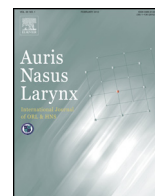




Contents lists available at ScienceDirect

Auris Nasus Larynx

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



Guiding principles of sublingual immunotherapy for allergic rhinitis in Japanese patients

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ARTICLE INFO

Article history:

Received 11 June 2015

Accepted 26 August 2015

Available online xxx

Keywords:

Allergic rhinitis

Guideline

Subcutaneous immunotherapy

Sublingual immunotherapy

ABSTRACT

Objective: Sublingual immunotherapy (SLIT) appears to offer practical advantages for the treatment of allergic rhinitis (AR). Based on a review of the scientific literature, we present recommendations as guiding principles to administer SLIT safely.

Methods: Clinical questions concerning SLIT were prepared. Literature published between January 2003 and December 2012 was searched from PubMed, the Cochrane Library, and Japana Centra Revuo Medicina. Qualified studies were analyzed and the results were evaluated, consolidated, and codified. We answered 17 clinical questions and, based on this, presented evidence-based recommendations.

Results: Sublingual immunotherapy improved symptoms (e.g., quality of life [QOL]) and reduced medication scores in seasonal AR and perennial AR. Most SLIT-induced adverse effects were local oral reactions, although systemic adverse effects such as gastrointestinal symptoms, urticaria, and asthma are occasionally reported. There have been no reports of lethal anaphylactic reactions by SLIT. When SLIT is continued for 3–4 years, its effect persists long after discontinuation.

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<http://dx.doi.org/10.1016/j.anl.2015.08.015>

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Conclusion: A correct diagnosis of AR and sufficient informed consent from patients are required before initiating SLIT. Sublingual immunotherapy should be continued for 3 years or longer. The initial administration of SLIT during the up-titration of an allergen vaccine and the general condition of patients are critical for the safe performance of SLIT.

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1. Introduction

Allergic rhinitis (AR) represents a global health care problem that greatly affects daily activity, work productivity, learning, sleep, and quality of life (QOL) in people of all ages [1]. Japanese cedar pollinosis (JCP) is a unique allergic disease not seen outside of Japan. A massive amount of pollen is dispersed in the spring. The disease affects many people in cities far from the source of the pollen because pollen travels long distances. The disease has high morbidity (35%) in the adult Japanese population and the prevalence of JCP is increasing [1,2].

Allergen-specific immunotherapy (IT) is recognized as the only curable treatment for AR. Subcutaneous immunotherapy (SCIT) has been used for treating AR in Japan. However, SCIT has several drawbacks such as the requirement for frequent hospital visits, injection site pain, and the risk of rare serious adverse drug reactions such as anaphylaxis [3]. Sublingual immunotherapy (SLIT) was developed to overcome these drawbacks and can be administered at home under a physician's direction. However, SLIT should be started after a correct diagnosis of AR and administered by the appropriate method [4,5].

Clinical trials have demonstrated the effectiveness of SLIT for patients with JCP [6,7]. National health insurance in Japan has covered SLIT for JCP since October 2014 and for house dust mite (HDM) since 2015. Based on research by the Japanese Rhinologic Society (JRS), the present guideline was prepared to provide accurate knowledge of SLIT and to contribute to the development of this therapy [8]. The JRS is an independent academic organization that receives no sponsorship or funding from specific organizations or businesses. Furthermore, the JRS has not obtained funds for the preparation of the present guidelines from any businesses, which include businesses representing the pharmaceutical industry.

2. Criteria for determining recommendation grades

This article discusses some clinical questions (CQs). Clinical questions were prepared with regard to the procedures, effects, adverse reactions, and mechanisms of SLIT. The literature published between January 2003 and December 2012 was searched for evidence using the databases of PubMed, the Cochrane Library, and the Japan Medical Abstracts Society (Web version 4). The principal search period was between October 2012 and June 2013 and the main search terms were “allergic rhinitis”, “pollinosis”, and “sublingual immunotherapy”. Two people from the committee selected articles relevant to each CQ and collected information. The development committee then assessed and summarized the information and codified the findings, after achieving a consensus.

Level of evidence I–IV were determined, as follows: Ia, meta-analysis (with homogeneity) of randomized controlled trials; Ib, at least one randomized controlled trial; IIa, at least one well-designed, controlled study, but without randomization; IIb, at least one well-designed, quasi-experimental study; III, at least one well-designed, nonexperimental descriptive study (e.g., comparative studies, correlation studies, and case studies); and IV, expert committee reports, opinions, and/or experience 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; and D: evidence suggests ineffectiveness or harm and implementation of the treatment is not recommended [3].

3. Indication and methods of SLIT

3.1. CQ1: does SLIT improve symptoms and QOL in patients with seasonal allergic rhinitis?

A meta-analysis of randomized placebo-controlled double-blind trials (RCTs) on the use of SLIT for seasonal allergic rhinitis (SAR) demonstrated that symptom scores and medication scores improved significantly in the active treatment group (Level Ia) [9], the symptoms of the active treatment group improved in all trials, and a significant effect was observed in 21 (58%) of 36 trials (Level Ia) [10], and that high efficacy rates were observed in adults and in patients who received preseason treatment of 12 weeks or longer before the pollen season (Level Ia) [11]. In 4 trials of 8 RCTs, disease-specific improvement in QOL was reported, which provided moderate evidence of efficacy for QOL by SLIT (Level Ia) [10]. In an RCT of JCP patients, SLIT for 3 months significantly improved symptoms and QOL during the pollen season (Level Ib) [6,7]. In an open-label study of children with JCP, SLIT for 2 months kept symptoms mild in all patients during the pollen season (Level III) [12].

The recommendation level is B. Sublingual immunotherapy improves symptoms and QOL in patients with SAR.

3.2. CQ2: does SLIT improve symptoms and QOL in patients with perennial allergic rhinitis caused by HDM?

In a meta-analysis of SLIT for HDM-induced perennial allergic rhinitis (PAR), nasal symptoms and medication scores significantly improved in the SLIT group (Level Ia)

[13,14]. Symptoms also improved in elderly patients aged 60–75 years (Level Ib) [15]. The assessment of long-term outcome showed that the improvement of symptoms at 3 years after the completion of treatment was greater in the group that had been treated for 3 years than in the group that had been treated for 2 years (Level Ib) [16]. On reviewing RCTs of children, the efficacy of SLIT for nasal symptoms varied among reports (Level Ia) [17,18].

The recommendation level is B. Sublingual immunotherapy improved symptoms in patients with PAR caused by HDM.

3.3. CQ3: does SLIT improve symptoms and QOL in pediatric patients?

A meta-analysis of RCTs that investigated SLIT for childhood AR demonstrated significant improvement of symptom scores and medication scores in the SLIT group (Level Ia) [13,19]. In an open-labeled randomized controlled trial of SLIT for childhood house dust mite allergic rhinitis (HDM-AR), the rhinitis and asthma symptom scores, medication score, visual analog scale, and skin response all decreased significantly in the SLIT group. Sublingual immunotherapy significantly decreased the level of immunoglobulin E (IgE) specific for HDM, and significantly increased the threshold in the nasal provocation test (Level IIb) [20]. A systematic review of SLIT for childhood allergic rhinoconjunctivitis showed insufficient evidence that SLIT in any administration form has a positive effect on symptoms and/or medication use in children and adolescents (Level Ia) [21]. A systematic review and a meta-analysis of SLIT for childhood SAR demonstrated that the effect of SLIT was greater in adults than in children (Level IIa) [11].

The recommendation level is C1. In children with AR, SLIT is expected to significantly improve nasal symptom scores and significantly reduce drug doses. However, only a small number of high-quality studies have been reported. The effect of this therapy is reportedly weaker in children than in adults.

3.4. CQ4: does the addition of SLIT have an effect in patients who do not respond to pharmacotherapy?

In an RCT of patients with SAR that was poorly controlled by pharmacotherapy (e.g., steroid nasal sprays, oral antihistamines), 2 years of SLIT significantly improved symptoms (Level Ib) [22]. In an RCT of patients with moderate or severe SAR that was poorly controlled by pharmacotherapy, 3 years of SLIT significantly reduced symptoms and medication scores. The effect persisted for 2 years after the end of treatment. In addition, the effect was greater in a season with higher pollen levels (Level Ib) [23].

The recommendation level is B. Sublingual immunotherapy can improve symptoms and reduce drug doses in patients who have not responded to pharmacotherapy.

3.5. CQ5: does SLIT inhibit the onset of asthma in patients with AR who do not have asthma?

Sublingual immunotherapy was administered for 4–5 years in children with HDM-AR. At the end of SLIT and at 10 years

after the start of SLIT, the percentage of patients using antiasthma medications was significantly lower in the SLIT group than in the placebo group (Level IIa) [24]. In children who were only sensitized to pollen antigens and did not have asthma, SLIT was administered during the pollinosis season for 3 years. This 3-year regimen significantly inhibited the onset of asthma in the SLIT group (Level IIa) [25,26].

The recommendation level is C1. Sublingual immunotherapy significantly inhibits the onset of asthma and the effect is expected to persist after the completion of therapy.

3.6. CQ6: can SLIT prevent sensitization to new allergens?

The incidence of sensitization to new antigens was significantly lower in adults with PAR treated with SLIT for 3–5 years than in the control group (Level III) [27]. Sublingual immunotherapy for children with AR complicated by asthma did not result in decreased sensitization to new antigens after 10 years (Level III) [24].

The recommendation level is C1. Sublingual immunotherapy may prevent sensitization to new antigens in patients with AR. However, the evidence is limited.

3.7. CQ7: is SLIT effective for AR caused by multiple antigens and for associated allergic diseases (e.g., asthma, oral allergy syndrome, and conjunctivitis) in patients with AR?

A randomized open-label study of patients with pollinosis and asthma compared respiratory function between the SLIT group and a placebo group. Airway hypersensitivity and the percentage of the predicted forced expiratory volume in 1 s (FEV1.0%) improved significantly in the SLIT group (Level III) [28]. A meta-analysis of RCTs of SLIT for patients who had allergic conjunctivitis with or without AR revealed that symptoms of allergic conjunctivitis improved significantly in the SLIT group (Level Ia) [29]. In a randomized open study of patients with both birch pollinosis and oral allergy syndrome (OAS) to apples, SLIT did not improve the symptom of OAS and hypersensitivity to food allergens (Level IIb) [30]. One year of SLIT for children with sensitization to multiple allergens causing AR complicated by asthma achieved a significant decrease in the antigen sensitization rate and a significant improvement of rhinitis, asthma, and conjunctivitis symptoms (Level III) [31].

The recommendation level is C1. Sublingual immunotherapy may improve AR caused by multiple antigens, concomitant asthma, and conjunctivitis. There is limited evidence of its efficacy for OAS.

3.8. CQ8: how long does the effect of SLIT persist?

An RCT of 3 years SLIT showed that the effect of SLIT persisted for 1 year after discontinuing the therapy (Level Ib) [32]. Long-term observation after 3–5 years of SLIT for HDM showed that the effect of treatment for 4 years or more was maintained for 7 years after the discontinuation of the therapy. Furthermore, after the relapse of allergic symptoms, an additional 1 year of SLIT had an effect on relieving symptoms

(Level III) [28]. The effect of 2 years or 3 years of SLIT for HDM persisted for 3 years after the discontinuation of this therapy, and a stronger effect was noted after 3 years of therapy (Level III) [16]. A meta-analysis of 22 reports revealed that the efficacy of SLIT was maintained for 5 years after the completion of treatment (Level Ia) [33].

The recommendation level is B. Sublingual immunotherapy should be continued for 3 years or longer. If SLIT is continued for 3–4 years, its effect persists for a long term after discontinuation.

3.9. CQ9: various SLIT regimens—advantages and disadvantages

There are no reports of studies directly comparing the efficacy and safety of the treatment of AR by the sublingual spit and sublingual swallow methods. However, approximately 30% of the administered allergen dose is in the expectorated saliva with the sublingual spit method, which suggests the superiority of the sublingual swallow method for antigen exposure (Level III) [34]. It is impossible to conclude whether the sublingual spit method or the sublingual swallow method is superior in safety because serious adverse events associated with SLIT reportedly occur often within a few minutes after treatment (Level III) [35–37]. A meta-analysis of SLIT for SAR demonstrated a greater efficacy with tablets than with liquid preparations (Level IIa), and a significantly greater efficacy in the group that began treatment 12 weeks or more before the pollen season compared to the group that started treatment less than 12 weeks before the season (Level Ia) [11]. An RCT of SLIT also demonstrated that a dose of a major allergen greater than 1000 µg/month had a significant effect, even in liquid form (Level Ib) [38]. In SLIT for grass pollens, the efficacy of the preseasonal to intraseasonal regimen was nearly equivalent to the efficacy of the perennial regimen (Level Ib) [39]. Sustained efficacy of 2-month and 4-month preseasonal and coseasonal SLIT by tablets for three pollen seasons reduced symptoms and medication scores in patients with SAR (Level Ib) [40]. In most studies, a preseason to intraseasonal regimen was selected because it is cheaper than the perennial regimen (Level IV) [41]. The recommendation level is C1.

3.10. CQ10: starting concentration for SLIT and the upitration period

The ultrarush regimen in which the dose was increased to maintenance level within a short period was safe and caused no serious adverse effects (Level Ib) [42,43]. The administration of SLIT without an upitration period was also safe and effective in grass pollinosis (Level Ib) [44–46]. There was no difference in the incidence of adverse effects between the administration of SLIT with and without an upitration period in people with SAR (Level III) [47]. However, SLIT without upitration was performed in patients with timothy pollinosis who could not continue SCIT because of adverse effects, which resulted in anaphylactic reactions in two patients (Level IV) [48].

The recommendation level is C1. Sublingual immunotherapy is expected to be safe and effective, even without an upitration

period. However, patients who have experienced adverse effects of SCIT require attention because of the risk of anaphylaxis. The optimum schedule may depend on the allergen; therefore, the optimum schedule (including the starting concentration) for SLIT to treat JCP will require further investigation.

3.11. CQ11: the maintenance dose and duration of SLIT

In an RCT of grass pollinosis, symptom scores improved significantly in patients receiving a dose of 300 index of reactivity (IR) (antigen content, 15–25 µg) and patients receiving a dose of 500 IR (antigen content, 33–40 µg), compared to the placebo group patients. However, there was no significant difference between patients receiving 100 IR (antigen content, 5–7 µg) and the placebo group patients (Level Ib) [49]. A meta-analysis demonstrated that SLIT with a maintenance dose of 150–240 IR was effective (Level IIa) [50]. Higher doses had a superior effect in patients with HDM-AR (Level IV) [51]. A systematic review showed that the preseason administration of SLIT for 12 weeks or more had a better therapeutic effect (Level Ia) [10]. A meta-analysis of SLIT for childhood AR showed that treatment for more than 18 months was more effective than treatment for 18 months or less (Level Ia) [19].

The recommendation level is B. It is recommended that the duration of treatment should be 18 months or longer.

The recommendation level is C1. A dose of 15–25 µg of the major antigen is recommended. However, the optimum maintenance dose appears to depend on the allergen.

3.12. CQ12: adverse effects of SLIT—nature, frequency, and points requiring attention

The types and frequency of adverse effects in 60 high-quality RCTs are shown in Table 1 (Level Ia) [9,13]. In 3030 patients from 38 RCTs, the incidence of adverse effects was 21.0% in the SLIT group and 11.7% in the placebo group. In the SLIT group, local adverse effects occurred 4.2% and systemic adverse effects occurred 0.08%, whereas the corresponding numbers were 0.2% and 0.04%, respectively, in the placebo group (Level IIa) [52]. Systemic adverse effects were primarily asthma attacks or gastrointestinal symptoms. Other severe systemic adverse effects included edema of the uvula and urticaria persisting for 48 h (Level III) [52]. Eleven cases of anaphylaxis were reported after SLIT. There have been no reports of death. Factors associated with the onset of anaphylaxis included previous generalized reactions, complicating immunodeficiency, poor compliance, rechallenge after the interruption of treatment, severe or poorly controlled asthma, high seasonal pollen levels, use of an unstandardized extract, and lack of an upitration period (Level IV) [53]. The recommendation level is B.

3.13. CQ13: is SLIT as effective as SCIT for improving symptoms and QOL?

In an RCT of patients with SAR, the SLIT group and the SCIT group experienced comparable therapeutic effects (Level

Table 1

Adverse events of randomized placebo-controlled double-blind trials [9].

Type of reaction	Studies	SLIT group		Placebo group	
		Patients	Total events	Patients	Total events
Local adverse effects					
Lip edema	11	604	55	536	7
Buccal pruritis	21	1126	1798	1075	492
Cheek/tongue edema	8	648	143	606	2
Throat irritation	10	770	243	747	29
Oral (nonspecified)	3	68	143	71	24
Local (nonspecified)	3	119	7	116	3
Systemic adverse effects					
Urticaria	8	204	7	199	9
Pruritus/rash	10	363	13	222	9
Conjunctivitis	8	262	774	238	786
Rhinitis	16	965	1403	912	1034
Rhinoconjunctivitis	6	184	60	176	58
Asthma/wheezing	15	488	51	450	42
Cough	8	337	313	304	211
Gastrointestinal	20	630	88	561	10
Headache	6	535	70	548	68
Anaphylaxis	6	291	0	288	0
Systemic (nonspecified)	5	330	4	36	0

SLIT, sublingual immunotherapy.

Ib) [54]. A meta-analysis demonstrated that SLIT had a similar therapeutic effect as SCIT in patients with SAR (Level IIa) [55]. However, another meta-analysis demonstrated that the improvement of symptom scores was significantly greater in the SCIT group than in the SLIT group (Level IIa) [56]. In an RCT of patients with childhood PAR and asthma, symptom scores were significantly better in the SCIT group than in the SLIT group (Level Ib) [57].

The recommendation level is C1. There is limited evidence from direct comparisons between SLIT and SCIT; however, both methods of IT are likely to achieve a similar improvement in symptoms.

3.14. CQ14: is SLIT safer than SCIT?

A meta-analysis of 36 RCTs showed that the incidence of adverse events was 0.86% in the SCIT group, 2.13% in the SLIT group, and 0.5–0.99% in the placebo group. Among these events, 12 anaphylactic reactions that required adrenaline occurred in the SCIT group and one anaphylactic reaction occurred in the SLIT group (Level IIa) [57]. A meta-analysis of 51 RCTs of SCIT demonstrated that adverse events that required treatment by adrenaline occurred after 19 (0.13%) of 14,085 injections in the active treatment group, but none of these reactions were lethal. Furthermore, in 60 RCTs of SLIT, there were no cases of anaphylaxis or use of adrenaline (Level Ia) [58]. A systematic review of 60 RCTs that involved patients with AR complicated by atopic asthma showed that SLIT did not result in adverse events such as major generalized symptoms or anaphylaxis, or the use of adrenaline (Level Ia) [9]. For local adverse reactions, the use of a grading system was recommended (Level Ia) [59].

The recommendation level is B. There were no fatal adverse events after SLIT for AR. The incidence of anaphylactic

reactions that require adrenaline is lower with SLIT than with SCIT.

3.15. CQ15: for which patients is SLIT contraindicated?

Sublingual immunotherapy is contraindicated for patients with serious immune disorders, serious cardiovascular disease, malignancy, chronic infection, hypersensitivity pneumonitis, allergic bronchopulmonary aspergillosis, acute infections such as the common cold with fever, chronic diseases causing intolerance of hypotension, and mental disorders; in patients taking beta-blockers or immunosuppressants; in asthma patients with a FEV1.0% of less than 70%; and in patients who cannot take the treatment as directed (Level IV) [60–62]. Initiation of immunotherapy during pregnancy is also contraindicated. The dose and concentration of SLIT should not be increased during pregnancy (Level IV) [60]. Immunotherapy is relatively contraindicated in very young patients (Level IV) [62]. The recommendation level is C2.

3.16. CQ16: what is the mechanism of action of SLIT (i.e., differences from SCIT)?

When antigens are administered sublingually, phagocytosis by antigen-presenting cells (APC) occurs in the oral mucosa within 15–30 min [63]. Most of these APCs are dendritic cells (DCs), called oral Langerhans cells, which phagocytose antigens via IgE-FcεRI [64,65]. There are fewer effector cells (e.g., eosinophils, basophils, and mast cells) in the oral mucosa than in the subcutaneous mucosa; therefore the administered antigens are less likely to be processed by these cells, which leads to fewer systemic anaphylactic reactions [66–68]. There are slightly more of these cells around the lips than in the oral mucosa; hence, symptoms such as lip swelling are likely to

occur early after the introduction of SLIT. However, SLIT reduces these cells; therefore, the local responses to the administration of antigens is less likely to occur [69,70].

Oral mucosal dendritic cells (oDCs) are myeloid cells, not plasmacytoid cells. The oDCs always express toll-like receptors 2 and 4 (TLR-2 and TLR-4, respectively) and are involved in protection against bacterial infection. Stimulation of TLR-2 and TLR-4 enhances the expression of the co-stimulatory molecules B7H1 (PD-L1) and B7H3, and the production and release of interleukin 10 (IL-10). Furthermore, oDCs promote the activation of regulatory T (Treg) cells and Tr1 cells [71]. Compared to skin DCs, the oDCs are characterized by a higher expression of other co-stimulatory molecules (e.g., CD80 [B7.1] and CD86 [B7.2]) and CD40 [72]. The oDCs do not express CD83 and CCR7, which are markers of mature DCs, and produce IL-10 and transforming growth factor beta (TGF- β) after coming into contact with antigens without migrating to other organs [73].

In the mucosa and submucosa of the floor of the mouth, oDCs are likely to induce FoxP3⁺CD4⁺CD25⁺ Treg cells (e.g., Tr1 cells and Th3 cells) during SLIT [72–74]. The Treg cells have an essential role in inducing and maintaining immune tolerance. They are also classified (1) as endogenous naturally occurring Treg (nTreg) cells, which differentiate in the thymus and (2) as induced Treg (iTreg) cells or adaptive Treg cells, which differentiate in the periphery. In response to the invasion of foreign antigens in patients with allergic diseases, iTreg cells apparently undergo peripheral differentiation and inhibit antigen-specific T cells and inflammatory cells [75].

Induced Treg cells and Tr1 cells produce IL-10 and TGF- β [11]. Immunotherapy induces TGF- β -producing CD4⁺ T cells (i.e., Th3 cells), whereas iTreg cells are induced by TGF- β . Interleukin 10 and TGF- β promote class switching to immunoglobulin A (IgA) and certain types of immunoglobulin G (IgG). They also induce the production of IgA and IgG, which may act as a blocking antibody. Interleukin 10 and TGF- β inhibit the activation and proliferation of Th2 cells, and inhibit the infiltration and activation of eosinophils and mast cells [76]. In addition, IL-10 and TGF- β decrease the antigen-presenting activity of DCs and their antigen-specific stimulation of T cells [77,78]. The oDCs capture antigens after oral or sublingual administration, and subsequently induce iTreg cells in a TGF- β -dependent manner. Induced Treg cells that express OX-40 bind to OX-40L on mast cells, and thereby inhibit degranulation and the release of chemical mediators after the cross-linking of IgE by the antigen [79]. Induced Treg cells that express cytotoxic T-lymphocyte-associated protein 4 (CTLA4) are activated by binding to CD80 on DCs and then they inhibit the activation of T cells undergoing antigen presentation by DCs. Furthermore, programmed cell death 1 (PD-1) is expressed on iTreg cells and binds to PD-L1 on DCs, which further inhibits the function of T cells [75,79,80]. Monocytes and B cells expressing PD-L1, a ligand of PD-1, are increased in patients receiving SLIT [81]. By contrast, IL-4-producing monocytes and B cells and T cells decrease during the pollen season.

Immunoglobulin G binds to the Fc γ RIIb receptor on mast cells. Signaling by Fc γ RIIb inhibits histamine release mediated

via IgE-Fc ϵ R through the immunoreceptor tyrosine-based inhibition motif (ITIM). Immunotherapy induces the production of antigen-specific IgG (possibly IgG4), which binds to IgE bound to antigens, and thereby forms the IgG-antigen-IgE complex. Immunoglobulin G then binds to Fc γ RIIb, and possibly inhibits histamine release from mast cells mediated via IgE-Fc ϵ RI.

The aforementioned mechanisms would exert clinical effects. However, many points remain unknown and further studies are required to clarify the detailed mechanisms.

3.17. CQ17: potential clinical markers for use in SLIT

Sublingual immunotherapy increases the level of serum antigen-specific IgG4 and IgA, the number of IL-10-secreting cells induced by antigen stimulation, and the number of PD-L1-expressing cells. These changes showed a significant correlation with the visual analog scale after treatment. At the same time, the expression of CD80 and CD86 both decreased [81]. After SLIT, there was a decrease in the serum concentration of neopterin secreted by monocytes and macrophages [82]. The level of soluble human leukocyte antigen (HLA) molecules (e.g., HLA-G, HLA-A, HLA-B and HLA-C) decreased after SLIT and significantly correlated with the visual analog scale [83]. After SLIT, Foxp3 cells increased while mast cells decreased in the lamina propria. Serum levels of IgG1, IgG4, IgA1, and IgA2 significantly increased, and significantly inhibited the IgE-facilitated allergen-binding assay with serum [74]. In SLIT for JCP, 3 days after in vitro stimulation with the Cry j1 allergen, IL-10⁺FoxP3⁺ (i.e., iTreg) cells showed a significant increase in the CD25⁺CD4⁺ cell population. In addition, an increase of iTreg (i.e., Cry j1-iTreg) cells was associated with excellent QOL scores [84]. The ratio of Japanese cedar-specific IgE to total IgE was significantly correlated with the symptom scores and drug scores during the Japanese cedar pollen season [85]. In an RCT of SLIT for JCP, an analysis of serum proteins showed that the induction of apolipoprotein A-IV significantly decreased the symptom score during the peak Japanese cedar pollen season, and there was a significant inverse correlation between apolipoprotein A-IV and SLIT or between apolipoprotein A-IV and the symptom score [86].

Immunoglobulin G4 is a promising clinical marker candidate for SLIT and SCIT. Submolecules and HLA molecules are also potential candidates. The number of regulatory T cells induced by SLIT is also promising because flow cytometry can easily measure the cells. Furthermore, there are reports on neopterin and apolipoprotein A-IV as marker candidates, which require further research.

Conflicts of interest

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 the following (the period of interest is between January 2012 and December 2013):

Astellas Pharma, Inc. (Tokyo, Japan), AstraZeneca K.K. (Osaka, Japan), Bayer Yakuhin, Ltd. (Osaka, Japan), Chugai Pharmaceutical Co., Ltd. (Tokyo, Japan), Daiichi Sankyo Co., Ltd. (Tokyo, Japan), Dainippon Sumitomo Pharma Co., Ltd. (Osaka, Japan), Eisai Co., Ltd. (Tokyo, Japan), GlaxoSmithKline K.K. (Tokyo, Japan), Kissei Pharmaceutical Co., Ltd. (Matsumoto, Japan), Kyorin Pharmaceutical Co., Ltd. (Tokyo, Japan), Kyowa Hakko Kirin Co., Ltd. (Tokyo, Japan), Kowa Pharmaceutical Co., Ltd. (Nagoya, Japan), Merck & Co., Inc. (Kenilworth, NJ, USA), Mitsubishi Tanabe Pharma Co. (Osaka, Japan), Meiji Seika Pharma Co., Ltd. (Tokyo, Japan), Nikken Chemical Laboratory Co., Ltd. (Yokohama, Japan), Nippon Shinyaku Co., Ltd. (Kyoto, Japan), Nippon Boehringer Ingelheim Co., Ltd. (Tokyo, Japan), Otsuka Pharmaceutical Co., Ltd. (Tokyo, Japan), Ono Pharmaceutical Co., Ltd. (Tokyo, Japan), Pfizer Japan, Inc. (Tokyo, Japan), Sanofi Aventis K.K. (Tokyo, Japan), Shionogi Co., Ltd. (Osaka, Japan), Senju Pharmaceutical Co., Ltd. (Osaka, Japan), Taiho Pharmaceutical Co., Ltd. (Tokyo, Japan), Takeda Pharmaceutical Co., Ltd. (Osaka, Japan), and Taisho Toyama Pharmaceutical Co., Ltd. (Tokyo, Japan).

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