanut-induced anaphylaxis and modulated oral sensitization-promoted cytokine production. Cutaneous OVA application also resulted in similar results as seen with CPE application. These experimental data in animal models suggest that allergic tolerance might be achieved via the cutaneous application of allergen. However, clinical data is needed to demonstrate the efficacy and safety profile of EPIT prior to approval for routine clinical applications.

Intralymphatic Immunotherapy

Yong et al. [161] evaluated the clinical efficacy and safety of intralymphatic Der p immunotherapy for house dust mites. Patients in a control group ($n = 36$) were prescribed budesonide and salbutamol aerosol, while those in the intralymphatic immunotherapy treatment group ($n = 36$) were prescribed additional intralymphatic immunotherapy every 4 weeks. After 20 weeks, medication scores and serum Der p sIgE of patients in the immunotherapy group decreased significantly compared with the control group, with no local and systemic adverse reactions.

Summary

The five most common allergens in China are HDM, *Artemisia* (wormwood), *Humulus japonicus* (Japanese hop), *Alternaria alternata*, and *Cladosporium herbarum*, but there is regional variability. AIT for AR, asthma, and other allergic diseases in China has developed very quickly in recent years. With the support of the Chinese Medical Association (CMA) and the Chinese Medical Doctor Association (CMDA), improvements in the Chinese AIT will continue to be developed and become more widely used among allergists. The Chinese College of Allergy and Asthma (CCAA), a specialized branch of the CMDA established in 2016, will be the main certification authority for AIT.

Since 1956, conventional SCIT has been the preferred route of administration in China. SLIT has recently been gaining more widespread acceptance. So far, HDM is the only extract available commercially in China, but other commercial extracts, standardized allergens, multi-allergen mixtures, recombinant allergens, and novel approaches will hopefully become available for clinical use. This is a growing field due to the expanding potential and increasing number of allergy patients in China.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

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