



SLIT's Prevention of the Allergic March

Federica Porcaro¹ · Giovanni Corsello² · Giovanni Battista Pajno³

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Abstract

Purpose of Review The progression of atopic disorders from atopic dermatitis in infants to allergic rhinitis and asthma in children, adolescents, and adults defines the allergy march. Allergen immunotherapy is the only causal treatment altering the immunological mechanism underlying the allergic diseases. The sublingual administration route is more acceptable than the subcutaneous one in pediatric age.

Recent Findings Several studies show the efficacy and safety profile of sublingual immunotherapy (SLIT) for the treatment of respiratory allergy diseases, but few data are available on its effect of primary and secondary prevention of allergic disease.

Summary The purpose of this manuscript is to review the latest studies addressing the effect of SLIT on the development of new sensitizations in not sensitized or already sensitized patients and progression of the allergy march.

Keywords Allergic march · Allergen immunotherapy · Sublingual immunotherapy · Primary prevention · Secondary prevention

Abbreviations

SLIT	sublingual immunotherapy
AD	atopic dermatitis
AR	allergic rhinitis
SIT	specific allergen immunotherapy
AIT	allergen immunotherapy
SCIT	subcutaneous immunotherapy
WHO	World Health Organization
EAACI	European Academy of Allergy and Clinical Immunology
TEWL	transepidermal water loss
TSLP	thymic stromal lymphopoietin
DBPC	double-blind placebo control

RCTs	randomized clinical trials
HDM	house dust mite
TGF- β	transforming growth factor
CCTs	controlled clinical trials
OIT	oral immunotherapy
EPIT	epicutaneous immunotherapy
QoL	quality of life
EE	eosinophilic esophagitis
FA	food allergy
JCP	Japanese cedar pollen
MCh	methacholine
ECP	eosinophil cationic protein
SPT	skin prick tests

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✉ Federica Porcaro
federica.porcaro@opbg.net

¹ Respiratory Unit, Pediatric Pulmonology & Respiratory Intermediate Care Unit, Sleep and Long Term Ventilation Unit, Academic Department of Pediatrics, Bambino Gesù Children's Hospital, Piazza S. Onofrio 4, 00165 Rome, Italy

² Neonatal Intensive Care Unit, A.O.U.P. "P. Giaccone", Department of Sciences for Health Promotion and Mother and Child Care "G. D'Alessandro", University of Palermo, Via Alfonso Giordano n. 3, 90127 Palermo, Italy

³ Allergy Unit, Department of Pediatrics, University of Messina, Messina, Italy

Introduction

During the past four decades, an increased prevalence of allergic disease—including atopic dermatitis (AD), rhinitis and/or conjunctivitis, asthma, drug, food or venom insect allergy, urticaria, and angioedema—has registered [1].

Among allergic diseases, the respiratory ones are the most common chronic diseases affecting up to 30% of the general population [2, 3].

Data suggest that a sequence of allergy manifestations, characterized by the progression from AD to allergic rhinitis (AR) and asthma, can occur in atopic patients [4–6].

Current guidelines recommend a combination of allergen exposure avoidance, medical treatment, and specific allergen immunotherapy (SIT) to manage allergy affected patients [7, 8•, 9•, 10•].

Because of allergen avoidance and pharmacotherapy are to some extent insufficient to obtain symptoms control and fail to prevent atopic march progression [11], scientific community draw more attention to the allergen immunotherapy (AIT). It is the only causal treatment affecting the immunological mechanisms underlying allergic disease and altering the progression of allergic march by the induction of immune tolerance [12].

AIT has traditionally been administered by subcutaneous injections (SCIT) and its efficacy has been demonstrated in AR and asthma treatment [13•, 14•]. The need of regular administration at a clinician's office over a period at least of 3 years and the potentially risk of serious systemic allergic reactions often represented barriers to its completion and patient medication adherence [15–17].

Therefore, other administration routes have been investigated and the sublingual one has been considered a viable treatment for allergic respiratory diseases.

Except for the first dose given in hospital setting and under medical supervision, subsequent doses of sublingual immunotherapy (SLIT) can be self-administered by patients or caregivers. Due to the easy administration and the lower risk of systemic allergy reactions, it is more accepted than SCIT by young patients and their parents.

In 1998 and 2009, also, the World Health Organization (WHO) recognized the promising role of SLIT and encouraged clinical investigation into this form of treatment [18, 19, 20]. In addition, in 2018, the European Academy of Allergy and Clinical Immunology (EAACI) published guidelines on AIT (SCIT plus SLIT) in order to inform and facilitate high quality clinical practice for AIT [21•].

Although data are available on efficacy and safety of SLIT, just a small number of studies have addressed the question of whether oral forms of immunotherapy can be used to alter disease progression or prevent the onset of other allergic diseases. The aim of this review is to discuss the knowledge on the mechanism underlying the allergic march and the potential preventative effects of SLIT.

Allergic March

The concept of the “allergic march” is used to describe the progression of atopic disorders from AD in infants to AR and asthma in children, adolescents, and adults [22•]. Indeed, atopic manifestations may persist for several years or sometimes resolve with increasing age [23].

A definition of “atopy” was provided by the EAACI [24] in order to allow understanding of the atopic march. Atopy is defined as a personal and/or familial tendency to produce

IgE antibodies and sensitization in response to low doses of allergens. Therefore, the atopic predisposition increases the risk of developing all atopic diseases. The temporal presentation of allergy diseases in the atopic march may not be the usual progression from AD to asthma because their development or outgrow is strongly influenced by both genetic and environmental factors [25].

One current hypothesis on potential biological mechanisms for the atopic march is that allergen penetration through a defective skin barrier can lead to transcutaneous sensitization initiating the atopic march [26].

Some studies have highlighted that IgE sensitization to food or inhalant allergens is an important risk factor for progressing in the atopic march in patients with AD if compared with those with AD and without IgE sensitization [27–29].

The risk of asthma is also strictly related to severity of eczema and clinical expression of allergy sensitization [30–32]. Furthermore, it is observed that patients with impaired skin barrier have increased total IgE and airway hyper-reactivity even in the absence of asthma symptoms [33].

These findings suggest that sensitization through the skin precedes airway sensitization [34] and that IgE-associated AD is the initial step of the atopic march predicting the development of childhood AR and asthma [35]. As allergic rhinitis is also a risk factor for lower airway reactivity and asthma, it can precede asthma onset in the atopic march [36, 37, 38•].

Many factors contribute to skin barrier impairment through which allergen sensitization occurs. Reduced expression of two cornified-envelope proteins (loricrin and involucrin) [39, 40], lipid (ceramide and sphingosine) [41], and dysfunctional filaggrin [42] allows the increased transepidermal water loss (TEWL) contributing to skin barriers impairment. Filaggrin mutations are involved both in acute than in chronic lesions. Patients carrying filaggrin mutations are significantly associated with the extrinsic form of the disease and are at risk of allergic rhinitis and asthma [43–45].

Expression of filaggrin, loricrin, and involucrin genes is down-regulated by Th2 cytokines (IL-4 and IL-13) [46, 47], suggesting that protein defects can develop as genetic and/or acquired defect.

Also AD keratinocytes produce a pattern of cytokines including IL-13, thymic stromal lymphopoietin (TSLP), and chemokines promoting Th2 inflammatory response in acute AD lesions followed by prominent Th1 inflammatory response that characterizes chronic AD lesions [48].

Bacterial and viral agents are adjunctive factors contributing to the activation of increased Th2 inflammatory response, to worsening AD and promoting respiratory allergy progression [49, 50].

Interventions of primary prevention that maintain and improve skin barrier function in infants not yet sensitized could

be useful to prevent the onset of new allergen sensitizations [51•], but the available evidence is still insufficient to make any recommendations.

Secondary prevention strategies, including AIT, may be possible to prevent new allergen sensitizations and the development of allergic rhinitis and asthma in patients affected by extrinsic form of AD.

SLIT

The first clinical trial on mucosal SLIT was reported by Black [52] and Feinberg [53] almost 80 years ago. The first double-blind placebo control (DBPC) randomized clinical trial (RCT) using low dose of house dust mite (HDM) allergen for SLIT was published in 1986. Authors concluded that SLIT was effective in reducing symptoms in 72% patients compared with controls [54]. Since then, the interest for SLIT for the treatment of respiratory allergies increased and several studies have been carried out. So, in 1998 and 2009, the WHO recognized the efficacy and safety of SLIT, concluding that SLIT was an acceptable method of AIT administration [18, 20].

Since then, several studies were carried out and information on mechanisms of action, and short- and long-term effects of SLIT were acquired.

SLIT consists of the sublingually (oral) administration of a certain quantity of allergen extract known to cause the allergy. The allergen is primarily taken up by dendritic cells in the oral mucosa and presented to T cells in the draining lymph nodes. After allergen presentation to T cells, T regulatory cells are activated and start to secrete interleukin (IL)-10 and transforming growth factor (TGF)- β , which induce the IgG, primarily the IgG4 subtype, and IgA antibodies production by B cells. Antigen-specific IgG antibodies can antagonize and block the allergic inflammation cascade resulting from antigen recognition by IgE. In addition, T regulatory cells down-regulate cytokine production in T helper (Th)2 cells, thus suppressing IgE production.

Both TGF- β and IL-10, directly or indirectly, suppress mast cells, basophils, and eosinophils that are the effector cells involved in the allergic inflammation [55].

Due to the lower number of mast cells within the oral and sublingual mucosa, lower rates of adverse systemic allergic reactions are seen in patients treated with SLIT [56].

Currently, AIT is indicated in the treatment of pediatric allergic rhinitis and conjunctivitis with or without asthma, and evidence of one or few clinically relevant allergens for which IgE sensitization is documented. Nevertheless, the decision to start the treatment depends also on several factors, such as the preference and acceptability of patient and caregiver, the adherence to treatment, the severity of symptoms, and the efficacy of avoidance measures [57••].

In addition, food allergy (FA) can be considered as a potential indication of AIT. Nurmatov and colleagues conducted a recent meta-analysis on 31 studies, including 25 RCTs and six non-randomized controlled clinical trials (CCTs) investigating the role of OIT, SLIT, or EPIT in children and adults with IgE-mediated FA. The study reported the evidence that AIT may be effective in raising the threshold of reactivity to foods in patients with IgE-mediated FA both during treatment and after its discontinuation [58••].

Different formulations of allergens are used including SLIT tablets and aqueous or glycerinated liquid preparations. The tablets are held under the tongue at least 1 min or until fully dissolved; differently, the drops are held under the tongue for 1–2 min prior to being swallowed. Patient should be instructed not to ingest food or beverage for 5 min following dissolution of the tablet and swallowing of the drops.

Both for tablet and drop formulations, the first dose is administered at the clinician's office under medical supervision and patients should be observed for at least 30 min for signs of allergic reactions. Subsequent doses can be administered once per day at home by the patients or their caregivers [59••].

Efficacy of SLIT is widely documented and a recent meta-analysis of double-blind RCTs reports that treatment with SLIT results in a statistically significant reduction in symptoms and medication scores both in children than adults compared with placebo groups [14••, 60].

Several regimens of administration doses (pre-seasonal, co-seasonal, pre-co-seasonal, continuous) have been tested. Usually, a pre-seasonal administration is preferred (3 to 4 months prior to the allergen season for patients with pollen allergies), and treatment is maintained through the end of the pollen season in patients with pollens sensitization. Continuous SLIT administration is another option that is more effective than co-seasonal during the first year, but this schedule does not appear to be superior to pre-seasonal administration in the subsequent years [61, 62].

Continuously or intermittently (2-month treatment alternate to 2-month suspension) schedules are equally effective in reducing allergic symptoms and improving quality of life (QoL) in children with perennial allergen sensitization (HDM allergy) [63].

Even though the optimal duration of SLIT is not standardized, a treatment course of at least 3 years has demonstrated beneficial and persistent effects also after treatment completion [64].

Due to the absence of systemic exposure to intact allergens, SLIT has good safety and tolerability profile characterized by the significant low incidence of systemic allergy reactions compared with SCIT.

Nevertheless, local reactions are described and oral itching and swelling of the lips are the most common side effects [65,66,67]. Usually, this adverse effects tend to disappear and self-limit, but clinician should address the attention to

persistent and severe local reactions in order to establish the appropriate treatment (epinephrine) and the need of prosecution of SLIT [68,69,70,71••].

Finally, a possible association has been reported between eosinophilic esophagitis (EE) and oral immunotherapy with aeroallergen and food allergens [72–74]. The diagnosis should be ruled out in patients treated with SLIT and reporting severe or persistent gastroesophageal symptoms, including dysphagia or chest pain, and discontinuation of SLIT is recommended.

SLIT and Prevention of the Allergic March

Children with FA and AD usually experience spontaneous remission of allergy disease by the age of 3 years, but they are at risk of acquiring AR and/or asthma in childhood or adolescence [6].

Furthermore, patients with AR have a sevenfold increased risk of incident asthma in preadolescence, a fourfold increased risk in adolescence, and a twofold increased risk in adult age when compared to those without AR [75].

In addition, patients already sensitized have increased risk of developing new sensitizations compared with patients without previous sensitizations [76].

Therefore, prevention of allergic diseases, symptoms, and sensitizations remains the most attractive objective for allergologists.

Due to the strong association of atopic diseases and the mechanism of action of AIT, SIT is considered an interesting candidate for a successful preventive intervention in the atopic diseases progression.

A recent revision of “prevention” definition applied in allergy patients suggests two possible levels of prevention: (1) prevention of immunological sensitization in patient not sensitized (primary prevention) and (2) prevention of the development of disease in sensitized individuals, or prevention of the development of asthma in children with rhino-conjunctivitis, or prevention of new sensitizations in individuals who are already sensitized to one allergen (secondary prevention) [77].

Studies assessing the long-term effectiveness of AIT show that AIT might reduce the risk of developing asthma in children with allergic rhinitis [78, 79, 80, 81, 82, 83••] and new sensitization in already sensitized patients [84, 79, 85, 86, 87, 88, 89, 83••].

A 6-year study, involving 138 children sensitized only to HDM and suffering from intermittent asthma, randomized patients to receive SCIT or pharmacotherapy for 3 years: at the end of the study, the rate of new sensitization in SCIT group was 24.6% compared to 66.7% in the control group [89]. The low rate of new sensitizations is well described in children mono-sensitized to HDM [79, 84, 85, 88, 89] than those with pollen sensitization [85–87].

Even if the proposed studies concern the subcutaneous administration (SCIT), several data are available also for the oral and sublingual administration routes.

The role of SLIT altering the atopic march raised the interest of the scientific community and overall, 17 studies addressing the topic are available in scientific literature and summarized in Table 1 and commented below.

Primary Prevention

The potential effects of oral AIT for the primary prevention of allergic disease (atopic eczema, FA, sensitizations, wheeze) is considered in a recent prospective, randomized, double-blind, placebo controlled study. Children not sensitized and considered at high risk of atopy, due to their family history of allergic diseases, were randomized to receive oral HDM AIT (drops) or placebo twice daily for 1 year. No significant difference in the active and placebo group was seen concerning the development of sensitization, AD, FA, and wheeze at the end of trial [90].

Therefore, the available data are still insufficient to support the role of AIT in the reduction of the risk of developing a first allergic disease in patients at risk of atopy.

Secondary Prevention

According to the recent revision proposed by Larsen and colleagues, the secondary prevention expresses on three levels. The first one consists in the prevention of the development of disease in sensitized individuals.

About this topic, Yamanaka randomized adult asymptomatic patient already sensitized to Japanese cedar pollen (JCP) to receive JCP extract or placebo, both administered sublingually for 2 years. At the end of the study, the ratio of development of cedar pollinosis was significantly lower in the SLIT group compared to the placebo, demonstrating the possible role of SLIT in the prevention of allergy symptoms in sensitized patients [91].

Conversely, more data are available on the role of AIT in the prevention of the development of asthma in children with allergic rhino-conjunctivitis.

The first study published in 1986 by Moller and colleagues randomized 30 children with AR and birch pollen sensitization to receive enteric-coated capsules containing birch pollen extract. None of the “active group” patients developed asthma compared to six patients (6/16) of the “control group” at the end of 10-month treatment period [92].

A retrospective survey, including 301 AR and/or asthma affected patients treated with SLIT for 2 years, analyzed the appearance of asthma symptoms in “non-asthma patients.” Only 1% of non-asthma patients reported an onset of respiratory symptoms at the end of the follow-up period of 5 years [93].

Table 1 Studies assessing the role of SLIT in altering the progression of atopic march

Authors	Study type	Patients	Formulation	Extracts	Treatment duration	Follow-up	Results
Moller, 1986 [92]	DBPCT	14 with AR treated with OIT	Enteric-coated capsules	Birch pollen	10 months	NA	None of the treated children developed asthma
Madonini, 2003 [93]	Retrospective survey	16 with AR treated with placebo 301 with AR and/or asthma treated with SLIT	Drops	Grass pollen, parietaria pollen, and HDM	2 years	5 years	Only 1% of non-asthma patients had respiratory symptoms; only 9.6% of patients undergoing new SPT had new sensitizations
Di Rienzo, 2003 [94]	Prospective, open, parallel group trial	35 with AR and/or mild asthma treated with SLIT 25 with AR and/or mild asthma treated with placebo	Drops	HDM	4–5 years	10 years	Significant difference vs. baseline for the presence of asthma ($P \leq 0.001$) in the SLIT group. No difference in the control group. The mean PEF was significantly higher in the active group than in the control group after 10 years. No difference was observed for new sensitizations. Specific IgE showed a near-significant increase (baseline vs. 10 years, $P = 0.06$) only in the control group
Novembre, 2004 [95]	Multicenter, randomized, open-controlled study	54 with AR treated with SLIT 59 with AR treated with placebo	Drops	Grass pollen	Co-seasonal administration (6 months)	3 years	Asthma development after 3 years was 3.8 times more frequent (95% confidence limits, 1.5–10.0) in the control subjects
Marogna, 2004 [96]	Randomized, open, controlled trial	271 with RA with/or without asthma treated with SLIT 170 with RA with/or without asthma treated with placebo	Drops	HDM or pollens	3 years	3 years	The number of patients with a positive MCh challenge decreased significantly after 3 years only in the SLIT group. New skin sensitizations appeared in 38% of the controls and in 5.9% of the SLIT patients ($P = 0.01$)
Marcucci, 2005 [98]	DBPCT	13 with RA with/or without asthma treated with SLIT for 3 years 11 with RA with/or without asthma treated placebo for 1 year then with SLIT for 2 years	Drops	HDM	2–3 years	3 years	Nasal ECP and nasal tryptase after specific nasal provocation tests were significantly reduced as compared to baseline values ($p = 0.0043$ and 0.0195 , respectively) in the third year of active treatment. In placebo treated patients all these parameters tended to decrease only after switching to active treatment
Marogna, 2008 [97]	RCT	144 with AR with/or without asthma treated with SLIT or SLIT + drugs 72 with AR with/or without asthma treated with drugs	NA	NA	3 years	3 years	New sensitizations appeared in 34.8% of controls and in 3.1% of SLIT patients (odds ratio, 16.85; 95% confidence interval, 5.73–49.13). Mild persistent asthma was less frequent in SLIT patients (odds ratio, 0.04; 95% confidence interval, 0.01–0.17). The number of children with a positive MCh challenge result decreased significantly after 3 years only in the SLIT group
Marogna, 2010 [64]	Prospective open controlled study	47 with RA treated with SLIT 12 with RA treated with placebo	Drops	HDM	3, 4, 5 years	15 years	New sensitizations occurred in all the control subjects over 15 years and in less than a quarter of the patients receiving SLIT (21%, 12%, and 11%, respectively)
Garcia, 2010 [103]	DBPCT	33 with peach allergy treated with SLIT	Drops	Peach	6 months	NA	

Table 1 (continued)

Authors	Study type	Patients	Formulation	Extracts	Treatment duration	Follow-up	Results
Holt, 2013 [99]	Multicenter, DBCT	16 with peach allergy treated with placebo 25 with AD or FA sensitized to egg white, cow's milk, peanut, or soybean treated with OIT 26 with AD or FA sensitized to egg white, cow's milk, peanut, or soybean treated with placebo	Tablets	Mix of timothy grass, cat, house dust mite	12 months	3 years	IgE to other purified allergens did not change significantly and no relevant neosensitizations were detected Participants with allergic sensitization at 36 months: 22 in active and 19 in placebo group (p 0.28, OR 2.3, CI95% 0.5 to 10.5). Participants with current asthma at 36 months: 4 in both active and placebo group (p 0.85, OR 1, CI95% 0.2 to 6.1)
Szepfalusi, 2014 [104]	DBPCT	15 asymptomatic and mono/oligosensitized treated with SLIT 16 mono/oligosensitized treated with placebo	Drops	HDM or grass pollen	2 years	2 years	The rate of allergen-specific sensitization (specific IgE and SPT reactivity) was comparable in the treatment and the placebo group
Zolikipi, 2015 [90]	Prospective, DBPCT	111 at risk of atopy treated with OIT	Drops	HDM	12 months	12 months	No significant preventive effect was observed on HDM sensitization or allergy-related symptoms
Yamanaka, 2015 [91]	Multicenter DBPCT	13 asymptomatic, sensitized to Japanese cedar pollen treated with SLIT 14 asymptomatic, sensitized to Japanese cedar pollen treated with placebo	Drops	JCP	Co-seasonal for 2 years	2 years	The ratio of development of cedar pollinosis was significantly lower in the SLIT group compared to the placebo group
Lim, 2017 [105]	Prospective cohort study	37 with AR treated with SLIT 184 treated with pharmacologic therapy	Drops	HDM	3 years	3 years	New-sensitization rate other than HDM between SLIT and non-SLIT group did not show any significant differences
Valovirta, 2011 [100], 2017 [101]	Multinational, parallel group, DBPCT	406 with RA without asthma treated with SLIT 406 with RA without asthma treated with placebo	Tablets	Grass pollen	Continuous for 3 years	5 years	Reduced risk of asthma symptoms in the active group at the end of trial, during the 2-year follow-up period and during the entire 5-year trial period
Zielen, 2018 [102]	Retrospective study	2851 with AR treated with SLIT 71,275 with AR treated with placebo	Tablets	Grass pollen	NA	NA	Asthma onset was less frequent in SLIT group than in non-SLIT group (odds ratio: 0.696, $P = .002$), and time to asthma was significantly longer (hazard ratio: 0.523; $P = .003$)

The preventive effect on asthma has been also investigated in a prospective study on 60 children with HDM sensitization. Patients with RA and/or mild asthma were divided in two groups: 35 treated with SLIT for 4–5 years and 25 treated only with drugs. Subjects in the treatment group presented a reduced incidence of asthma ($P < 0.01$) and a better PEF values, while no difference was observed in the control group at the end of 10-year follow-up period [94].

A multicenter, randomized, open-controlled study evaluated 113 children with grass pollen allergy and rhinitis: 54 patients received SLIT drops co-seasonally and 59 were treated with convention pharmacotherapy. At the end of the 3 year trial, the control group presented a 3.8 times greater risk of developing asthma compared with the active group [95].

Marogna and colleagues showed a decrease response to methacholine (MCh) challenge in RA affected patients with or without asthma treated with SLIT after 3 years of treatment [96]. In a second randomized controlled trial carried out by the same authors, 216 children with AR and with or without intermittent asthma were randomized to SLIT or conventional pharmacotherapy for a period of 3 years. The authors found a lower occurrence of mild persistent asthma in the SLIT group compared with the control group (OR = 0.04; 95% CI 0.01–0.17) and also, the number of children with a positive MCh challenge was lower in the SLIT group [97].

In the study proposed by Marcucci and colleagues, 24 patients sensitized to HDM and with RA with/or without asthma were treated with SLIT for 3 years or placebo for 1 year then switched to SLIT for 2 years. The study demonstrated that nasal eosinophil cationic protein (ECP) and tryptase after specific nasal provocation tests was reduced in the third year of active treatment. In placebo-treated patients, all these parameters tended to decrease only after switching to active treatment. Also, these results support indirectly the potential role of AIT in altering the atopic march [98].

The multicenter, double-blind, controlled trial carried out by Holt in 2013 showed different results: 51 patients with AD or FA sensitized to egg white, cow's milk, peanut, or soybean were randomized to receive OIT with mix of timothy grass, cat, and HDM. The therapy was administered for 12 months and patients were followed for 3 years. At 36 months, no statistically differences were detected concerning the development of asthma symptoms in both active and placebo group ($P = 0.85$, OR 1, 95% CI 0.2 to 6.1) [99].

A more recent study proposed by Valovirta enrolled 812 children with RA without asthma and sensitized to grass pollen and randomized them to SLIT or placebo. The therapy was administered for 3 years, and patients were followed overall for 5 years. Authors concluded that risk of asthma symptoms in the active group at the end of trial was reduced, during the 2-year follow-up period and during the entire 5-year trial period [100, 101].

Finally, a retrospective study carried out by Zielen and colleagues analyzed a large sample of patients sensitized to grass pollen with AR and without asthma that received SLIT or placebo. Also, in this case, asthma onset was less frequent in SLIT group than in placebo (odds ratio 0.696, $P = .002$) and also, the time to asthma was significantly longer (hazard ratio 0.523; $P = .003$) [102].

SLIT and Prevention of New Sensitizations

Developing new sensitizations is very frequent in the natural history of respiratory allergy. Therefore, the issue of preventing new sensitizations in individuals who are already sensitized to one allergen by AIT was investigated in various studies. Overall, limited to SLIT, nine studies addressing this topic are selected by revision of literature.

The retrospective survey proposed by Madonini showed that only 9.6% of all patients treated with SLIT and undergoing new skin prick tests (SPT) showed new sensitizations during the 5 years follow up period [93].

Another study showed no difference for new sensitizations in SLIT and placebo group at the end of the observation period, even if specific IgE showed a near-significant increase only in the control group [94].

Marogna and colleagues addressed the topic in three studies. New skin sensitizations appeared in 38% of the controls and in 5.9% of the SLIT patients ($P = 0.01$) during the 3-year period of treatment [96]. Similar data were detected in a second study, where new sensitizations appeared in 34.8% of controls and in 3.1% of SLIT patients (odds ratio, 16.85; 95% confidence interval, 5.73–49.13) [97]. In the last study published in 2010, new sensitizations occurred in all the control subjects over 15 years and in less than a quarter of the patients receiving SLIT for 3, 4, or 5 years (21, 12, and 11%, respectively) [64].

Garcia enrolled 49 patients with peach allergy that were randomized to SLIT with peach extract and placebo administered for 6 months. IgE to other purified allergens did not change significantly, and no relevant neo-sensitizations were detected in both group at the end of the study [103].

In the study proposed by Holt and colleagues, the number of participants with AD and FA, already sensitized to food allergens and randomized to SLIT or placebo, showed no statistical difference of allergic sensitization at 36 months [99].

Also, the study conducted by Szepefalusi showed that the rate of allergen-specific sensitization (specific IgE and SPT reactivity) was comparable in active and placebo group consisting of mono/oligosensitized asymptomatic patients underwent to treatment for 2 years [104].

Finally, in a recently published prospective cohort study, 221 patients with RA were randomized to receive SLIT with HDM extract or pharmacotherapy for 3 years. At the end of the study, the new-sensitization rate other than HDM between

active and control group did not show any significant differences [105].

Conclusions

The feasibility of the administration through the sublingual route, the possibility of administration of subsequent doses at home, the good efficacy, and safety profile make SLIT a preferable tool for the treatment of respiratory allergy diseases.

The results of preventive intervention studies provide sufficient evidences on the effective role of AIT in haltering the natural history of allergic respiratory diseases, even if it is unclear whether this benefit is maintained over the longer term.

Some evidence are also available in favor of a reduced risk of developing new sensitizations in patients who are already sensitized to one allergen (HDM), at least over the short period, but none on the long-term.

Currently, insufficient data are available on the preventive role of SLIT in the development of allergic disease in healthy individuals with atopy risk.

Even though, due to design heterogeneity of proposed studies, the evidence on preventive and long-term effects of AIT is suggestive but not definitive yet. Therefore, further standardized studies are needed to verify the preventive effect of SLIT on the development of new sensitizations and progression of the allergy march.

Compliance with Ethical Standards

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

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- Of importance
- Of major importance

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