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Guiding principles of subcutaneous immunotherapy for allergic rhinitis in Japan

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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.

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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