References

[1] Okamoto Y, Horiguchi S. Yonekura S, Yamamoto H, Hanazawa T: Present situation of cedar pollinosis in Japan and its immune responses. *Allergol Int* 2009;58:152-162.

[2] Okuda M: Epidemiology of Japaneses cedar pollinosis throughout in Japan. Ann Allergy Asthma Immunol 2003;91:288-296.

[3] Ozasa K, Dejima K, Takenaka H: Prevalence of Japanese cedar pollinosis in Japaneses school children. *Int Arch Allergy Immunol* 2002;128:165-167.

[4] Sakashita M, Hirota T, Harada M, Nakamichi R, Tsunoda T, Osawa Y, Kojima A, Okamoto M, Suzuki D, Kubo S, Imoto Y, Nakamura Y, Tamari M, Fujieda S: Prevalence of allergic rhinitis and sensitization to common aeroallergens in a Japnases population. *Int Arch Allergy Immunol* 2010;151:255-261.

[5] Yonekura S, Okamoto Y, Horiguchi S, Sakurai D, Chazono H, Hanazawa T, Aoki S, Konno A: Effect of aging on the natural history of seasonal allergic rhinitis in middle-aged subjects in south Chiba, Japan. *Int Arch Allergy Immunol* 2012;157:73-80.

[6] Fujieda S, Kurono Y, Okubo K, Ichimura K, Enomoto T, Kawauchi H, Masuyama K, Goto M, Suzuki H, Okamoto Y, Takenaka H: Examination, diagnosis and classification for allergic rhinitis: Japanese guideline. *Auris Nasus Larynx* 2012;39:553-556.

[7] Bernstein DI, Wanner M, Borish L, Liss GM. Immunotherapy Committee, American Academy of Allergy, Asthma and Immunology: Twelve-year survey of fatal reactions to allergen injections and skin testing: 1990-2001. *J Allergy Clin Immunol* 2004;113:1129-1136.

[8] Durham SR, Emminger W, Kapp A, de Monchy JG, Rak S, Scadding GK, Wurtzen PA, Andersen JS, Tholstrup B, Riis B, Dahl R: SQ-standardized sublingual grass immunotherapy: Confirmation of disease modification 2 years after 3 years of treatment in a randomized trial. *J*

Allergy Clin Immunol 2012;129:717–725.

[9] Didier A, Worm M, Horak F, Sussman G, de Beaumont O, Le Gall M, Melac M, Malling HJ: Sustained 3-year efficacy of pre- and coseasonal 5-grass-pollen sublingual immunotherapy tablets in patients with grass pollen-induced rhinoconjunctivitis. *J Allergy Clin Immunol* 2011;128:559–566.

[10] Nelson HS, Nolte H, Creticos P, Maloney J, Wu J, Bernstein DI: Efficacy and safety of timothy grass allergy immunotherapy tablet treatment in North American adults. *J Allergy Clin Immunol* 2011;127:72–80.

[11] Cox LS , Casale TB, Nayak AS, Bernstein DI, Creticos PS, Ambroisine L, Melac M, Zeldin RK: Clinical efficacy of 300IR 5-grass pollen sublingual tablet in US study. *J Allergy Clin Immunol* 2012;130:1327–1334.

[12] Horiguchi S, Okamoto Y, Yonekura S, Okawa T, Yamamoto H, Kunii N, Sakurai D, Fujimura T, Nakazawa K, Yasueda H: A randomized controlled trial of sublingual immunotherapy for Japanese cedar pollinosis. *Int Arch Allergy Immunol* 2008;146:76-84.

[13] Okubo K, Gotoh M, Fujieda S, Okano M, Yoshida H, Morikawa H, Masuyama K, Okamoto Y, Kobayashi M: A randomised double-blind comparative study of sublingual immunotherapy for cedar pollinosis. *Allergol Int* 2008;57:265–275.

[14] Fujimura T, Yonekura S, Horiguchi S, Taniguchi Y, Saito, A, Yasueda H, Inamine A, Nakayama T, Takemori T, Taniguchi M, Sakaguchi M, Okamoto Y. Increase of regulatory T cells and the ratio of specific IgE to total IgE are candidates for response monitoring or prognostic biomarkers in two-year sublingual immunotherapy (SLIT) for Japanese cedar pollinosis. *Clinical Immunology* 2011;139:65-74.

[15] Durham OC. The volumetric incidence of atmospheric allergens; a proposed standard method of gravity sampling, counting, and volumetric interpolation of results. *J Allergy* 1946;

17:79–86.

[16] Okuda M, Ohkubo K, Goto M, Okamoto H, Konno A, Baba K, Ogino S, Enomoto M, Imai T, So N, Ishikawa Y, Takenaka Y, Manndai T, Crawford B: Comparative study of two Japanese rhinoconjunctivitis quality-life questionnaires. *Acta Oto-Laryngologica* 2005;125,736-744.

[17] Okuda M, Okubo K, Gotoh M, Okamoto Y, Imano A, Baba K, Ogino T, Ishikawa K, Takenata Y, So N, Imai T, Enomoto M, Mandai T, Crawford B: Standard questionnaire for QOL of Japanese patients with allergic rhinitis. *Arerugi* 2003;52 Supple 1:21-56.

[18] Sasaki K, Okamoto Y, Yonekura S, Okawa T, Horiguchi S, Chazono H, Hisamitsu M, Sakurai D, Hanazawa T, Okubo K: Cedar and cypress pollinosis and allergic rhinitis: Quality of life effects of early intervention with Leukotriene receptor antagonists. *Int Arch Allergy Immunol* 2009;149:350-358.

[19] Dahi R, Kapp A, Colombo G, de Monchy JG, Rak S, Emminger W, Rivas MF, Ribel M, Durham SR: Efficacy and safety of sublingual immunotherapy with grass allergen tablets for seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2006; 118:434-440.

[20] Pajno GB, Caminiti L, Crisafulli G, Vita D, Valenzise M, De Luca R, Passalacqua G: Direct comparison between continuous and coseasonal regimen for sublingual immunotherapy in children with grass allergy: a randomized controlled study. *Pediatr Allergy Immunol* 2011; 22:803-807.[21]Stelmach I, Kaluzinska-Parzyszek I, Jerzynska J, Stelmach P, Stelmach W, Majak P: Comparative effect of pre-coseasonal and continuous grass sublingual immunotherapy in children. *Allergy* 2012; 67:312-320.

[22] Nelson HS, Nolte H, Creticos P, Mloney J, Wu J, Bernstein DJ: Efficacy and safety of timothy grass allergy immunotherapy tablet treatment in North American adults. *J Allergy Clin Immunol* 2011;27:72–80.

[23] Didier A, Malling HJ, Worm M, Horak F, Jäger S, Montagut A, André C, de Beaumont O, Melac M: Optimal dose, efficacy, and safety of once-daily sublingual immunotherapy with a 5-grass pollen tablet for seasonal allergic rhinitis. *J Allergy Clin Immunol* 2007; 120:1338-1345.

[24] Cox LS , Casale TB, Nayak AS, Bernstein DJ, Criticos PS, Ambroisine L, Melac M, Zeldin RK: Clinical efficacy of 300IR 5-grass pollen sublingual tablet in US study. *J Allergy Clin Immunol* 2012;130:1327–1334.

[25] Di Lorenzo G, Mansueto P, Oacor ML, Rizzo M, Castello F, Martinelli N, Ditta V, Lo Bianco C, Leto-Barone MS, D'Alcamo A, Di Fede G, Rini GB, Ditto AM: Evaluation of serum s-IgE/ total IgE ratio in predicting clinical responses to allergen-specific immunotherapy. *J Allerg Clin Immunol* 2009;123:1103-1110.

[26] Canonica GW, Bousquet J, Casale T, Lockey RF, Baena-Cagnani CE, Pawanker R, *et al.* Sub-lingual immunotherapy: World Allergy Organization position paper 2009. *World Allergy Organ J* 2009;2:233–281.

[27] Bousquet J, Lockey R, Malling HJ: Allergen immunotherapy: therapeutic vaccines for allergic diseases. A WHO position paper. *J Allergy Clin Immunol* 1998;102:558–562.

[28] Durham SR, Emminger W, Kapp A, de Monchy JG, Rak S, Scadding GK, Wurtzen PA, Andersen JS, Tholstrup B, Riis B, Dahl R: SQ-standardized sublingual grass immunotherapy: Confirmation of disease modification 2 years after 3years of treatment in a randomized trial. *J Allergy Clin Immunol* 2012;129:717–725.

Auris Nasus Larynx 41 (2014) 1–5

Contents lists available at ScienceDirect

Auris Nasus Larynx

journal homepage: www.elsevier.com/locate/anl

Guiding principles of subcutaneous immunotherapy for allergic rhinitis in Japan

Yoshitaka Okamoto [a,*], Nobuo Ohta [b], Mitsuhiro Okano [c], Atsushi Kamijo [d], Minoru Gotoh [e], Motohiko Suzuki [f], Sachio Takeno [g], Tetsuya Terada [h], Toyoyuki Hanazawa [a], Shigetoshi Horiguchi [i], Kohei Honda [j], Shoji Matsune [k], Takechiyo Yamada [l], Atsushi Yuta [m], Takeo Nakayama [n], Shigeharu Fujieda [l]

[a] *Chiba University, Department of Otorhinolaryngology and Head and Neck Surgery, Japan*
[b] *Yamagata University, Department of Otorhinolaryngology and Head and Neck Surgery, Japan*
[c] *Okayama University, Department of Otorhinolaryngology, Japan*
[d] *Saitama Medical University, Department of Otorhinolaryngology/Allergy Center, Japan*
[e] *Nippon Medical School, Department of Otorhinolaryngology and Head and Neck Surgery, Japan*
[f] *Nagoya City University, Department of Otorhinolaryngology and Head and Neck Surgery, Japan*
[g] *Hiroshima University, Department of Otorhinolaryngology and Head and Neck Surgery, Japan*
[h] *Osaka Medical University, Department of Otorhinolaryngology, Japan*
[i] *Iida Hospital, Departments of Otorhinolaryngology and Allergology, Japan*
[j] *Akita University, Department of Otorhinolaryngology and Head and Neck Surgery, Japan*
[k] *Nippon Medical School, Department of Otorhinolaryngology, Musashikosugi Hospital, Japan*
[l] *University of Fukui, Department of Otorhinolaryngology and Head and Neck Surgery, Japan*
[m] *Yuta Clinic, Japan*
[n] *Department of Health Informatics, Kyoto University School of Public Health, Japan*

ARTICLE INFO

Article history:
Received 16 May 2013
Accepted 27 September 2013
Available online 1 November 2013

Keywords:
Allergic rhinitis
Subcutaneous immunotherapy
Principles
Guideline

ABSTRACT

Objective: In anticipation of the development of guidelines for antigen-specific subcutaneous immunotherapy (SCIT), we present recommendations that can serve as guiding principles based on a review of the scientific literature.
Methods: Clinical questions (CQs) concerning SCIT were prepared. Literature searches for publications between January 1990 and February 2011 were performed in PubMed, the Cochrane Library, and Japana Centra Revuo Medicina Web version 4. Qualified studies were analyzed and the results were evaluated, consolidated, and codified.
Results: We present answers for 13 CQs on the indications, methods, effectiveness and mechanisms of SCIT, with evidence-based recommendations.
Conclusion: The guiding principles are intended to be applied to children (≤15 years old) and adults (≥16 years old) with allergic rhinitis (AR). These principles can be used by otorhinolaryngologists for diagnosis of AR, evaluation of severity and rhinoscopic findings, performance of antigen challenge tests, and management of systemic anaphylactic reactions associated with SCIT.

1. Introduction

The incidence of allergic rhinitis (AR) is increasing in Japan. Spontaneous resolution of AR is relatively infrequent, except in elderly individuals, and its symptoms have marked adverse effects on quality of life (QOL). Evidence-based guidelines for use of antigen-specific subcutaneous immunotherapy (SCIT) for treatment of AR have been prepared [1,2]. Antigen extracts entered the Japanese market in 1963, and subsequently SCIT for AR was initiated. The present guiding principles were prepared based on research by the Japanese Rhinologic Society (JRS) [3] to provide accurate knowledge of immunotherapy for AR and contribute to development of this therapy.

The JRS is an independent academic organization that receives no sponsorship or funding from specific organizations or businesses. The JRS has not obtained funds for preparation of the present guidelines from any businesses, including those representing the pharmaceutical industry.

* Corresponding author at: Chiba University, Department of Otorhinolaryngology and Head and Neck Surgery, 1-8-1 Inohana, Chuo-ku, Chiba 260-8670, Japan. Tel.: +81 43 226 2137; fax: +81 43 227 3442.
E-mail address: yokamoto@faculty.chiba-u.jp (Y. Okamoto).

0385-8146/$ – see front matter © 2013 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.anl.2013.06.003

2. Criteria for determining recommendation grades

Clinical questions (CQs) were prepared concerning the methods, effects, side effects, and mechanisms of SCIT. A comprehensive literature search was performed for studies published between January 1990 and February 2011. The databases used were PubMed, the Cochrane Library, and Japana Centra Revuo Medicina Web version 4. The search was executed primarily between October 2010 and July 2011, and used the primary index words "allergic rhinitis", "pollinosis", and "SCIT". Subsequently, two members were assigned to the task of collecting scientific evidence concerning each CQ from the selected papers. After a consensus was reached by the preparation committee, the results were evaluated, consolidated, and codified.

Levels of evidence I–IV were determined as follows: Ia, meta-analysis (with homogeneity) of randomized controlled trials; Ib, at least 1 randomized controlled trial; IIa, at least 1 well-designed, controlled study, but without randomization; IIb, at least 1 well-designed, quasi-experimental study; III, at least 1 well-designed, non-experimental descriptive study (e.g., comparative studies, correlation studies, case studies); IV, expert committee reports, opinions, and/or the experiences of respected authorities. The recommendation levels of the Medical Information Distribution Service (MINDS) were adopted as follows: A, strong scientific evidence, and implementation of the treatment is strongly recommended; B, scientific evidence, and implementation of the treatment is recommended; C1: no scientific evidence, but implementation of the treatment is recommended; C2: no scientific evidence, and implementation of the treatment is not recommended; D: evidence suggesting ineffectiveness or harm, and implementation of the treatment is not recommended.

These recommendation levels are not absolute and diagnostic or therapeutic decisions should be made based on the patient's condition and wishes, and the available resources of each medical facility. However, the guiding principles presented here can be applied tentatively in clinical settings. After evaluation of the results of this process and reviews by external experts, the principles will be developed into guidelines for diagnosis and treatment. The principles and handling of conflicts of interest will be reevaluated on the basis of the results of the preparation of guidelines by the JRS.

3. Indication and methods of SCIT

AR is defined as a type I allergic disorder of the nasal mucosa with 3 major manifestations: repetitive sneezing, watery rhinorrhea, and nasal obstruction [4]. The specific antigen should be determined prior to SCIT.

3.1. CQ01: What administration methods are used for SCIT and what are their advantages and disadvantages?

Administration methods used for SCIT for AR include the 50% incremental method, 100–200% incremental method, cluster method, and rush method. All can be performed until a maintenance dose is reached.

(1) The 50% incremental method is the commonly used method, in which the antigen concentration is increased 10 times from the threshold of the intradermal reaction using 7 injections (0.05, 0.07, 0.1, 0.15, 0.2, 0.3, and 0.5 mL) at a rate of 2 injections/week. This method has a high level of safety, but it requires frequent hospital visits over a long period until the maintenance dose is reached.
(2) The 100–200% incremental method is a rapid method in which the antigen concentration is increased 10 times from the threshold of the intradermal reaction using 3 injections (0.1, 0.3, and 0.5 mL) at a rate of 1 injection/week. The therapeutic effect of the 100–200% incremental method is comparable to that of the conventional 50% incremental method. No adverse reactions were noted while using the 100–200% incremental method with house-dust antigen extract [5] (Level IIb).
(3) In the cluster method, 3 injections are performed in one day at 1 h intervals and a maintenance dose is reached by repeating the treatment once weekly for approximately 5 weeks. The maintenance dose can be reached in a short period with a high level of safety. Moderate adverse reactions have been observed with the cluster method, but their frequency was lower than that with a placebo and the safety of the method was high [6] (Level Ib).
(4) In the rush method, the maintenance dose is reached in 3 days by repeating 5–6 injections every 2 h in one day. The rush method performed in hospitalization (3 days and 2 nights) is likely to produce effects in a short period and to be effective [7] (Level IIb). The nasal symptoms score was significantly better using the rush method compared to the rapid method. Systemic adverse reactions were observed in 40% of the patients, but none of these reactions were severe [8] (Level IIb).

3.2. CQ02: How should the maintenance dose and administration period for SCIT be determined?

The effect of SCIT is insufficient at low doses, but systemic adverse events increase at high doses. For many antigens, administration as a single injection of 5–20 μg as the major antigen is recommended. If a long-term effect is required, it is generally necessary to continue the therapy for 3 years [9] (Level Ia). Three-year SCIT (32 subjects, maintenance dose 20 μg, timothy antigen) was effective for 3 years after discontinuation of treatment [10] (Level Ib). SCIT administered over 3 years (20 subjects, maintenance dose 12 μg, ragweed antigen Amb a1) suppressed antigen-evoked responses in the nasal mucosa [11] (Level Ib). One-year SCIT (35 subjects) reduced the total nasal symptom score (TSS) and medication score (MS) [6] (Level Ib). Three-year SCIT in 147 children aged 6–14 years old was effective for 7 years after the end of the therapy [12] (Level Ib). In 28 patients with a cat allergy, in whom the effects of the cat antigen Fel d 1 were compared using maintenance doses of 0.6, 3, and 15 μg, nasal symptoms were alleviated in a dose-dependent manner [13] (Level Ib). The TSS was significantly lower in 5-year SCIT (239 subjects, maintenance dose 3.6 μg, mite antigen Der p1) than in 3-year SCIT [14] (Level IIa). In patients with mite-induced asthma, the recurrence rate 3 years after discontinuation of treatment was lower in those who underwent SCIT for ≥3 years (19 patients) than in those treated for <3 years (21 patients) [15] (Level III). Recommendation level is A.

3.3. CQ03: What are the types and frequencies of the side effects of SCIT and how are they managed?

SCIT has a risk of systemic adverse reactions and anaphylaxis, with prompt treatment required after 0.13% of treatments (19/14,085 subcutaneous inoculations) [9,10] (Level Ia). Systemic adverse reactions have also been observed after 0.025% of inoculations [16] (Level Ia). Severe anaphylactic reactions due to SCIT for SAR occurred in 5.4 of 1,000,000 injections (0.0005%) and were most frequently observed during the pollen season (46%). In most cases, the cause of anaphylaxis was an error in the dose (25%) and epinephrine was administered within 20 min as a life-saving treatment [17] (Level III). The incidence of local adverse reactions to SCIT using a standardized mite or weed allergen was 10.5% and

that of systemic reactions was 4.8% (0.37% of all injections). Adverse systemic reactions occurred significantly more frequently in patients with asthma, in those sensitized to mites, and when the dose of antigen extract was increased [18] (Level III). Recommendation level is B.

3.4. CQ04: What kinds of patients are not indicated for SCIT?

Adverse reactions are more likely to occur in patients with AR complicated by asthma than in those with AR alone [19] (Level III). Malignant diseases, autoimmune disorders, patients under treatment with β-blockers, patients who are pregnant at the start of SCIT, asthmatic patients with FEV1 <70%, and patients with acute infections such as a cold are contraindicated for SCIT for AR. SCIT should also not be performed in patients aged <5 years old [20] (Level IV). Pregnancy is not a specific contraindication for SCIT, but the dose or concentration of drugs used for SCIT must not be increased during pregnancy to avoid the possibility of anaphylaxis. Initiation of new SCIT is not recommended in patients who are pregnant [21] (Level IV). SCIT is contraindicated for patients with severe cardiovascular diseases; those using β-blockers; those with severe asthma, irreversible chronic airway obstructions, hypersensitivity pneumonitis, allergic bronchopulmonary aspergillosis, and immunodeficiencies; those with psychiatric disorders, and those who cannot follow instructions concerning the therapy. Beginning SCIT during pregnancy is also a contraindication and a very young patient is a relative contraindication. Patients with mild AR that can be sufficiently managed by occasional medication and those who cannot understand explanations of SCIT are considered to be inappropriate for SCIT. In addition, patients with nasal polyps are not expected to respond markedly to SCIT [22] (Level IV). Recommendation level is C2.

4. Effectiveness of SCIT

4.1. CQ05: Can AR in children (including QOL) be improved by SCIT?

We searched the literature for randomized studies of SCIT against AR in children published since 1990 and found 2 small-scale studies: 1 on perennial AR (PAR), and the other on SAR. Symptoms were alleviated by SCIT relative to administration of a placebo [23,24] (Level Ib). SCIT for 1 year significantly lowered the TSS and MS in children with PAR [23] (Level Ib). Many of the adverse reactions were mild, but systemic adverse reactions must be managed appropriately [23,25] (Level Ia). SCIT significantly reduced symptoms and drug scores in children with AR or asthma due to a fungal allergy [26] (Level Ib). SCIT administered over 3 years significantly controlled the symptoms of SAR in children for 7 years following completion of the therapy [12] (Level IIa). The efficacy of antihistamines and topical nasal steroids was higher in children with PAR for 2 years after the start of treatment, but was surpassed by the efficacy of SCIT after 3 or more years [27] (Level IIb). Recommendation level is B.

4.2. CQ06: Can AR in adults (including QOL) be improved by SCIT?

SCIT is likely to be effective with use of a sufficient amount of standardized allergen [9,28,29] (Level Ia). For many allergens, the optimal dose of the primary allergen is 5–20 μg per administration [28,29] (Level Ia). The efficacy of SCIT as a treatment for AR is also enhanced in combination with other drug therapies [29] (Level Ia). Using the Cochrane Collaboration, 1111 papers were evaluated, and 15 of 51 papers fulfilling the criteria of scientific assessment were used in a meta-analysis, in which SCIT was found to be effective based on the TSS. Using the MS, SCIT was also found to be effective in a meta-analysis of 13 papers. However, the degree of efficacy varied and was not easily evaluated [25] (Level Ia). There is a risk of an anaphylactic reaction as a systemic side effect; although rare, appropriate management is required should this reaction occur [28,29] (Level Ia). In a domestic evaluation of SAR, SCIT was more effective than drug therapy alone for improving symptoms and QOL scores [30] (Level III). Recommendation level is B.

4.3. CQ07: Is addition of SCIT effective in patients not responding to regular drug therapy?

Drug therapy is the most widely used method for treatment of AR, but some patients do not respond to this therapy. Therefore, studies have been performed to examine whether symptoms can be alleviated and whether the quantity of drugs administered can be reduced by additional SCIT in such patients. In a randomized, double-blind, placebo controlled study (RCT) of SCIT in 40 patients with severe SAR that was poorly controlled by antihistamines, topical nasal steroids, and disodium cromoglycate in the previous year, improvements in TSS, MS, and VAS scores were observed in the active group [31] (Level Ib). In an RCT of SCIT in 36 patients with severe PAR that was not sufficiently controlled by standard antiallergic medicine, improvements in TSS and MS were observed in the SCIT group [32] (Level Ib). Recommendation level is C1.

4.4. CQ08: Does SCIT suppress the occurrence of asthma in nonasthmatic children?

The results of a 3-year open study comparing the incidence of asthma between SCIT and control drug therapy in 205 children with SAR showed that SCIT significantly suppressed the occurrence of asthma [33] (Level IIa). A 2-year follow-up of the patients in this study (183 patients) indicated that the occurrence of asthma was significantly lower in the SCIT group than in the control group [24] (Level IIa). Follow-up at 7 years after completion of SCIT (147 patients) showed that the occurrence of asthma was still significantly lower in the SCIT group, and that asthma and airway hypersensitivity were significantly alleviated [12] (Level IIa). Recommendation level is C1.

4.5. CQ09: Can sensitization to novel allergens be suppressed by SCIT in patients (children/adults)?

In children sensitized to house dust-mite antigen alone (including those with AR), the percentage of those sensitized to new antigens was significantly lower after SCIT for 2 years (22 patients) [34] and 3 years (75 patients) [35], compared to age-matched controls (Level IIa). In 147 children with AR and asthma, the percentage of those sensitized to new antigens was significantly lower in the SCIT group than in the control group [36] (Level IIa). In a retrospective study in 8396 patients with an airway allergy (asthma, AR) sensitized to house dust antigen alone, the percentages of those sensitized to new antigens at 4 years and 7 years were significantly lower in the SCIT group compared to the control group (23.8% vs. 68.0% at 4 years, and 27.0% vs. 76.8% at 7 years) [37] (Level III). Recommendation level is C1.

4.6. CQ10: How long are the effects of SCIT sustained in children?

The total symptom score was significantly lower in 13 children with SAR who underwent SCIT for 3 years than in 10 age-matched controls after 6 [38] and 12 [39] years (Level IIa). Improvements in the condition of 25 children with PAR and 12 with SAR who underwent SCIT for ≥2 years were sustained over a long period of ≥17 years, compared to children who received drug therapy [40,41] (Level III). Recommendation level is C1.

4.7. CQ11: How long are the effects of SCIT sustained in adults?

The duration of the SCIT effect after discontinuation of therapy depends on the duration of treatment and responses to a skin test [42] (Level III). The effect of the therapy in 32 patients who underwent SCIT for SAR due to grass pollen persisted for 3 to 4 years regardless of whether SCIT was continued for more than 3 years [10] (Level Ib). In 108 patients who underwent SCIT for 3 to 4 years, symptoms exacerbated in 2.7%, 16.7%, 30.6% and 32.8% of the patients at 1, 2, 3 and 4 years after therapy discontinuation, respectively [43] (Level III). The therapeutic effect in 36 patients who underwent SCIT for tree pollinosis for 3 years was maintained in 86% of those with rhinitis and 68% of those with asthma at 6 years after discontinuation of treatment [44] (Level III). In patients with AR/conjunctiva, reactivation at 2 years after discontinuation of SCIT occurred in 36% of 87 patients treated for 4 years and in 18% of 61 patients treated for 6 years [45] (Level III). Recommendation level is C1.

4.8. CQ12: Can the systemic adverse effects of SCIT be prevented by pretreatment with antiallergic drugs?

In a double-blind trial, systemic adverse reactions occurred in 7 (33%) of 21 patients who received loratadine prior to subcutaneous injection and in 19 (79%) of 24 patients who received a placebo. Thus, the incidence of severe adverse reactions was reduced by premedication with an antihistamine [46] (Level Ib). Another study showed a reduced incidence of severe adverse reactions after administration of an antihistamine before subcutaneous injection [47] (Level IV). Recommendation level is C1.

5. Mechanisms of SCIT

5.1. CQ13: What are the mechanisms underlying the effects of SCIT for AR?

Regulatory $Foxp3^+$ $CD4^+$ and $Foxp3^+$ $CD25^+$ T cells are significantly increased in the nasal mucosa in patients treated with SCIT [48]. Antigen-specific serum IgG in patients receiving SCIT inhibits binding of antigen IgE to B cells [49] and SCIT suppresses IL-4 production by $CD4^+$ T cells [50]. Expression of IL-5 mRNA in peripheral blood mononuclear cells (PBMCs) stimulated with Cry j 1 was significantly lower in patients with a marked response to SCIT compared to an untreated group and patients who did not respond to SCIT [51]. Expression of the co-inhibitory molecule BTLA in PBMCs stimulated with Cry j 1 was significantly higher in the SCIT group than in the control group. The increase in the serum cedar-specific IgE antibody level during the pollen dispersion season was suppressed by SCIT [52]. IgG antibodies (particularly IgG4) are increased by SCIT and have been reported to act as a blocking antibody and to correct the tilt to Th2 dominance by suppressing Th2 cytokines and Th2 cells. Recently, SCIT has also been reported to induce regulatory T cells and control allergic reactions via production of regulatory cytokines such as IL-10 and TGF-β.

6. Conclusion

Administration of SCIT for AR involves use of the 50% incremental, 100–200% incremental, cluster, and rush methods until a maintenance concentration is reached, but there has been no direct comparison of the effectiveness of these methods. A major antigen dose of 5–20 μg is recommended to minimize adverse reactions. The incidence of systemic adverse reactions including anaphylaxis is about 1 in 1000–4000 inoculations, and prompt and appropriate treatment is required for such reactions. The risk of systemic adverse reactions might be reduced by oral premedication with an antihistamine. SCIT administered to children with AR significantly improved the total symptom score and significantly reduced the medication score. The effect of SCIT for children with AR is also likely to continue over a long period after discontinuation of the therapy. Sensitization to new allergens can be prevented by SCIT. SCIT for adults with AR is recommended because it alleviates nasal symptoms and reduces the quantity of required drugs. In patients not responding to drug therapy, SCIT can also alleviate symptoms and reduce the use of other drugs. SCIT for AR significantly suppresses the occurrence of asthma and its effect is likely to persist after completion of SCIT. We recommend that SCIT is continued for 3 years or longer. The effect of SCIT is sustained over a long period, even after its discontinuation, and the duration of the effect of SCIT after discontinuation is related to the duration of the treatment.

Conflicts of interest

Any organizations or businesses that have provided research funding (for contract research, joint research, clinical trials, etc.), scholarship donations, and monetary compensations for lectures, manuscripts, and pamphlets to members of the guideline preparation committee are listed. (The period of interest is between January 2010 and December 2011). Astellas Pharma Inc., AstraZeneca KK, Eisai Co., Ltd., Merck & Co., Inc., Otsuka Pharmaceutical Co., Ltd., Ono Pharmaceutical Co., Ltd., Kissei Pharmaceutical Co., Ltd., Kyorin Pharmaceutical Co., Ltd., Kyowa Hakko Kirin Co., Ltd., GlaxoSmithKline KK, Kowa Pharmaceutical Co., Ltd., Sanofi Aventis KK, Shionogi Co., Ltd., Senju Pharmaceutical Co., Ltd., Daiichi sankyo Co Ltd, Dainippon Sumitomo Pharma Co., Ltd., Taiho Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., Mitsubishi Tanabe Pharma Co., Chugai Pharmaceutical Co., Ltd., Nikken Chemical Laboratory Co., Ltd., Nippon Shinyaku Co., Ltd., Nippon Boehringer Ingelheim Co., Ltd., Bayer Yakuhin, Ltd, Pfizer Japan Inc, Meiji Seika Pharma Co., Ltd., Taisho Toyama Pharmaceutical Co., Ltd.

References

[1] Okubo K, Kurono Y, Fujieda S, Ogino S, Uchio E, Odajima H, et al. Japanese guideline for allergic rhinitis. Allergol Int 2011;60:171–89.
[2] Brozek JL, Bousquet J, Baena-Cagnani CE, Bonini S, Canonica GW, Casale TB, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 revision. J Allegy Clin Immunol 2010;126:466–76.
[3] A guide to immunotherapy for allergic rhinitis. Japan J Rhinol 2012;51:119–54 [in Japanese].
[4] Fujieda S, Kurono Y, Okubo K, Ichimura K, Enomoto T, Kawauchi H, et al. Examination, diagnosis and classification for Japanese allergic rhinitis: Japanese guideline. Auris Nasus Larynx 2012;39:553–6.
[5] Yokoshima K, Yamagishi S, Goto M, Ookubo K, Okuda M, Yagi S. New rapid step up protocol for immunotherapy in house dust mite nasal allergy. Otolaryngol-Head Neck Surg 1998;70:722–7 [in Japanese].
[6] Bødtger U, Poulsen LK, Jacobi HH, Malling HJ. The safety and efficacy of subcutaneous birch pollen immunotherapy a one-year, randomised, double-blind, placebo-controlled study. Allergy 2002;57:297–305.
[7] Miyoshi M, Terada T, Hyo S, Takenaka H. Effectiveness of immunotherapy for Japanese cedar pollinosis. Japan J Rhinol 2005;44:131–5 [in Japanese].
[8] Bousquet J, Guerin B, Dotte A, Dhivert H, Djoukhadar F, Hewitt B, et al. Comparison between rush immunotherapy with a standardized allergen and an alum adjuved pyridine extracted material in grass pollen allergy. Clin Allergy 1985;15:179–93.
[9] Calderón MA, Casale TB, Togias A, Bousquet J, Durham SR, Demoly P. Allergen-specific immunotherapy for respiratory allergies: from meta-analysis to registration and beyond. J Allergy Clin Immunol 2011;127:30–8.
[10] Durham SR, Walker SM, Varga EM, Jacobson MR, O'Brien F, Noble W, et al. Long-term clinical efficacy of grass-pollen immunotherapy. N Engl J Med 1999;341:468–75.
[11] Naclerio RM, Proud D, Moylan B, Balcer S, Freidhoff L, Kagey-Sobotka A, et al. A double-blind study of the discontinuation of ragweed immunotherapy. J Allergy Clin Immunol 1997;100:293–300.
[12] Jacobsen L, Niggemann B, Dreborg S, Ferdousi HA, Halken S, Høst A, et al. Specific immunotherapy has long-term preventive effect of seasonal and perennial asthma: 10-year follow-up on the PAT study. Allergy 2007;62:943–8.

[13] Nanda A, O'connor M, Anand M, Dreskin SC, Zhang L, Hines B, et al. Dose dependence and time course of the immunologic response to administration of standardized cat allergen extract. J Allergy Clin Immunol 2004;114: 1339–44.
[14] Tabar AI, Arroabarren E, Echechipía S, García BE, Martin S, Alvarez-Puebla MJ. Three years of specific immunotherapy may be sufficient in house dust mite respiratory allergy. J Allergy Clin Immunol 2011;127:57–63.
[15] Des Roches A, Paradis L, Knani J, Hejjaoui A, Dhivert H, Chanez P, et al. Immunotherapy with a standardized *Dermatophagoides pteronyssinus* extract. V. Duration of the efficacy of immunotherapy after its cessation. Allergy 1996;51:430–3.
[16] Roy SR, Sigmon JR, Olivier J, Moffitt JE, Brown DA, Marshall GD. Increased frequency of large local reactions among systemic reactors during subcutaneous allergen immunotherapy. Ann Allergy Asthma Immunol 2007;99:82–6.
[17] Amin HS, Liss GM, Bernstein DI. Evaluation of near-fatal reactions to allergen immunotherapy injections. J Allergy Clin Immunol 2006;117:169–75.
[18] Tabar AI, García BE, Rodríguez A, Olaguibel JM, Muro MD, Quirce S. A prospective safety-monitoring study of immunotherapy with biologically standardized extracts. Allergy 1993;48:450–3.
[19] Schiappoli M, Ridolo E, Senna G, Alesina R, Antonicelli L, Asero R, et al. A prospective Italian survey on the safety of sub- cutaneous immunotherapy for respiratory allergy. Clin Exp Allergy 2009;39:1569–74.
[20] Zuberbier T, Bachert C, Bousquet PJ, Passalacqua G, Walter Canonica G, Merk H, et al. GA^2 LEN/EAACI pocket guide for allergen-specific immunotherapy for allergic rhinitis and asthma. Allergy 2010;65:1525–30.
[21] Piette V, Daures JP, Demoly P. Treating allergic rhinitis in pregnancy. Curr Allergy Asthma Rep 2006;6:232–8.
[22] DuBuske LM. Appropriate and inappropriate use of immunotherapy. Ann Allergy Asthma Immunol 2001;87:56–67.
[23] Eifan AO, Akkoc T, Yildiz A, Keles S, Ozdemir C, Bahceciler NN, et al. Clinical efficacy and immunological mechanisms of sublingual and subcutaneous immunotherapy in asthmatic/rhinitic children sensitized to house dust mite: an open randomized controlled trial. Clin Exp Allergy 2010;40:922–32.
[24] Niggemann B, Jacobsen L, Dreborg S, Ferdousi HA, Halken S, Høst A, et al. Five-year follow-up on the PAT study: specific immunotherapy and long-term prevention of asthma in children. Allergy 2006;61:855–9.
[25] Calderon MA, Alves B, Jacobson M, Hurwitz B, Sheikh A, Durham S. Allergen injection immunotherapy for seasonal allergic rhinitis. Cochrane Database Syst Rev 2007;1:CD001936.
[26] Dreborg S, Agrell B, Foucard T, Kjellman NI, Koivikko A, Nilsson S. A double-blind, multicenter immunotherapy trial in children, using a purified and standardized *Cladosporium herbarum* preparation. I. Clinical results. Allergy 1986;41:131–40.
[27] Ohashi Y, Nakai Y, Tanaka A, Kakinoki Y, Washio Y, Yamada K, et al. A comparative study of the clinical efficacy of immuno- therapy and conventional pharmacological treatment for patients with perennial allergic rhinitis. Acta Otolaryngol 1998;538:102–12.
[28] Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens WJ, Togias A, et al. Allergic rhinitis and its impact on asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). Allergy 2008;63:8–160.
[29] Bousquet J, Lockey R, Malling HJ. Allergen immunotherapy: therapeutic vaccines for allergic diseases; a WHO position paper. J Allergy Clin Immunol 1998;102:558–62.
[30] Ogihara H, Yuta A, Miyamoto Y, Takeo T, Takeuchi K.. Quality of life in allergic rhinitis immunotherapy for Japanese cedar pollen. Japan J Rhinol 2010;49:26–32 [in Japanese].
[31] Varney VA, Gaga M, Frew AJ, Aber VR, Kay AB, Durham SR. Usefulness of immunotherapy in patients with severe summer hay fever uncontrolled by antiallergic drugs. BMJ 1991;302:265–9.
[32] Varney VA, Tabbah K, Mavroleon G, Frew AJ. Usefulness of specific immunotherapy in patients with severe perennial allergic rhinitis induced by house dust mite: a double-blind, randomized, placebo-controlled trial. Clin Exp Allergy 2003;33:1076–82.
[33] Möller C, Dreborg S, Ferdousi HA, Halken S, Høst A, Jacobsen L, et al. Pollen immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis (the PAT-study). J Allergy Clin Immunol 2002;109:251–6.
[34] Des Roches A, Paradis L, Menardo JL, Bouges S, Daurés JP, Bousquet J. Immunotherapy with a standardized *Dermatophagoides pteronyssinus* extract. VI. Specific immunotherapy prevents the onset of new sensitizations in children. J Allergy Clin Immunol 1997;99:450–3.
[35] Pajno GB, Barberio G, De Luca F, Morabito L, Parmiani S. Prevention of new sensitizations in asthmatic children monosensitized to house dust mite by specific immunotherapy. A six-year follow-up study. Clin Exp Allergy 2001;31:392–7.
[36] Inal A, Altintas DU, Yilmaz M, Karakoc GB, Kendirli SG, Sertdemir Y. Prevention of new sensitizations by specific immunotherapy in children with rhinitis and/or asthma monosensitized to house dust mite. J Investig Allergol Clin Immunol 2007;17:85–91.
[37] Purello-D'Ambrosio F, Gangemi S, Merendino RA, Isola S, Puccinelli P, Parmiani S, et al. Prevention of new sensitizations in monosensitized subjects submitted to specific immunotherapy or not. A retrospective study. Clin Exp Allergy 2001;31:1295–302.
[38] Eng PA, Reinhold M, Gnehm HP. Long-term efficacy of preseasonal grass pollen immunotherapy in children. Allergy 2002;57:306–12.
[39] Eng PA, Borer-Reinhold M, Heijnen IA, Gnehm HP. Twelve-year follow-up after discontinuation of preseasonal grass pollen immunotherapy in childhood. Allergy 2006;61:198–201.
[40] Honda K, Asaka C, Fukui N, Ito E, Ishikawa K. Long-term allergen-specific immunotherapy results in allergic rhinitis. Pract Otol (kyoto) 2010;129:64–7 [in Japanese].
[41] Okamoto Y, Horiguchi S, Hanazawa T, Yonekura S. Study on the establishment of treatment to prevent the prolongation of allergic rhinitis in children to adulthood. J Japan Soc Immunol Allergol Otolaryngol 2007;25:315–8 [in Japanese].
[42] Cox L, Cohn JR. Duration of allergen immunotherapy in respiratory allergy: when is enough, enough? Ann Allergy Asthma Immunol 2007;98:416–26.
[43] Ebner C, Kraft D, Ebner H. Booster immunotherapy (BIT). Allergy 1994;49: 38–42.
[44] Jacobsen L, Nũchel Petersen B, Wihl JA, Løwenstein H, Ipsen H. Immunotherapy with partially purified and standardized tree pollen extracts. IV. Results from long-term (6-year) follow-up. Allergy 1997;52:914–20.
[45] Goksal K, Ozan B, Gulsen D. Long-term allergen-specific immunotherapy correlates with long-term allergen-specific immunological tolerance. Adv Ther 2008;25:29–36.
[46] Nielsen L, Johnsen CR, Mosbech H, Poulsen LK, Malling HJ. Antihistamine premedication in specific cluster immunotherapy: a double-blind, placebo-controlled study. J Allergy Clin Immunol 1996;97:1207–13.
[47] Ohashi Y. Present state and problems of immunotherapy for pollinosis. Japan J Allergol 2006;21:197–203 [in Japanese].
[48] Radulovic S, Jacobson MR, Durham SR, Nouri-Aria KT. Grass pollen immunotherapy induces Foxp3-expressing CD4+ CD25+ cells in the nasal mucosa. J Allergy Clin Immunol 2008;121:1467–72.
[49] James LK, Shamji MH, Walker SM, Wilson DR, Wachholz PA, Francis JN, et al. Long-term tolerance after allergen immunotherapy is accompanied by selective persistence of blocking antibodies. J Allergy Clin Immunol 2011;127. 509-16.e1-5.
[50] Se Secrist H, Chelen CJ, Wen Y, Marshall JD, Umetsu DT. Allergen immunotherapy decreases interleukin 4 production in CD4+ T cells from allergic individuals. J Exp Med 1993;178:2123–30.
[51] Kakinoki Y, Ohashi Y, Nakai Y, Washio Y, Nasako Y, Tanaka A, et al. Allergen induced mRNA expression of interleukin-5, but not of interleukin-4 and interferon-gamma, in peripheral blood mononuclear cells obtained before the pollen season predicts the clinical efficacy of immunotherapy for seasonal allergic rhinitis. Scand J Immunol 2000;51:202–8.
[52] Okano M, Otsuki N, Azuma M, Fujiwara T, Kariya S, Sugata Y, et al. Allergen-specific immunotherapy alters the expression of B and T lymphocyte attenuator, a co-inhibitory molecule, in allergic rhinitis. Clin Exp Allergy 2008;38:1891–900.

本報告書は、厚生労働科学研究委託事業による委託業務として、国立大学法人千葉大学が実施した平成 26 年度「免疫療法による花粉症治療の新しい展開を目指した研究」の成果をとりまとめたものです。