

Clinical practice

Allergen-specific immunotherapy in children: facts and FAQs

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Received: 13 September 2010 / Accepted: 4 November 2010
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Abstract Allergen-specific immunotherapy (SIT) in its various application forms represents the main treatment approach of IgE-mediated allergic diseases in adults and children. Despite this clear recommendation, many particularities of products, patient characteristics, and product availability in different countries hamper the use of allergen-specific immunotherapy in particular in children. The frequently asked questions by parents, patients, and physicians are the backbone of this review. Thus, the potentials and limitations of allergen-specific immunotherapy in children and adolescents will be highlighted. IgE-mediated allergic diseases are affecting about 20% of the population. They manifest commonly early in life, and hence, the use of SIT should be considered also early in the course of the disease.

Keywords Allergen-specific immunotherapy · SIT · SCIT · SLIT · Immunotherapy · Allergen · IgE-mediated allergy · Allergy

Abbreviations

SIT	Allergen-specific immunotherapy
SLIT	Sublingual allergen-specific immunotherapy
SCIT	Subcutaneous allergen-specific immunotherapy
Allergoids	Chemically modified allergen extracts

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Introduction

The concept of allergen-specific immunotherapy (SIT) for the treatment of allergic diseases is a hundred years old. Over the past decades, the rapidly growing body of scientific data, novel treatment strategies, and frequently changing recommendations as well as guidelines have been overwhelming. Especially in pediatric patients, the decision whether or not a SIT should be started is complicated by additional practical issues such as choice of the right compound and application route or the minimum age to start SIT. This is of particular importance since SIT represents to date the only causal treatment approach. We thus decided to structure this review based on frequently asked questions (FAQ) by parents, patients, and physicians (Table 1).

Frequently asked questions about allergen-specific immunotherapy

1. Indications. When should SIT be considered?

Allergic rhinitis and conjunctivitis, episodic and mild-persistent allergic bronchial asthma, and insect venom allergy are clear indications for a SIT in children, given:

- Evidence for IgE-mediated sensitization (skin prick test (SPT) and/or in vitro specific IgE) and clear association of clinical symptoms with allergen exposure
- Availability of a standardized and high-quality allergen extract
- Evidence for safety and efficacy of the particular SIT compound for the particular indication
- Inefficient or non-feasible allergen avoidance measures

Table 1 Physicochemical characteristics of allergenic extracts marketed in Austria by 2009 (modified from [136])

Extract	Extract denomination	Physically bound	Application route	Products
Unmodified	Aqueous	–	s.c.	ALK wässrig® (bee/wasp)
		–	s.c.	Venomenhal® (bee/wasp)
		–	s.l.	Oralvac plus® (pollen, HDM, animal dander, molds)
		–	s.l.	Sublivac® (pollen, HDM,...)
		–	s.l.	Staloral 300® (pollen, HDM, animal dander, molds)
		–	s.l.	PangraminSLIT® (pollen, HDM, animal dander, molds)
		–	s.l.	Novo-Helisen® oral (pollen, HDM, animal dander, molds)
		–	s.l.	SLIT®one (pollen, HDM, animal dander, molds)
		–	s.l.	Grazax® (grass pollen)
	Semidepot	L-Tyrosine	s.c.	Tyro-SIT® (pollen, HDM, animal dander, molds)
		Aluminum hydroxide	s.c.	Depot-HAL® F.I.T. (pollen, HDM, animal dander, molds)
		–	s.c.	Alutard SQ® (pollen, HDM, animal dander, bee/wasp)
		–	s.c.	Novo-Helisen® Depot (pollen, HDM, animal dander, molds)
Chemically modified	Formaldehyde	–	s.c.	Pangramin® (pollen, HDM)
		–	s.c.	Acaroid® (HDM)
		–	s.c.	Allergovit® (pollen)
	Glutaraldehyde	L-Tyrosine+monophosphoryl lipid A	s.c.	Pollinex Quattro® (pollen)
		–	s.c.	Purethal® (pollen, HDM)

Classification of allergenic extracts was set according to chemically unmodified or modified (formaldehyde, glutaraldehyde), physically binding to aluminum hydroxide, L-tyrosine, L-tyrosine+monophosphoryl lipid A or no binding and application route

s.c. subcutaneous, s.l. sublingual

Insect venom allergy can occur at very young age. Is SIT to be started at any age?

The answer is yes. Between 0.8% and 5% of the general population suffers from systemic allergic reactions to wasp or bee stings [53, 123]. Subcutaneous allergen-specific immunotherapy (SCIT) is the only effective treatment option for insect venom allergy. SIT for insect venom allergens is more effective than SIT for respiratory allergies, and SIT for wasp venom is more effective than SIT for bee venom [90, 144, 146] with an overall response rate of 75–95%. An indication for a SIT requires a moderate systemic reaction on a bee or wasp sting and evidence for specific IgE antibodies to be involved (skin prick test or specific IgE detection). The restriction to moderate-to-severe systemic reaction as basis for a SIT indication results from self-limiting courses of insect sting allergy [52, 53]. Long-term efficacy of bee and wasp SIT has been demonstrated in particular for children even after termination of the treatment [53]. Rush- as well as ultra-rush therapies can be applied safely in children and adolescents [75, 133]. Repeated insect sting challenge tests to evaluate the need for SIT are controversial [124] and are currently not recommended for diagnostic purposes [119]. In addition, due to the limited availability of bees and wasps, such

diagnostic insect sting challenges were also rarely performed in clinical practice [106, 155].

Shall SIT be considered in atopic eczema?

The answer is yes. In adults and children with relevant house dust mite allergy, SIT is an option to reduce eczema severity scores (SCORAD) and itch scores [23, 51, 76, 89, 98, 112, 153, 157]. Fewer data are available for grass pollen and cat allergy. Therefore, allergological societies have not yet released a general recommendation for a broad use of SIT in atopic dermatitis. On the other hand, there are no contraindications for SIT in atopic eczema patients with relevant house dust mite sensitization/allergy [156].

2. Contraindications. When is SIT not applicable?

Contraindications for a SIT in children are:

- Uncontrolled bronchial asthma
- Severe cardiovascular disease, treatment with beta-blocker
- Severe immunodeficiency and auto-immune disease
- Present malignancy
- Lack of compliance

3. Does SIT lead to a cure of allergy?

The answer is no. Although there is clear evidence for an improvement of quality of life, reduced medication scores (30–45%), and reduced clinical scores (45–60%) [2, 17, 25, 27, 30, 69, 70, 83, 84, 100, 158], clinical data from children and adults does not prove a true cure of allergy. Parents should be informed about this important fact before SIT is started.

4. Can all IgE-mediated allergic diseases be treated with SIT?

The answer is no. Best results in terms of safety and efficacy for SIT have been shown for allergic rhinitis, allergic conjunctivitis, mild-persistent allergic bronchial asthma, and insect venom allergy [1, 2, 17, 25, 27, 30, 40, 69–71, 83, 84, 100, 158]. Because of concerns of either efficacy or safety, SIT is currently not recommended for children and adults with IgE-mediated persistent food allergy, drug allergy, or severe-persistent allergic bronchial asthma [13, 26, 28, 49, 57, 61, 64, 79, 94, 116, 127, 131, 132].

Not all allergies to all allergens can be treated with SIT. The spectrum of allergies that can be treated with SIT is limited by the availability of standardized allergen extracts. Validated SIT compounds are available for tree pollen, grass pollen, insect venom, and house dust mite. For allergies to fur-bearing animals (cats, dogs), molds, and latex, SIT products are on the market [11, 12, 56, 77, 137, 138], but safety and efficacy data in children are scarcely available. Hence, most allergological societies do not recommend the use of these extracts [2, 17, 25, 27, 30, 69, 70, 83, 84, 100, 158].

5. Is SIT safe? How common are side effects?

SIT can be considered to be a safe treatment, but side effects do happen. In subcutaneous immunotherapy, minor side effects include local reactions at the injection site (soreness, swelling, and hyperemia) and mild systemic reactions (rhinitis and conjunctivitis, hives). Minor adverse events occur in 0.05–47% of patients [135]. In sublingual immunotherapy, in particular with the high-dose tablet, local oral side effects such as local swelling or itching are frequently observed within the first weeks of treatment. Patients and their caregivers need to be informed about these local reactions, and first dose should be given under medical surveillance [20]. Severe, life-threatening systemic adverse reactions occur very rarely in SCIT and scarcely in sublingual allergen-specific immunotherapy (SLIT) [22, 85, 118]. According to the Paul Ehrlich Institute (1991–2000), the incidence of side effects was 0.002–0.0076% for non-modified allergen extracts and 0.0005–0.01% for chemically modified allergen extracts (allergoids) [81]. Nevertheless, since there is a potential risk of life-threatening adverse reactions during SCIT, medical

staff must be trained in handling such emergencies (for details, refer to “Who should perform SIT in children?”).

6. Is the mechanism of action of SIT known?

The answer of the first question is yes and no. Numerous immunological effects have been described during a successful SIT. However, there is currently no single parameter that could be used to predict or guarantee the success of a SIT. Immunological changes on T lymphocytes, B lymphocytes, monocytes [103, 104], basophils, eosinophils, and mast cells [24] have been well documented. The main effects on T and B lymphocytes are described in more detail.

1. T lymphocytes

- “Switch” of T-lymphocyte toward an IFN γ -dominated TH-1 response [10, 44, 66, 125], away from an allergy prone TH-2 response. It has to be acknowledged though that these changes have not been seen in all studies [47, 141, 150]
- Activation of regulatory T cells with predominant production of IL10 and transforming growth factor- β altogether promoting tolerance induction [3, 6, 10, 65, 78, 95, 122]
- Hyporesponsiveness of T cells upon stimulation with allergens [14, 43, 68, 86, 93]

2. B lymphocytes

- Induction of allergen-specific IgG (in particular IgG4) production, which is thought to be protective [3, 50, 65, 151] and has been linked to IL10 production
- Reduced allergen-specific IgE production with increasing age [5, 50, 74, 148]

There are no biomarkers to predict the clinical outcome of SIT. In the previous paragraph, we summarized immunological changes during successful SIT. Unfortunately, these immunological changes were neither seen in all clinical trials nor with all SIT products. Thus, no single or combination of biomarkers can predict the clinical success in the individual patient.

7. Should a specific application route (SLIT versus SCIT) be preferred in children?

Due to the lack of comparative studies in particular in children, this question cannot be answered correctly. Many clinical studies have been performed to assess safety and efficacy of either application route of SIT in children. Yet, systematic side-by-side comparisons of SCIT versus SLIT in children are still lacking [40]. We thus have to consider individual factors when deciding for either application route. First, the indication for SIT is crucial.

Seasonal allergic rhinitis In general, SLIT has been shown to be effective in seasonal allergic rhinitis [20, 32, 60, 147, 152]. However, some ineffective studies have also been reported [21, 113, 115]. SCIT, being the much older application form, has mainly been investigated in adults and adolescents. Data for the efficacy of SCIT in children are limited, and some authors even question its clinical efficacy in this age group at all [39, 46, 91, 113, 154].

Bronchial asthma Evidence for the efficacy of both SCIT and SLIT in bronchial asthma is scarce [20, 99, 134].

For perennial allergies to house dust mite, cat, and dog fur, for example, clinical data do not consistently support the use of SIT [54, 72]. For cat allergy, SIT might be considered when cat exposure cannot be avoided. Also for mold allergy, SCIT might be considered if exposure cannot be eliminated and a specific standardized extract is available [39, 58].

8. Are there any limitations for the use of SIT in children compared to adults?

The answer is yes and no. Many studies provide evidence for the safety and efficacy of various SIT compounds in adults and children likewise. However, in the past, it was common to extrapolate data from adult patients to children and adolescents. This practice turned out not to be applicable for many drugs in pediatrics. The European Commission recognized this crucial issue and fostered new legislation forcing companies to provide pediatric investigation plans whenever children/adolescents might benefit from a new drug formulation (EC No. 1901&1902/2006) [109].

The answer is yes because there are limitations, since not all SIT products on the market have been tested in children, and it is not known whether the dosage can be extrapolated from adult data.

The answer is no because besides the above-mentioned restrictions, there are no other limitations for SIT in children compared to adults (see “Contraindications. When is SIT not applicable?”). In contrast, there are even circumstances in which children might benefit from additional effects of SIT, in particular the prevention of new sensitizations or prevention of disease progression from allergic rhinitis to bronchial asthma.

The issue whether SIT can be started at preschool age is controversial. Most of the pediatric studies showing efficacy and safety of SIT have been conducted in children older than 5 years [16, 18]. On the other hand, young children represent a patient group, which might benefit from an additional, preventive effect of SIT. In allergic rhinitis patients, SIT reduced the incidence of bronchial asthma compared to the placebo group [62, 91]. Non-placebo-controlled studies in mono-/oligosensitized chil-

dren revealed that SCIT [34, 42, 59, 97, 110] and SLIT [35, 82, 107] can prevent the spreading of sensitizations. Therefore, many allergological societies recommend early treatment with SIT in order to prevent disease progression. However, randomized placebo-controlled studies are needed to justify this new indication as tertiary prevention measures in sensitized/allergic children.

9. Who should perform SIT in children?

All physicians with hands-on training in SIT should perform SIT if indicated. Systemic reactions after subcutaneous immunotherapy are rare and generally occur within the first 30 min after injection. Thus, patients must be monitored during this time for at least 30 min at the doctor's office. Physicians must be trained in treating anaphylactic reactions. Treatment ranges, depending on the severity of the reaction, from inhalation of beta-mimetics for mild adverse events to administration of epinephrine, inserting a venous line and giving i.v. fluids, steroids, and antihistamines as part of advanced life support measures [126, 128–130]. Adequate equipment and frequent emergency training for physicians and all involved caregivers are mandatory [121].

10. What kinds of SIT compounds are available?

SIT compounds comprise either unmodified, native allergen extracts in aqueous or physically bound form or chemically modified extracts (allergoids) in physically bound form (semidepot; Table 1, modified from [136]). All physically bound extracts are called semidepots. Chemically modified extracts have a reduced B cell epitope and IgE-binding capacity with an unaffected T cell recognition, altogether reducing the side effect potential. It cannot be stated yet whether unmodified or modified SIT compounds should be preferred, since no side-by-side comparative studies are available. Efficacy and safety data in children are available for many, but not for all products. Our recent survey on immunotherapy products for children licensed in Austria listed the clinical studies that have been performed with each IT product [136]. The aim of the consensus group was to promote the use of SIT for children whenever indicated and to particularly support products with documented clinical safety and efficacy in children and adolescents (Table 2, modified from [136]) [7, 9, 15, 19, 20, 29, 35–38, 41, 42, 45, 55, 59, 60, 67, 73, 87, 88, 91, 92, 96, 97, 99, 100, 105, 111, 114, 117, 120, 139, 142, 143, 147, 149, 159].

Discussion

Allergic diseases increased dramatically over the past decades. All age groups and practically all regions of the

Table 2 Pediatric SIT studies and SIT studies with inclusion of children/adolescents using marketed extracts in Austria by 2009 are referenced (modified from [136])

Subcutaneous	Marketed allergen extract	Licensed from age (years)	Pediatric study	Studies with children	Population	Indication	Control group	Allergen	Study conclusion
	ALK wässrig® (bee/wasp)	5		Wenzel, Allergy 2003	Children $n=?$, 10–76 years, $\xi=178$	Ana	retresp.	Bee and wasp venom	18% side effects with rush IT
	Venomenhal® (bee/wasp)	5			Children $n=136$, 5–18 years, $\xi=136$	A	o.k.	HDM	Efficacy doubtful
	Tyro-SIT® (pollen, HDM, animal dander, molds)	6			Children $n=85$, 6–45 years, $\xi=129$	A	P.k.	HDM	Safe, effective
	Depot-HAL® F.I.T. (pollen, HDM, animal dander, molds)	5	Zimmermann, Allergologie 1988		Children $n=39$, 3–16 years, $\xi=39$	A	P.k.	Grass pollen	Safe, effective
	Altard SQ® (pollen, HDM, animal dander, bee/wasp)	5	Roberts, J Allergy Clin Immunol 2006 Pajno, Clin Exp Allergy 2001 Möller, J Allergy Clin Immunol 2002		Children $n=134$, 5–8 years, $\xi=134$	R, A	o.k.	HDM	Prevention of new sensitization
					Children $n=205$, 6–14 years, $\xi=205$	R	o.k.	Tree and grass pollen	Prevention of asthma
				Dolz, Allergy 1996	Children $n=?$, 15–35 years, $\xi=30$	R	P.k.	Grass pollen	Safe, effective
			Valovirta, Annals of Allergy 1986		Children $n=27$, 5–18 years, $\xi=27$	A	P.k.	Dog dander	Safe, moderately effective
			Bertelsen, Allergy 1989	Sundin, J Allergy Clin Immunol 1986	Children $n=22$, $\xi=45$	A	P.k.	Cat and dog dander	Moderately safe, not effective
					Children $n=27$, $\xi=27$	A	o.k.	Cat and dog dander	Safe, effective
				Hedlin, J Allergy Clin Immunol 1991	Children $n=20$, 9–47 years, $\xi=32$	A	P.k.	Cat and dog dander	Safe, moderately effective
				Hedlin, J Allergy Clin Immunol 1995	Children $n=20$, $\xi=40$	A	P.k.	Cat and dog dander	Moderately safe, not effective
	Novo-Helisen® Depot (pollen, HDM, animal dander, molds)	5	Inal, J Invest All Clin Immunol 2007		Children $n=147$, 6–16 years, $\xi=147$	R, A	o.k.	HDM	Prevention of new sensitization
				Ullrich, Allergo J 2007	Children $n=96$, 5–71 years, $\xi=523$	R, A	n.k.	HDM, pollen	Safe, effective
			Cevit, J Invest All Clin Immunol 2007 Shim, Clin Exp Allergy 2003		Children $n=31$, 6–16 years, $\xi=31$	A	o.k.	HDM	Effective
					Children $n=14$, 6–13 years, $\xi=14$	A	n.k.	HDM	Histamine and SPT after SIT reduced
	Acaroid® (HDM)	6			Children $n=39$, 6–18 years, $\xi=39$	R, A	o.k.	Grass pollen	Safe, effective
	Allergovit® (pollen)	6	Keskin, Ped Allergy Immunol 2006 Eng, Allergy 2002		Children $n=23$, 5–16 years, $\xi=23$	R, A	o.k.	Grass pollen	Long-term effective (>6 years after SIT)
			Eng, Monatsschr Kind 1994 Eng, Allergy 2006		Children $n=28$, 7–16 years, $\xi=28$	R, A	o.k.	Grass pollen	Safe, effective
					Children $n=22$, 5–16 years, $\xi=22$	R, A	o.k.	Grass pollen	Long-term effective (>12 years after SIT)

Table 2 (continued)

	Marketed allergen extract	Licensed from age (years)	Pediatric study	Studies with children	Population	Indication	Control group	Allergen	Study conclusion
Sublingual	Pollinex Quattro® (pollen)	6		Zielen, Allergologie 2007	Children $n=422$, 6–18 years, $\xi=3114$	R, A	n.k.	Tree and grass pollen	Safe
				Drachenberg, Allergologia et Immunopathol. 2003	Children $n=90$, 6–17 years, $\xi=159$	R	n.k.	Tree and grass pollen	Safe
				Drachenberg, Allergologie 2001	Children $n=104$, 6–18 years, $\xi=1736$	R	n.k.	Tree and grass pollen	Safe
	Puretha® (pollen, HDM)	5		Ariano, Allergy 1999	Children $n=?$, 13–62 years, $\xi=25$	R	P.k.	<i>Parietaria</i> pollen	Safe, effective
				Brewczynski, Allergologie 1998	Children $n=?$, 14–32 years, $\xi=20$	R, A	P.k.	Grass pollen	Safe, effective
	Sublivac® (pollen, HDM,...)	5			Children $n=49$, 7–17 years, $\xi=49$	R, A	P.k.	Olive pollen	Safe, effective
	Staloral300® (pollen, HDM, animal dander, molds)	5	Vourdas, Allergy 1998		Children $n=41$, 6–14 years, $\xi=41$	R	P.k.	Grass pollen	Safe, effective
			La Rosa, J Allergy Clin Immunol 1999		Children $n=15$, 7–18 years, $\xi=15$	R, A	P.k.	HDM	Effective
			Bahceciler, Ped Pulmonol 2001	Sabbah, Allergy 1994	Children $n=?$, 13–51 years, $\xi=58$	R	P.k.	Grass pollen	Effective
				Clavel, Allergy 1998	Children $n=?$, 8–55 years, $\xi=120$	R	P.k.	Grass pollen	Safe, effective
				Pradaliat, Allergy 1999	Children $n=17$, 7–58 years, $\xi=123$	R	P.k.	Grass pollen	Safe, effective
				Grosclaude, Int Arch Allergy Immunol 2002	Children $n=30$, $\xi=64$	R	P.k.	Grass pollen	?
				Bousquet, Allergy 1999	Children $n=?$, 7–42 years, $\xi=85$	A	P.k.	HDM	Safe, effective
				Mortemousque, Clin Exp Allergy 2003	Children $n=?$, 6–60 years, $\xi=60$	C	P.k.	HDM	Effective
				Tonnel, Allergy 2004	Children $n=?$, 9–38 years, $\xi=32$	R	P.k.	HDM	Effective
					Children $n=113$, 5–14 years, $\xi=113$	R, A	P.k.	Grass pollen	Safe, effective
					Children $n=97$, 3–14 years, $\xi=97$	R	P.k.	Grass pollen	Safe, effective
					Children $n=126$, 3–5 years, $\xi=126$	R, A	n.k.	Grass pollen	Safe
					Children $n=38$, 8–14 years, $\xi=38$	R, A	P.k.	<i>Parietaria</i> pollen	Safe, effective
					Children $n=24$, 4–16 years, $\xi=24$	R, A	P.k.	HDM	Safe, effective
					Children $n=60$, 3–17 years, $\xi=60$	R, A	P.k.	HDM	Safe, effective
					Children $n=30$, 8–14 years, $\xi=30$	A	P.k.	<i>Parietaria</i> pollen	Safe, effective
					Children $n=?$, 14–48 years, $\xi=34$	R, A	n.k.	Grass pollen	Safe, effective
					Children $n=?$, 3–50 years, $\xi=90$	R, A	n.k.	Grass pollen	Safe
	PangraminSLIT® (pollen, HDM, animal dander, molds)	5	Novembre, J Allergy Clin Immunol 2004		Children $n=113$, 5–14 years, $\xi=113$	R, A	P.k.	Grass pollen	Safe, effective
			Rolnick-Werninghaus, Allergy 2004		Children $n=97$, 3–14 years, $\xi=97$	R	P.k.	Grass pollen	Safe, effective
			Di Rienzo, Clin Exp Allergy 2005		Children $n=126$, 3–5 years, $\xi=126$	R, A	n.k.	Grass pollen	Safe
			Pajno, Clin Exp Allergy 2003		Children $n=38$, 8–14 years, $\xi=38$	R, A	P.k.	<i>Parietaria</i> pollen	Safe, effective
			Marcucci, Allergy 2003		Children $n=24$, 4–16 years, $\xi=24$	R, A	P.k.	HDM	Safe, effective
					Children $n=60$, 3–17 years, $\xi=60$	R, A	P.k.	HDM	Safe, effective
					Children $n=30$, 8–14 years, $\xi=30$	A	P.k.	<i>Parietaria</i> pollen	Safe, effective
					Children $n=?$, 14–48 years, $\xi=34$	R, A	n.k.	Grass pollen	Safe, effective
					Children $n=?$, 3–50 years, $\xi=90$	R, A	n.k.	Grass pollen	Safe

Immunol 2003						
Pajno, Allergy 2000		Children $n=24$, 8–15 years, $\xi=24$	A	P.k.	HDM	Safe, effective
Valovirta, Allergy 2006		Children $n=98$, 8–15 years, $\xi=98$	R, A	P.k.	Tree pollen	Safe, effective
Marcucci, Ped Allergy Immunol 2005		Children $n=24$, 4–16 years, $\xi=24$	R, A	P.k.	HDM	Safe, effective
Tari, Allergol Immunopathol 1990		Children $n=66$, 5–12 years, $\xi=66$	R	P.k.	HDM	Safe, effective
Ippoliti, Ped Allergy Immunol 2003,		Children $n=86$, 5–12 years, $\xi=86$	R, A	P.k.	HDM	Safe, effective
Wüthrich, J Invest Allergol Clin Invest 2003		Children $n=28$, 4–11 years, $\xi=28$	R, A	P.k.	Grass pollen	Safe, effective
		Children $n=18$, 3–13 years, $\xi=18$	A	P.k.	HDM	Safe, effective
Novo-Helisen® oral (pollen, HDM, animal dander, molds)	5	Children $n=71$, 2–13 years, $\xi=71$	R, A	n.k.	?	Good compliance
SLIT®one (pollen, HDM, animal dander, molds)	5	Children $n=40$, 7–55 years, $\xi=135$	R, A	P.k.	HDM and grass pollen	Safe
		Children $n=253$, 5–16 years, $\xi=253$	R, A	P.k.	HDM and grass pollen	Safe, effective
Grazax® (grass pollen)	5					

Classification has been performed according to route of application (subcutaneous, sublingual), marketed extract in Austria by 2009, licensed lower age limit for use, assignment to either pediatric study with exclusive inclusion of children/adolescents or adult study including also children/adolescents, specification of the pediatric study population (number of children included, age range), treatment indication group (anaphylaxis, allergic rhinitis/conjunctivitis, bronchial asthma), inclusion of control group

world are affected [8]. The reasons for this rise are not clearly understood. It becomes more and more evident that there is not one single cause but rather an interplay of agents, such as environmental factors, diet, microbial exposure, and living habits (housing) which ultimately contribute to allergy development. Some of these factors bias the immune system directly toward allergy while others are thought to induce epigenetic changes that increase the risk to develop allergy. Based on the multifactor nature of the disease, scientific approaches to investigate the causes for allergy development have changed as well. Single factor intervention studies did not identify any single allergy risk or preventive factor; hence, sophisticated multivariable intervention studies had to be designed. However, no effective and feasible allergy prevention strategies have been found yet [4].

Therapy of allergic diseases such as allergic rhinitis, bronchial asthma, allergic conjunctivitis, insect venom allergy, and food allergy with or without atopic eczema comprises pharmacological treatment that targets end-organ manifestations on one hand and immunomodulatory treatment with the objective to re-balance the underlying immune deviation on the other hand [1, 2, 17, 31]. Allergen-specific immunotherapy is such an immunomodulatory approach: Gradually rising doses of allergen are given to the patients, with the objective to induce clinical tolerance toward this allergen. This way, SIT does not only improve clinical symptoms but also leads to profound immunologic changes. A similar approach is used in IgE-mediated allergy to drugs that cannot be substituted by other products [33]. Allergens for SIT are provided in different forms [70, 80]:

- In native form
- In combination with adjuvants such as aluminum hydroxide or L-tyrosine
- In chemically modified form (paraformaldehyde, glutaraldehyde) to reduce the IgE-binding and mast cell degranulation capacity [7, 19, 37, 38, 41, 42, 67, 159], so-called allergoids

SIT compounds are administered either via the subcutaneous (SCIT) or the sublingual (SLIT) route, both of which have been proven to be safe and effective in controlled studies. Other allergen preparations and new application routes are under investigation, but not yet available to clinical routine: hypoallergenic allergen fragments [48, 102, 140, 145], intralymphatic immunotherapy [63], and recombinant allergenic molecules [101, 108].

Despite or maybe even due to our long tradition in the use of SIT, there is still no common recommendation on the appropriate route or treatment scheme (up-dosing and maintenance phase of the highest tolerated dose) of allergen application. Up-dosing schemes vary widely between

different products: Slow, intermediate, rush, and ultra-rush up-dosing schemes are available mostly for the subcutaneous form. Traditional schemes, in particular slow allergen up-dosing via the subcutaneous route over 2 to 3 months, were defined empirically and turned out to be very effective and safe. The most recently marketed sublingual compounds, however, also use very short or no up-dosing phases [20, 152]. Pre-seasonal or co-seasonal application schemes are also available. For the sublingual route, up-dosing is generally very short (within 1 week); the latest sublingual tablet compound even omits up-dosing and starts with single high-dose allergen deposition.

The lesson we learned from these different application forms and dosing schemes is that there appear to be more ways to overcome the dys-balanced allergen-driven immune response. A generic recommendation for the choice of immunotherapeutic thus might not be possible.

However, for all immunotherapeutic drugs, safety and efficacy data in adults and children must be provided. Since this is not the case for all products with licenses in different European countries, physicians prescribing allergen-specific immunotherapy should be aware of compounds that have been tested in children and adolescents in controlled clinical studies. We recently published a survey on allergen-specific immunotherapy products licensed in Austria in which we emphasize such compounds [136] to help physicians in their choice of allergen-specific immunotherapy compounds. Even though there is some confusion on availability, efficacy, and benefit of particular immunotherapy products over Europe, physicians should not hesitate to use/prescribe allergen-specific immunotherapy in general. It is definitively the most potent immunomodulatory intervention in IgE-mediated respiratory allergies, in particular in children.

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