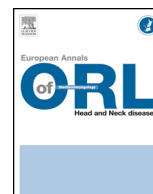




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Review

Specific immunotherapy in allergic rhinitis

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ABSTRACT

Allergic rhinitis is a common condition, with significant impact on quality of life depending on severity and quality of control. Allergen-specific immunotherapy (allergen-SIT) is the only known treatment able to alter the natural course of allergic rhinitis. Although well known to allergologists, it has yet to be fully adopted by the ENT community. This review, based on the most recent meta-analyses and clinical studies, shows that SIT significantly reduces symptoms and medication requirements (nasal corticosteroids, H1-antihistamines) in allergic rhinitis. It can reduce the risk of progression to asthma and, if initiated early enough, of developing new sensitizations. Immunobiological analysis shows an altered inflammatory profile following SIT, with immune tolerance involving T-regulatory lymphocyte induction and IgG production. Sublingual SIT with drops is as effective as subcutaneous SIT and is simpler to use, with less anaphylactic risk. Standardization of trial protocols in terms of treatment response assessment and side effect grading is recommended to improve comparative studies. Sublingual SIT with tablets has recently been introduced, providing a good opportunity for ENT practitioners to adopt the SIT approach in rhinitis triggered by allergy to pollens and, in the near future, to house dust mites.

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1. Introduction

Allergic rhinitis affects more than 400 million people worldwide; in Europe, prevalence ranges between 17% and 29% [1,2]. The associated functional disorders impair quality of life, sleep and occupational performance by 20% according to a survey of 683 patients conducted in 2016 [3]. Economic impact is significant, with an annual cost of \$4.2 m due to productivity loss in the USA in 2010 [4].

The clinical profile of allergic rhinitis in France was drawn up in 2011 in the REALIS study, concerning 1200 pneumologists and allergologists. On the ARIA criteria [1], allergic rhinitis was moderate to severe in 80.3% of cases, and persistent in 65.8%. Asthma

was associated in 40.3% of cases. Allergy most frequently concerned house dust mites (64.5%), followed by grass pollen (61.5%), tree pollen (41.6%) and cat dander (30.5%). Polysensitization was found in 73.6% of cases [5].

Symptomatic treatment is based on antihistamines, corticosteroids and antileukotrienes (in case of associated asthma). Apart from eliminating allergens, which can be difficult, allergen-specific immunotherapy (allergen-SIT) is at present the only etiological treatment able to alter disease progression [6,7]. The first clinical description of SIT was made by Noon and Freeman in 1911 in grass pollen allergic rhinitis [8]. Subsequently, several studies developed the approach, reporting results with subcutaneous immunotherapy (SCIT) and, more recently, sublingual immunotherapy (SLIT) using drops or tablets. Although widely used by pneumologists and allergologists, especially in the SLIT drops form, SIT is still insufficiently well adopted by the ENT community [8].

The present review describes the immunobiologic action of SIT, specifies indications and modalities for SCIT and SLIT, compares

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clinical efficacy and tolerance, and assesses impact on allergic disease (new sensitization, and asthma).

2. Discussion

2.1. Immunobiologic mechanisms of SIT

Atopy is a genetic predisposition leading to production of immunoglobulin E (IgE) in response to inhalation of common allergens (Fig. 1). The allergic immune reaction involves a T-helper (Th2) cell response and IgE humoral response. After antigen fixation to the mucosa, antigen-presenting cells (APCs) bind to Th lymphocytes by interaction between class III major histocompatibility complex (MHC) proteins and T-cell receptors (TCRs). The type of antigen-APC binding and the atopic immune susceptibility of the host induce an immune response in the form of Th2 lymphocyte production. In this allergic context, release of pro-Th2 cytokines (IL-4, IL-5, IL-9 and IL-13) induces lymphocyte-B production of IgE [9]. With repeated exposure to the allergen, IgE-antigen immune complexes trigger mast-cell degranulation, leading to an inflammatory mucosal reaction and recruitment of other effector cells (eosinophils, basophils) [6].

SIT consists in regular administration of purified specific allergen extract. This repeated exposure alters the patient's immune profile, guiding the immune response toward production of Th1 and regulatory T-cell (Treg) lymphocytes, releasing the immune-suppressive cytokines IL-10 and TGF β [7,10]. At the humoral level, IFN γ (produced by Th1 lymphocytes), IL-10 and TGF β induce isotopic class switch in B lymphocytes, with increased levels of IgG4, a possible marker of immunomodulation in competition with IgE [11,12]. Transient IgE elevation is observed at the beginning of SIT [13,14]; these are non-functional IgEs, unable to activate mast-cell degranulation [15]. IL-10 and TGF β also inhibit recruitment of effector cells (eosinophils, basophils), thereby limiting local inflammatory reaction [16].

2.2. Indications for and application of SIT in allergic rhinitis

In the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines (1) and the reports by the Transparency Commission of the French Health Authority (HAS), SIT is indicated in severe or moderate, persistent (perennial) or intermittent (seasonal) allergic rhinitis insufficiently controlled by symptomatic treatment. It is recommended only from the age of 5 years, as early signs of anaphylactic reaction are difficult to discern earlier. Absolute and relative contraindications were listed, on the basis of a literature review, in a 2015 position paper by an international expert group set up by the European Academy of Allergy and Clinical Immunology (EAACI) [17] (Table 1). SIT should not be initiated during pregnancy, but may be continued if previously well-tolerated [6,18]. Non-controlled asthma is an absolute contraindication.

SIT may be administered by subcutaneous injection (SCIT) or sublingually (SLIT) as drops or as tablets. Allergens administered by SCIT or SLIT drops are what is known in France as allergens prepared specifically for an individual (APSi), not requiring market authorization, and with a reimbursement of 65% under the French national health insurance system. The list of available allergens is regularly updated by the health products safety agency (ANSM: Agence nationale de sécurité du médicament et des produits de santé), and covers house dust mites, grass, tree and herbaceous plant pollens, animal dander, mold and certain insects. Certain allergens have been the focus of published clinical studies: dermatophagoides pteronyssinus and farinae, most grasses, silver birch, alder, hazel and ragweed [1]. SLIT by tablet was recently introduced, with market authorization and 15% reimbursement:

Table 1

Absolute (A) and relative (R) contraindications to SIT.

Clinical conditions	SCIT	SLIT
Asthma (partially controlled)	R	R
Asthma (non-controlled)	A	A
Autoimmune disease in remission	R	R
Active autoimmune disease (treatment-resistant)	A	A
Malignant tumor	A	A
β -blockers	R	R
Angiotensin-converting enzyme inhibitors (ACEI)	No	No
Monoamine oxidase inhibitors (MAOI)	No	No
Cardiovascular disease	R	R
Pregnancy (SIT initiation)	A	A
Pregnancy (SIT continuation)	No	No
Child (< 2 years)	A	A
Child (2–5 years)	R	R
Other age group	No	No
HIV (stage A, B; CD4 + > 200/ μ L)	R	R
AIDS	A	A
Psychiatric disorder	R	R
Chronic infection	R	R
Immunodepression	R	R
Use of immunosuppressors	R	R

SIT: specific immunotherapy; SCIT: subcutaneous immunotherapy; SLIT: sublingual immunotherapy.

Grazax[®] Phleum pratense 75000SQ-T and Oralair[®] (RI 300; 5 grasses) for grass pollen, and shortly (in France) Acarizax[®] for house dust mites. Tablets against Timothy grass and ragweed, taken simultaneously, are presently under development [19].

Prescription requires a physician with training in allergology, able to cope with any anaphylactic shock. It involves prick-tests and/or specific IgE assays [radioallergosorbent tests (RAST)]. The implication of the sensitization in the allergic clinical symptomatology has to be demonstrated. SCIT begins with an initiation phase of weekly allergen injections, progressively increasing over 3–4 months, then a maintenance phase with injection every 4–6 weeks [20]. The patient should remain on the premises for at least 30 minutes after injection, due to the risk of systemic allergic reaction. SLIT by drops begins with a shorter incremental initiation phase, with treatment self-administered at home; the drops are to be left under the tongue for 2–3 minutes before being swallowed. SLIT by tablets is also self-administered at home although, since all tablets are full-dose, the first should be administered in the physician's office, with 15 minutes' surveillance, as reaction to the first dose is very quick [21].

The SIT schedule depends on the administration route, perennial or seasonal nature of the rhinitis and the manufacturer's recommendations (Fig. 2) [22]. SCIT is generally administered continuously for at least 3 years. Given the increased risk of systemic reaction, the maintenance dose is decreased during the pollen season (Fig. 2) [20]. SLIT in drops for pollen allergy is usually delivered ahead of and during the season [23]. For SLIT in tablets for pollen allergy, randomized double-blind clinical trials against placebo validated the efficacy of Grazax[®] 75000 SQ-T in continuous administration for 3 years [24,25]. Oralair[®] RI 300 (5 grasses) was validated for administration ahead of and during the pollen season for 3 years [26]. The efficacy of SLIT against pollen allergy is greater if pre-season administration is started at least 4 months ahead of the pollen season [27]. SLIT in tablets for house dust mite allergy was validated using Acarizax[®] 12 SQ in continuous treatment for 1 year in a phase III study with 992 patients [28].

2.3. SIT results

2.3.1. Efficacy against symptoms

Several reviews and meta-analyses have focused on perennial and seasonal allergic rhinitis, assessing the efficacy of SIT

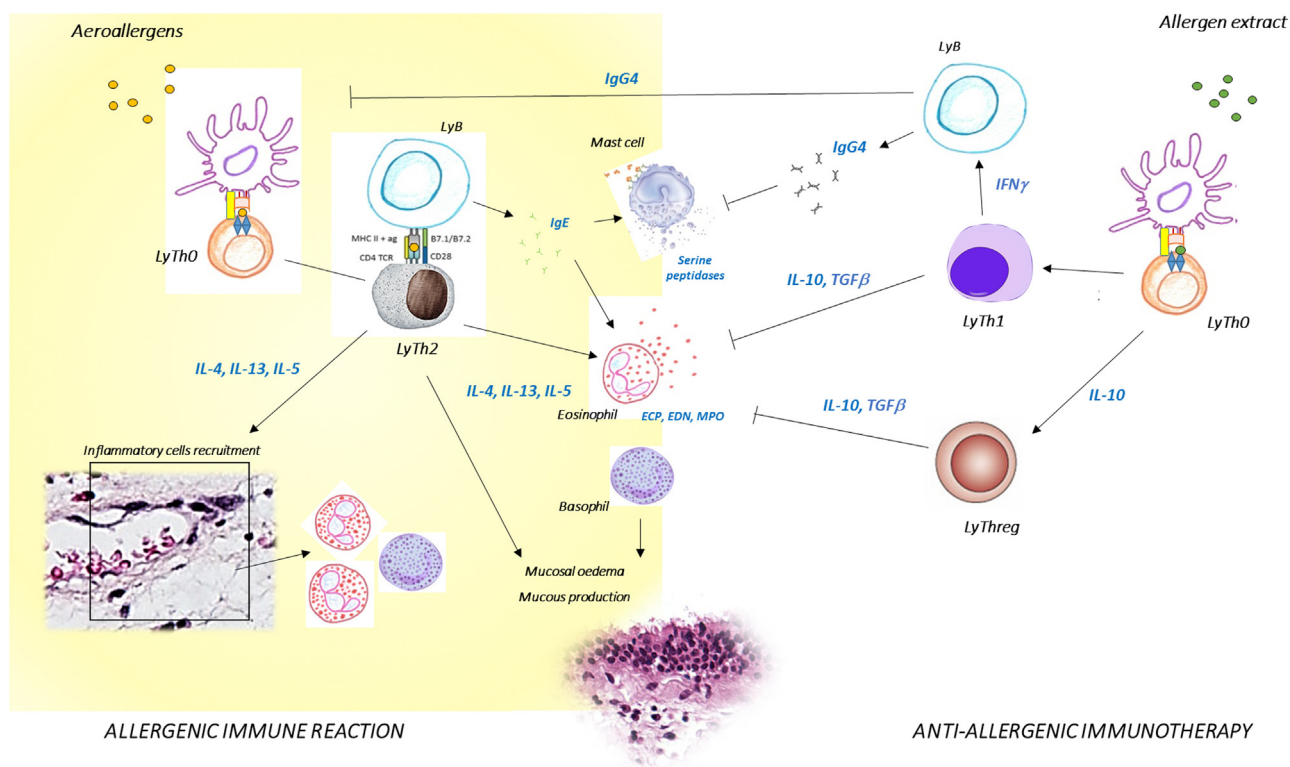


Fig. 1. Comparison of inflammation pathways during allergic reaction and immunotherapy.

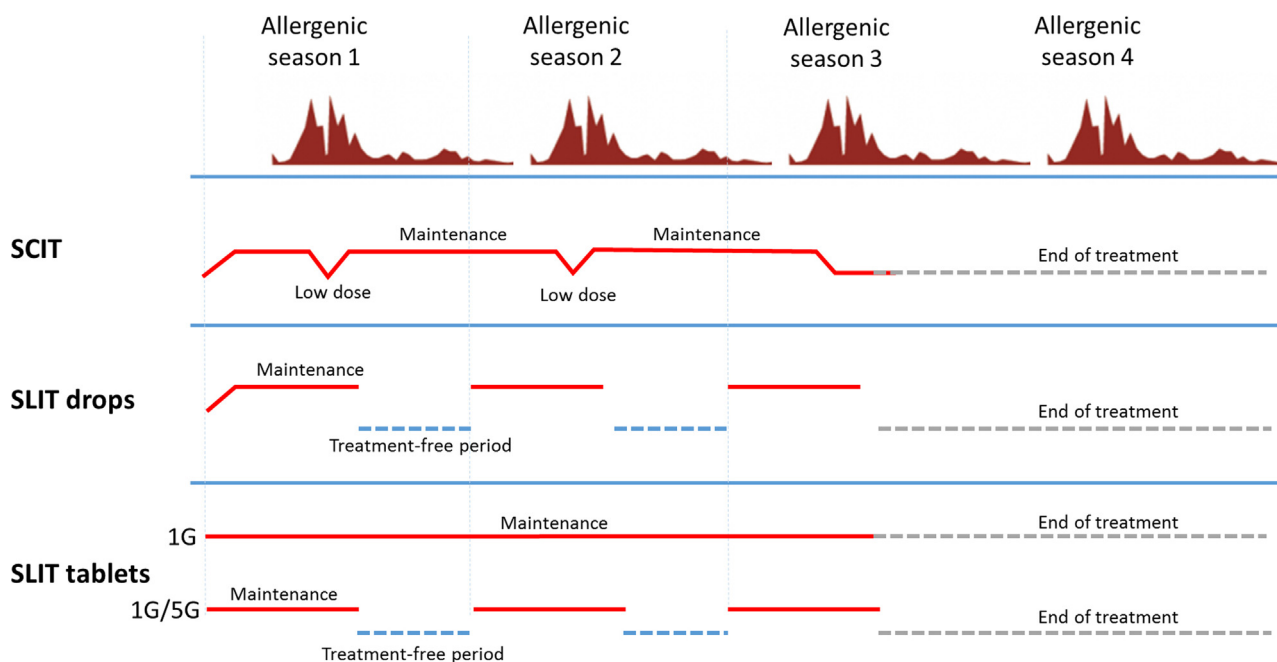


Fig. 2. Specific immunotherapy (SIT) administration flow-chart in seasonal allergic rhinitis (pollen-related) according to route. 1G: preparation with 1 grass pollen; 5G: preparation with 5 grass pollens.

in relieving symptoms, improving quality of life and reducing use of medication. However, even concentrating on double-blind randomized trials against placebo, studies remain heterogeneous due to variety in allergen type and dose, administration route, treatment duration, and assessment parameters and tools [8]. To harmonize trials and enable comparative analysis, the World Allergy Organization (WAO) task force drew up guidelines on study

protocols for SIT [29]. Dose-effect studies are also recommended, to optimize posology [30,31].

A 2007 meta-analysis by Calderon et al. assessed SCIT in seasonal allergic rhinitis based on 15 double-blind randomized trials against placebo with 1,063 patients (adults and children). The combined standardized mean difference between SCIT and placebo effects showed significant reduction in symptom scores and

medication consumption scores with SCIT [13]. Another meta-analysis based on the same methodology, published in 2005 and updated in 2011, assessing the effect of SLIT drops and tablets in 979 patients (adults and children) [7,12] likewise showed significant reduction in symptom and medication scores with SLIT. To assess SIT and symptomatic treatment, a 2014 meta-analysis compared efficacy between SLIT by tablets and medical treatments (antihistamines, topical corticosteroids, and antileukotrienes) in seasonal allergic rhinitis, via indirect comparison of respective combined standardized mean differences versus placebo in 10 studies of SLIT and 28 of medical treatments (in adults and children). The mean relative clinical impact of SLIT was comparable to that of topical corticosteroids and greater than those of antihistamines or antileukotrienes [32].

Regarding perennial house dust mite-related allergic rhinitis, the GA²LEN group's meta-analysis of 8 double-blind randomized trials against placebo compared 194 patients (adults and children) receiving SLIT by drops versus 188 patients receiving placebo, and found overall significantly reduced symptoms and medication with SLIT [33].

In several dedicated studies, SLIT by tablets showed significantly reduced symptoms and medication in grass pollen [24–26] and, more recently, in house dust mite-related allergic rhinitis [28,34,35].

Very few studies have directly compared efficacy between SCIT and SLIT [36–40] (Table 2). Mungan et al. compared SCIT and SLIT by drops in a single-blind study of house dust mite-related allergic rhinitis in 36 patients versus a single administration of sublingual placebo [38]. Another study used double administration of inactive substance plus active treatment (“double dummy”) to compare SCIT and SLIT by drops in pollen-related allergic rhinitis in 20 patients, and reported no efficacy in symptom reduction [37]; small sample sizes (23–53 patients) and poor study robustness (open trial without placebo arm) precluded any reliable demonstration of superiority [41]. A Danish medico-economic study of house dust mite-related allergic rhinitis reported SLIT by tablets to be less expensive than SCIT over 3 years' treatment [42].

2.3.2. Treatment duration and carry-over effect

There is no present consensus on optimal SIT duration. Meta-analyses published in 2005 and 2011 found greater efficacy in SLIT prolonged beyond 12 months [7,12].

Carry-over effect has been assessed. Some reports show effect persistence for at least 3 years after cessation of both SCIT and SLIT [7,43]. Eng et al. reported persistence at 12 years in a limited cohort of children with 3 years' SCIT for grass-related allergic rhinitis [44]. On the basis of these long-term carry-over findings, manufacturers usually recommend a 3-year treatment duration.

2.3.3. Efficacy in mono- and polysensitization

Patients with monosensitization are better candidates for SIT; however, polysensitization is extremely frequent (70–80%) in allergic rhinitis [45]. Recent studies showed that SIT targeting a single allergen (house dust mites or grass pollen) showed equivalent efficacy in polysensitized subjects (adults and children) [28,45–47], but it is important that symptoms relate principally to the target allergen [48].

On the other hand, when SIT targets each relevant allergen, APSI concentrations and their respective efficacies are reduced [14]. When more than 2 allergens are targeted, the effective efficacy of SIT needs discussing.

2.3.4. Biological impact of SIT

In parallel to analyses of clinical impact, several studies have focused on the immunobiological effects of SIT, reporting varied results. Kim et al. found no change in eosinophil levels with

anti-mite SCIT versus placebo [14]. Calderon et al.'s meta-analysis of SCIT found significant elevation of IgG and IgG4 following SIT, while results for specific IgE levels differed between studies [13]. Results for nasal challenge test in another SCIT study were variable [49]. The 2011 meta-analysis of SLIT (drops and tablets) found results comparable to those for SCIT, with IgG and IgG4 elevation [12]. The GA²LEN meta-analysis of SLIT drops found reduced prick-test results in only 3 of the 12 selected studies [33].

SIT efficacy assessment could be based on measuring nasal secretion Th2 cytokines and effector-cell activation proteins (tryptase, eosinophil cationic protein) [50]; these potential markers require testing in future trials [6].

2.3.5. Tolerance and compliance

SIT incurs a risk of severe systemic reaction, depending on type of SIT, allergen, initiation phase protocol and severity of allergy. Local reactions are frequent in SCIT, in 26–86% of injections, but are often well-tolerated [6]. The 2007 *Cochrane* review of SCIT, including 13 studies with 557 patients, reported severe anaphylactic reaction requiring adrenaline in 3.5% of cases [13]. A similar rate was reported in a multicenter study including 17,526 injections in 423 patients [51]. In 70% of cases, such severe reactions occur within 30 minutes of injection, confirming the surveillance period recommended in SCIT by the EAACI. A review of severe adverse events in SCIT estimated mortality at 1/2,000,000 injected doses [52].

SLIT is well-tolerated and risk is limited. A review of the literature on adverse effects in SLIT (drops and tablets) in 4378 patients (the equivalent of 1,181,000 doses) mainly highlighted oral mucosa reactions, found in 40–75% of cases, especially in the initiation phase. Systemic gastrointestinal reactions were also observed. There were 11 severe anaphylactic reactions (0.2% of patients) on the WAO criteria in patients undergoing deviant protocols with non-standard doses or overdose and in patients with history of intolerance on previous SCIT [41]. Although SLIT can be considered the safer technique, reliable comparison of tolerance between SLIT and SCIT would require exhaustive analysis of pharmacovigilance data, taking account of the heterogeneity of treatments and protocols [41]. Treatment- and patient-related factors for severe reaction have been identified: overdose, interruption then resumption of treatment, history of severe reaction, significant local reaction, oral lesion or infection, severe or non-controlled asthma, and period of intense allergen exposure.

SIT efficacy requires optimal compliance. A review of 81 double-blind randomized trials against placebo including 9998 patients treated by SLIT (drops or tablets) reported 14% abandon in both treatment and placebo arms. Rates were higher for study periods exceeding 12 months, for SLIT by tablets or in case of adverse events [53]. A retrospective analysis conducted in the Netherlands, including 6486 patients receiving SIT between 1994 and 2009, showed that real-life compliance was much poorer: only 18% of patients completed the 3-year course (23% with SCIT, 7% with SLIT) [54]. These findings underscore the need for regular follow-up and patient information regarding usual adverse effects to improve compliance in clinical practice.

2.4. SIT impact on allergic disease

Allergic disease is an entity involving both the upper and lower airway [55]. When rhinitis precedes onset of asthma, SIT might delay or prevent this occurrence. The PAT (Preventive Allergy Treatment) randomized study in 205 6- to 14-year-olds presenting with allergic rhinitis implicating grass or birch pollen found significantly less asthma onset in patients without prior bronchial involvement with 3 years' SIT as compared to controls [56]. The effect persisted at 10 years post-protocol. A preventive action of SLIT against onset of asthma remains to be determined [16]; preliminary results

Table 2
Studies comparing clinical efficacy between SLIT and SCIT.

Authors	Date	Design	Number	Age (years)	Allergen	Duration	Conclusion
Bernardis et al. [36]	1996	Open, controlled, without placebo	23	5–26	<i>Alternaria tenuis</i>	2 yrs	SLIT > SCIT
Quirino et al. [37]	1996	RCT, double administration, without placebo	20	13–39	5 grasses	1 yr	SLIT = SCIT
Mungan et al. [38]	1999	RCT, single-blind, vs. placebo	36	18–46	<i>Der p</i> , <i>Der f</i>	1 yr	SLIT = SCIT
Khinchi et al. [39]	2004	RCT, double administration, vs. placebo	58	20–58	Birch	2 yrs	SLIT = SCIT
Mauro et al. [40]	2007	RCT, without placebo	47	18–59	Birch + hazet	Not specified	SLIT = SCIT

SLIT: sublingual immunotherapy; SCIT: subcutaneous immunotherapy; Der p: *Dermatophagoides pteronyssinus*; Der f: *Dermatophagoides farinae*; RCT: randomized clinical trial; yr(s): year(s).

awaiting publication from the GAP (Grazax Asthma Prevention) study comparing SLIT tablets versus placebo in 812 5–12-year-old patients seem not to be in favor of preventive efficacy. Kristiansen et al.'s 2016 meta-analysis of 17 double-blind randomized trials against placebo confirmed the PAT findings for the short-term, but long-term benefit seemed uncertain [57].

In confirmed asthma associated with allergic rhinitis, SIT may be of therapeutic benefit at both sinonasal and bronchial levels. Virchow et al., in 834 adults presenting with asthma and house dust mite-related allergic rhinitis, found reduced exacerbation of asthma after ≥ 7 months' SLIT by tablets [58]. Mosbech et al. reported reduced inhaled corticosteroid requirement to control asthma associated with house dust mite-related allergic rhinitis after SLIT by tablets [59]. The ARIA guidelines suggested that SIT could be implemented in allergic rhinitis associated with asthma, although the level of evidence was low [1].

SIT may also prevent the development of new sensitization. In a study of 147 children with rhinitis implicating monosensitive house dust mite allergy, 75% of those receiving 5 years' SCIT developed no new sensitizations, compared to 46% of controls [60]. Eng et al. reported similar findings for 3 years' SCIT in rhinitis implicating grass pollen allergy; effects persisted at 12 years' follow-up [44]. Comparable studies focused on SLIT. An open trial in 216 children with monosensitive (house dust mite, pollen or birch) allergic rhinitis receiving 3 years' SLIT drops versus medical treatment found 3.1% versus 34.8% new sensitization respectively [61]. Kristiansen et al.'s meta-analysis confirmed these findings in the short-term, without tangible proof of persistent benefit over the long-term [57].

3. Conclusion

The present literature review confirms the efficacy of SIT in allergic rhinitis in terms of functional improvement and reduced symptomatic medication. It further prevents onset of asthma and new sensitizations, although these benefits need confirming over the long-term. The possibility of primary prevention of pneumoallergen sensitization in at-risk children is under investigation [62].

SIT administration has been facilitated by the development of the sublingual forms. Implementation and tolerance make these an option of choice. The recent introduction of tablet forms for grass pollen and soon for house dust mite-related allergic rhinitis makes this treatment even more accessible. New tablets are under assessment for birch pollen [63] and ragweed allergic rhinitis [64].

These findings should encourage ENT physicians to get involved in this field of treatment. Teamwork with an allergologist, however, remains mandatory in complex cases such as food allergy or discrepancy between clinical and Prick-test data. Acquiring this skill will enable the ENT specialist to ensure global management of allergic rhinitis by SIT, from clinical (positive and differential) and biological diagnosis to both symptomatic (medical and surgical) and etiological treatment.

Disclosure of interest

The authors declare that they have no competing interest.

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