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Summary Allergen immunotherapy (AIT) is a proven treatment for allergic diseases such as allergic rhinoconjunctivitis (ARC), allergic asthma (AA) and insect sting allergy. Particularly in children and adolescents, who have a high prevalence of these diseases, AIT plays a crucial role in not only alleviating symptoms but also influencing the natural course of the disease. This article examines the use and importance of AIT in children and adolescents in Germany in the final phase of the Therapy Allergen Ordinance (TAV). The focus is on the efficacy and safety of the therapy, as well as the approval of the respective therapeutic allergens for the respective age group.

Keywords Therapy Allergen Ordinance (TAV) · Supply gap · Approval · Clinical studies · Therapy adherence

Abbreviations

AA	Allergic asthma
AIT	Allergen immunotherapy
AR	Allergic rhinitis
ARC	Allergic rhinoconjunctivitis
GPAU	Society for Pediatric Allergology and Environmental Medicine
NVL	National health care guideline
RWE	Real-world evidence
SCIT	Subcutaneous allergen immunotherapy
SLIT	Sublingual allergen immunotherapy

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Importance of allergen immunotherapy in childhood and adolescence

In Germany, the 12-month prevalence for allergic rhinitis is 8.8% and for bronchial asthma 3.5% [1]. These diseases not only have a significant impact on the quality of life and the performance and development potential of the next generation [2–4] but also harbor the risk of chronicity with impairments that persist into adulthood [5, 6].

In many cases, symptomatic treatment does not sufficiently control symptoms and improve performance [3] or quality of life. Symptomatic therapy has no influence on long-term morbidity [7]. A causal therapy, AIT, should therefore be considered as soon as symptoms correlate with sensitization upon allergen exposure [8].

There is evidence in the literature of disease modification by AIT. For example, the risk of a new manifestation of asthma is reduced if subcutaneous AIT (SCIT) [9] or sublingual AIT (SLIT) [10] is used for ARC in children and adolescents. In real-world evidence (RWE) studies, a reduction in the consumption of asthma medication was observed both after SLIT [11–13] and after SCIT [14, 15].

Indications and contraindications

Indications

AIT is indicated in children and adolescents for severe anaphylaxis after bee or wasp stings [16], moderate and severe forms of allergic rhinoconjunctivitis [17] and all degrees of asthma [18]. With regard to insect venom allergy, please refer to the current guideline [16]. Subcutaneous aqueous therapy solutions are available to achieve rapid top-up dosing. The supply situation for these preparations has eased again

in recent months. These preparations can continue to be used to maintain SCIT for 3–5 years. Alternatively, a depot preparation can be used for the maintenance. In principle, no dose reduction is required when switching to a depot product [19]. Attention must be paid to the correct dosage when changing each pack [20].

Allergic rhinoconjunctivitis is divided into intermittent and persistent courses. The severity is classified as mild, moderate, or severe. AIT in AR/ARC is indicated for all persistent courses as well as for moderate and severe intermittent courses as soon as allergen avoidance and symptomatic therapy do not lead to symptom control [17]. Especially in children and adolescents with allergic rhinoconjunctivitis, the desire for prevention of asthma is also an indication for early initiation of AIT. [8, 21].

According to the National Disease Management Guideline for Bronchial Asthma (NVL-Asthma) and the specialist guideline on bronchial asthma, it should be checked whether clinically relevant sensitization is present for all severity levels of bronchial asthma. In these cases, allergen immunotherapy should be considered in addition to consistent symptomatic asthma therapy [18, 22].

Contraindications

As part of the revision of the S2k guideline AIT published in 2022, the list of contraindications was critically reviewed. Significantly fewer contraindications are listed.

In children, uncontrolled bronchial asthma in particular is still considered a contraindication to starting or continuing allergen immunotherapy [8, 18]. Accordingly, every effort should be made to control bronchial asthma as quickly as possible with consistent symptomatic pharmacotherapy so that allergen immunotherapy can be started or resumed.

Oncological diseases in stable remission, chronic inflammatory bowel diseases, or stable rheumatological diseases are not a contraindication to starting or continuing indicated allergen immunotherapy ([8]; Table 1).

Table 1 Contraindications for allergen immunotherapy (modified according to [8])

Contraindications for AIT
Uncontrolled asthma
Malignant neoplastic diseases with current disease value
Severe systemic autoimmune diseases, immunodeficiencies, relevant immunosuppression (due to possible reduced efficacy of AIT)
Insufficient adherence, severe psychiatric illnesses
Untreated, chronic infection (e.g., HIV, hepatitis B virus)
Additionally for SLIT
History of inflammatory gastrointestinal diseases (e.g., eosinophilic esophagitis) acute and chronic recurrent diseases and open wounds of the oral cavity

Therapy adherence

Adherence to treatment is a key success factor for AIT, and not just for children and adolescents. As AIT is a long-term form of therapy that is carried out over 3–5 years, it is crucial that patients and their families understand and accept the principle of the treatment. The more autonomous the AIT is, the more important it is that the instructions for its implementation are communicated in a way that is understandable to the patient and family.

It is important to inform the entire family about the aims of AIT and the expected stresses and strains of the therapy. A central medical task is therefore to work out the correct therapy modalities (subcutaneous or sublingual) with the family and then to make a joint decision on which therapy to choose after providing age-appropriate information. For information and consent, we recommend using the documents available on the AIT guideline homepage for SLIT [23] and SCIT [24]. Further information can be found as a parent guide [25] or as information for children and parents [26] also on the homepage of the GPAU (Society for Pediatric Allergology and Environmental Medicine).

Consistent patient management is essential over the entire duration of allergen immunotherapy. Subcutaneous therapies are objectively easier to monitor, but if injections are missed, it is imperative that patients are reminded and offered prompt replacement appointments.

Sublingual therapies also require regular personal contact with motivating discussions between patient and practitioner. SLIT patients should be seen with their family once a quarter [27]. In addition to causal therapy, optimization of symptomatic therapy is always indicated during these contacts.

Subcutaneous and sublingual immunotherapy

Both sublingual and subcutaneous preparations are available for the common therapeutic allergens according to the Therapy Allergen Ordinance (TAV allergens). TAV allergens (grass, birch, alder and hazel pollen, house dust mites and insect venoms) are subject to approval by the authorities in Germany. For children and adolescents, attention must always be paid to the approval for the respective age group [28].

The advantage of subcutaneous allergy immunotherapy (SCIT) is that several therapy preparations from different manufacturers are available for all age groups of TAV allergens. Both native preparations and allergoids can be used from the age of five within the scope of the approval. The subcutaneous injections are generally well tolerated. Adherence to therapy can be recorded very well by documenting the injections. The disadvantages are the need for regular visits to the doctor and the subsequent monitoring period of 30 min [8].

For sublingual allergen immunotherapy, only treatment with grass pollen (two preparations) is currently approved from the age of 5 years. Two preparations are available for the treatment of house dust mite allergy from the age of 12. A clinical trial has been successfully completed for one preparation in the 5- to 11-year-old age group [29]. According to the manufacturer, the documents for approval have been submitted. It is expected that the gap for children in the area of house dust mite SLIT can be closed in the short term. For birch pollen (and hazel and alder pollen), SLIT preparations are currently only available after the 18th birthday. A study on SLIT for birch pollen in children and adolescents (5–17 years) has already been completed [30]. Approval has also been applied for here. Another study on birch pollen in the same age group is currently in its second year [31]. Here, too, it is foreseeable that the supply gap for children and adolescents can be closed. Current information on the approval status of TAV allergens can be found in the regularly updated tables for the Allergen Immunotherapy Guideline at https://dgaki.de/leitlinien/s2k-leitlinie-ait ([32]; Fig. 1).

SLIT is less invasive and has a lower risk of systemic allergic reactions. However, local allergic reactions can certainly be perceived as stressful and therefore impair compliance with treatment. As a rule, however, the local effects at the site of application only occur for a short period of around 30 min and only in the first 2 weeks [33]. Active premedication with modern antihistamines should therefore be offered before starting sublingual therapy. Only small pack sizes should be prescribed at the start of therapy. After starting treatment under medical supervision, a short-term check-up after around 2 weeks is recommended to discuss the effects and local side effects and to maintain treatment adherence. One problem with sublingual therapy is early discontinuation, which can be prevented by this procedure [34].

Evidence base and effectiveness in children and adolescents

An overview of the evidence base of approved and still marketable therapeutic allergens can be found in the regularly updated tables provided for the guideline on allergen immunotherapy [32].

No double-blind placebo-controlled studies have yet been published for subcutaneous therapy in children or adolescents. However, an initial study for a grass pollen is being planned [35].

Double-blind placebo-controlled studies with grass preparations have been completed for sublingual therapy in children and adolescents [10, 36].

In Japan, 438 children and adolescents between the ages of 5 and 16 were examined for house dust mite preparations. There were significant improvements in the symptom score. The side effect profile did not differ from that of adults [37]. In another study from Japan, 946 adolescents and adults aged 12–16 years were examined. A post hoc subgroup analysis showed no inferior efficacy in the 12–17 age group compared to adults [38].

There is currently only one pediatric safety study published for SLIT birch pollen preparations: 54 children and adolescents with bronchial asthma aged between 6 and 14 years were examined in a double-blind, placebo-controlled study in Germany. In an ultra-rush dosing regimen, the target dose of 300 IR was reached within 90 min under peak flow control. There were no differences in the peak flow values between the placebo and treatment groups, no systemic allergic reactions and no other serious adverse events [39].

There will be no further clinical trials for already approved subcutaneous preparations in the foreseeable future. The reasons for this are the lack of economic necessity for the manufacturer to present new studies and the expected unwillingness of study centers and patients to participate in placebo-controlled studies

	Children (5 to 11 years)		Teenagers (12 to 17 years)	
	SCIT	SLIT	SCIT	SLIT
Grass pollen	ALK depot SQ Allergovit Purethal TA top	Grazax Oralair	ALK depot SQ Allergovit Purethal TA top	Grazax Oralair
Tree pollen (birch/alder/hazel)	ALK depot SQ Allergovit Purethal TA top		ALK depot SQ Allergovit Purethal TA top	
House dust mites	ALK-depot SQ Depigoid Novo-Helisen		ALK-depot SQ Depigoid Novo-Helisen	Acarizax Orylmyte

▪ Not approved for the age group ▪ Approved for the age group

Fig. 1 SCIT and SLIT preparations[a] for children and adolescents (modified according to [28]). [a]The products are listed in alphabetical order, the ranking does not imply any rating. Criteria for inclusion in the table are the market authorization for the corresponding age group according to documents of the Paul Ehrlich Institute (as of 10 August 2024). SCIT subcutaneous immunotherapy; SLIT sublingual immunotherapy. Red: Not approved for the age group. Green: Approved for the age group

if approved therapies are available. Alternative study approaches must therefore be used to prove efficacy. Results from real world evidence studies are primarily suitable here [28].

In 2023, however, members of the GPAU's scientific working group on allergen immunotherapy also identified alternatives to classic placebo-controlled studies. In polyallergic children, for example, treatment of one allergen with verum therapy allergen and a second allergen with placebo or a staggered introduction of the verum with reduction of the placebo group was proposed. A randomized comparative study of different therapy allergens from different manufacturers could also reduce the number of patients treated with placebo [28]. The funds required for this would have to be raised via industry-independent sponsors as a joint study approach from the pharmaceutical industry has not yet been possible.

Supply problems with AIT preparations for children and adolescents

According to the framework guidelines of the German National Association of Statutory Health Insurance Physicians (KBV), since 2021 only therapy allergens approved for the age group should be used for new initiations of AIT. This nationwide requirement has now been implemented regionally as a prescription recommendation [40, 41]. Marketable therapeutic allergens (nonapproved therapeutic allergens for which approval has been applied for under the TAV) can still be used for the continuation of ongoing treatments.

Marketable therapeutic allergens may still be sold by the manufacturer until the end of the TAV, presumably in 2026, after which they must be withdrawn from the market if they have not been approved. Anyone who starts using a nonapproved preparation today therefore runs the risk of not having it available for the entire 3-year treatment period. A new prescription of an unapproved preparation would also contradict the treatment recommendations of the Association of Statutory Health Insurance Physicians (KBV). There would therefore be a nonnegligible risk of recourse.

The changes and requirements resulting from the TAV thus lead to a variety of challenges and problems in the practical implementation of allergen immunotherapy in pediatric allergology, which are the subject of ongoing intensive discussion. One particular problem is the requirement for placebo-controlled pediatric phase III studies for the approval of new preparations. In practice, the problem arises that the recruitment of the necessary number of patients can fail due to the unwillingness of families to participate. In particular, the aspect of receiving placebo for 3 years is considered unreasonable by many relatives [28]. Recruitment for a planned SCIT grass pollen study, which is due to start at the end of 2024, will be a litmus test. From the point of view of many pediatric allergists, evidence for the safety and efficacy of allergen immunotherapy in children can also be generated through REW studies.

Synopsis

Allergen immunotherapy is currently experiencing a low point, particularly in children and adolescents. Many established products are no longer available due to allergen therapy regulations and lack of approval. New approvals are linked to the age group studied in trials and are often not granted for children and adolescents. This has led to a gap in the availability of sublingual allergens for children and adolescents for tree pollen and house dust mite allergies. However, it is expected that in the medium term, at least for these indications, one or two more products will be approved for use in children and adolescents.

It remains to be seen to what extent placebo-controlled trials of subcutaneous therapy will be possible in the future. Alternative approaches to generating knowledge from large amounts of data could provide the necessary evidence of safety and efficacy in children and adolescents. In particular, long-term therapeutic success in preventing asthma can only be demonstrated in the foreseeable future with new study approaches.

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Conflict of interest M. Gerstlauer: Clinical studies: Allergopharma, Bencard Allergie, Boehringer, InfectoPharm, Stallergenes-Greer; Consultancy work/lecture fees: AstraZeneca, Aimmune, ALK-Abelló, Allergopharma, Bencard Allergie, Leti Pharma, Meda Pharma, Novartis Pharma, Sanofi, Stallergenes-Greer; Professional associations: AGPAS, GPAU, GPP, DGKJ, EAACI, ERS; Guidelines: NVL bronchial asthma, AWMF: Allergen immunotherapy, Insect venom allergy, Allergy prevention, Bronchial asthma, Severe bronchial asthma in children, Allergic rhinoconjunctivitis.

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