



# White paper peanut allergy

## Part 3: management and therapy of peanut allergy

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**Abstract** The current management of a primary IgE-mediated peanut allergy consists of the two basic pillars “exposure prophylaxis” with avoidance of the allergen and “emergency therapy” with short-term treatment of an acute allergic reaction after accidental ingestion. Accidental reactions are common despite attempted avoidance. The severity of an allergic or even anaphylactic reaction after accidental ingestion is difficult to assess prior to reaction. In addition, reaction thresholds may vary depending on the accompanying augmentation factor. Therefore, every peanut allergic patient should receive individual dietary counseling as well as instructions for the use of the emergency kit and a structured patient education program (anaphylaxis group training), if necessary. For the first time, since fall 2021 a causal treatment option with a drug for oral immunotherapy will now

be available for 4- to 17-year-old peanut-allergic children and adolescents. The oral immunotherapy with peanut protein as defatted powder of *Arachis hypogaea L., semen* (peanuts) leads to desensitization with a good efficacy record and an acceptable safety profile. Other treatment options with different therapeutic approaches are also under development and will probably expand the range for treatment in the coming years.

**Keywords** Allergen avoidance · Accidental reaction · Oral immunotherapy · Epicutaneous immunotherapy · Anti-IgE

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## Introduction

Up to now, the management of peanut allergy, and also of all other ImmunoglobulinE (IgE)-mediated food allergies, consisted of two major pillars: (1) exposure prophylaxis with allergen avoidance (see also part 3: Nutrition therapy in peanut allergy [1]) and (2) management of an acute allergic reaction after accidental consumption of peanut protein [2]. With diagnosis there is the fear of a severe allergic reaction in case of unintentional allergen exposure. In order to avoid this fear and avoid unnecessary strict diets as well as to improve the significantly reduced quality of life of patients and their families, a confirmed diagnosis is certainly the first priority in the management of patients (see part 2: Diagnosis of peanut allergy with special emphasis on molecular component diagnostics [3]). For primary peanut allergy with immediate-type reactions a strict avoidance of the allergen is recommended. In case of solely skin exacerbation of atopic dermatitis after peanut consumption as a single symptom, a strict avoidance of peanut is not recommended, since only regular consumption of peanut protects against the development of an immediate-type reaction [4]. Also in case of the rarer, secondary, pure pollen-associated peanut allergy, a strict avoidance is not necessary. With this form of peanut allergy, however, products that lead to oral allergy syndrome should be avoided [5]. Therefore, the individual diagnosis is very important for risk assessment. Patients with primary peanut allergy and thus an increased risk of anaphylaxis are recommended an individually adapted therapeutic elimination diet to prevent further reactions [6].

The second pillar for primary peanut allergic patients consists of the management of an acute allergic reaction after accidental consumption of peanut protein. It is recommended that patients and their parents/caregivers receive training in the prescribed emergency kit including training for the epinephrine auto-injector and including anaphylaxis group training [6]. In anaphylaxis group training, patients learn how to reliably recognize an emergency situation and how to use the emergency medication. A further goal of such a training is the reduction of irrational fears in everyday life. For example, the fear could be that when a peanut snack bag is opened in the vicinity of the patient (school, airplane) this exposure to peanut protein via inhalation could trigger a severe allergic reaction. However, different studies on this topic showed that only very small, clinically irrelevant amounts of peanut protein and only in close proximity of the opening of the snack bag were detectable (e.g., [7] summarized in [8]). Moreover, only few patients had any symptoms when exposed to a bowl with roasted peanuts standing in front of them [9]. If there were any symptoms at all, only rhinoconjunctival symptoms occurred, which did not require any treatment. Furthermore, for example,

there are reports that skin contact with peanut butter on its own will lead to only mild skin reactions [10]. Evidence suggests that communicating this information as such to the patient may help reduce anxiety in affected individuals in their daily lives [11].

Since December 2020, oral immunotherapy with peanut protein as defatted powder of *Arachis hypogaea L., semen* (peanuts) in children with primary peanut allergy aged 4–17 years has been approved in the European Union and is available in Germany since fall of 2021. It can be considered as a new, third pillar of peanut allergy management.

### Pillar 1: exposure prophylaxis

The updated guideline on the management of IgE-mediated food allergy recommends that an appropriate elimination diet be implemented [2]. For a detailed explanation of the elimination diet as it relates to peanut allergy, see part 3 of the White paper peanut allergy: nutrition therapy in peanut allergy [1]. In summary, patients and their families should be trained in allergen labeling according to the Food Information Regulation and its gaps by a dietitian experienced in allergy. They should learn to understand ingredient lists, to recognize risk situations (e.g., Asian restaurant, eating at a buffet), and to avoid peanut in an individual, appropriate manner. The issue of “avoidance of traces” always leads to uncertainty. It is a gray area in the field of exposure prophylaxis (see part 3 of the White paper peanut allergy: nutrition therapy in peanut allergy [1]). Whether “avoidance of traces” is necessary is certainly to be determined on an individual basis. For example, a patient is more likely not to react to “traces” if he or she reacts to higher amounts of peanuts (e.g., 1000 to 4500 mg of peanut protein, equivalent to about 3–15 peanuts) in oral provocation tests. However, it should be kept in mind that it is not clear-cut how large the peanut amount in the given “trace” is. It can range from 0 to 650 mg of peanut protein per 100 g of food [12]. Furthermore, reaction thresholds are not equally stable in every situation and may vary depending on the augmentation factor(s). Such cofactors include physical activity, sleep deprivation, alcohol intake or infections [13]. Taking into account all clinical available information, the individual risk assessment should be discussed with the patient/family [14].

### Pillar 2: treatment of acute allergic reaction after accidental peanut consumption

Despite all attempts to strictly adhere to the elimination diet, allergic reactions frequently occur after accidental consumption of peanut. In a prospective study, 41 children with confirmed peanut allergy were followed. Of these, 41% suffered from an accidental reaction in the subsequent 3 years [15]. The annual incidence of an accidental reaction in peanut aller-

gic patients has been calculated in several studies and ranges from 3.1 to 23.5% depending on the study population [16–20]. Acute reactions most commonly occur at home or with friends/acquaintances [16, 19]. Other important potential locations with a higher risk for accidental reactions include restaurants (especially Asian restaurants), bakeries, and ice cream parlors [21]. For schools and daycare facilities, the risk of an accidental reaction is lower; moreover, no difference was shown between “peanut-free” schools/daycare facilities and facilities where peanut-containing foods were allowed [22]. The severity of an allergic reaction to accidentally consumed peanuts ranges from mild skin symptoms to anaphylaxis. In a study of 785 patients (including 86% children and adolescents) with peanut sensitization or known peanut allergy, 30% reported severe accidental reactions such as severe systemic reactions, acute asthma, laryngeal edema, or shock [23]. In 238 of these patients, the eliciting dose could be estimated to a median of 125 mg peanut protein (approximately ½ peanut) [23]. In the European Anaphylaxis Registry, it has been shown that food is the most common trigger for anaphylaxis in childhood and that, across all age groups in childhood, peanut is the most common trigger of food-induced anaphylaxis [24]. Of the 459 peanut-allergic children in the European Anaphylaxis Registry with recorded anaphylaxis due to an accidental reaction to peanut, the amount of peanut that triggered a reaction could be estimated in 197 children. In 66% of these children, it was  $\leq 1$  teaspoon of peanut (e.g., equivalent to approximately  $\leq 5$  g of ground peanut/peanut mousse, therewith 1.25–1.5 g peanut protein) [25]. Peanut also represents the most common cause of death from food-related fatal anaphylaxis [26]. Particularly problematic for counseling affected individuals is the fact that the severity of an allergic reaction following accidental peanut ingestion is unpredictable [20]. Of 83 peanut allergic patients followed up for a median of up to 5 years, 43 children had a mild, nonlife-threatening initial reaction after peanut exposure, with a follow-up reporting of life-threatening reactions in 44% of these children after repeated accidental peanut ingestion [20]. Also, no validated biomarker for predicting severe reactions (e.g., the reaction dose at oral challenge) has been identified to date [27]. A lower reaction threshold does not seem to be necessarily predictive of a severe allergic reaction during oral challenges [27].

### Emergency kit

Thus, as explained above, due to the increased risk of anaphylaxis peanut allergic patients are recommended to treat these reactions early in the event of an accidental reaction and thus also to treat these reactions themselves (or by caregivers). This is also verified again in the updated S2k guideline of the German Society for Allergology and Clinical Immunology

(DGAKI) on the management of anaphylaxis of 2021 [6]. Patients with primary peanut allergy and systemic allergic reactions in their medical history or patients with suspected primary peanut allergy and high sensitization to peanuts (e.g., never eaten peanut before or having experienced only local mild symptoms in history before but exhibiting a high sensitization, before oral challenge) should be prescribed an emergency kit for immediate aid. The kit should include an epinephrine auto-injector, a histamine H1 receptor antagonist, a glucocorticoid, and in the case of bronchial asthma or previous reaction with bronchospasm, an inhaled bronchodilator ( $\beta$ 2-adrenoceptor agonist), if necessary with an appropriate inhalation aid. In case of a previous severe laryngeal edema, an inhaled epinephrine preparation may possibly be considered (Table 1). An anaphylaxis passport or anaphylaxis action plan should also be provided with each emergency kit (Fig. 1). The anaphylaxis action plan (in English) can be ordered via [www.daab.de](http://www.daab.de). The anaphylaxis passport (only available in German) can be ordered via [www.daab.de](http://www.daab.de) or [www.gpau.de](http://www.gpau.de) (Gesellschaft für Pädiatrische Allergologie und Umweltmedizin e.V.). An equivalent can be retrieved in Austria under IGAV-Interessengemeinschaft Allergenvermeidung ([aleeb@allergenvermeidung.org](mailto:aleeb@allergenvermeidung.org)) or via ÖGKJ-Öst. Ges. Kinder und Jugendheilkunde under [www.paediatrie.at](http://www.paediatrie.at).

### Adrenaline

Intramuscular, systemic, rapid administration of epinephrine is the first-line medication for severe allergic reactions involving the respiratory system (dyspnea, cough, bronchial obstruction), the circulatory system (hypotension, shock, unconsciousness), or two organ systems (e.g., skin and gastrointestinal tract) [6]. In addition, if a true peanut consumption happens and symptoms (even mild) subsequently occur, it is recommended that epinephrine be administered (Fig. 1). Controlled studies on the efficacy of epinephrine in anaphylactic reactions do not exist for ethical reasons. However, an older US study was able to show that in the studied cases of fatal food-induced anaphylaxis, delayed epinephrine administration was predominant (5/6 patients received epinephrine only  $\geq 60$  min after ingestion) compared to severe cases of anaphylaxis without fatal outcome (6/7 patients received epinephrine  $\leq 30$  min after ingestion) [28]. It can be inferred that safe and rapid self-medication by patients or their caregivers is necessary. Epinephrine should be administered intramuscularly into the outer thigh, as this results in a rapid onset of action (as opposed to subcutaneous administration) with little risk of cardiac side effects. Adrenaline auto-injectors are used for this purpose, which are drug licensed according to weight (Table 1) and can be used for lay injection. Different epinephrine auto-injectors are available, which differ in dose, handling,

**Table 1** Components of an “emergency aid kit” (modified after [6])

<i>Epinephrine auto-injector</i> for intramuscular administration, weight-adapted	
>7.5–25 kg weight or >15–30 kg weight	150 µg <sup>a</sup>
>25–50 kg weight or >30–50 kg weight	300 µg <sup>a</sup>
>50 kg weight	300–500–600 µg
<i>H1-antihistamine</i> oral, according to age and preference as liquid or (melting) tablet The dose may be increased up to four times the approved single dose of the antihistamine in question to: e.g., cetirizine drops (CAUTION: off-label! <sup>b</sup> ) maximum:	
2–6 years	10 mg = 20 drops
>6–12 years	20 mg = 40 drops
>12 years	40 mg = 80 drops
e.g., desloratadine melting tablets (CAUTION: off-label! <sup>b</sup> ) maximum:	
6–11 years	10 mg = 4 tablets with a dose of 2.5 mg
>12 years	20 mg = 4 tablets with a dose of 5 mg
e.g., dimetindene drops maximum:	
<7.5 kg weight	1 mg = 20 drops
7.5–25 kg weight	1 mg/10 kg = 20 drops per 10 kg, max. 80 drops
30–60 kg weight	4 mg = 80 drops
<i>Glucocorticoid</i> according to age and preference as oral or rectal administration e.g., betamethasone syrup à 0.5 mg/ml (0.5 mg/kg weight)	
<15 kg weight	5 to 7.5 mg = 10 to 15 ml = 1/3 to 1/2 bottle
15–30 kg weight	7.5 mg = 15 ml = 1/2 bottle
>30 kg weight	15 mg = 30 ml = 1 bottle
e.g., prednisolone syrup à 6 mg/ml (2–3 mg/kg weight)	
<6 kg weight	18 mg = 3 ml (draw up with syringe)
6–12 kg weight	36 mg = 6 ml (draw up with syringe)
12–15 kg weight	45 mg = 7.5 ml (draw up with syringe)
15–30 kg weight	90 mg = 15 ml = 3/4 bottle
>30 kg weight	120 mg = 20 ml = 1 bottle
e.g., prednisone suppositories	
–	100 mg = 1 suppository
<i>Beta2-adrenoceptor agonist</i> With diagnosed bronchial asthma or previous reaction with bronchospasm Beta2-adrenoceptor agonist metered-dose inhaler (e.g., salbutamol)	
–	2–4 puffs (via inhalation aid if necessary)
<i>Inhaled epinephrine</i> If a history of severe laryngeal edema is present, inhaled epinephrine preparation with spray head for drug vial (ask pharmacist for extra)	
–	7 puffs
<i>Anaphylaxis passport or anaphylaxis action plan</i>	
<sup>a</sup> Drug licensing depending on individual auto-injector preparation <sup>b</sup> CAUTION: off-label, but also recommended in guideline [6] because less sedating side effect than first-generation antihistamines	

trigger mechanism and needle length. Because of differences in handling, patients/caregivers should be demonstrated proper use using a preparation-specific trainer pen. A trainer pen should also be handed out for home practice. When prescribing the auto-injector, the “Aut-idem box” should be checked on the prescription so that the patient also receives the autoinjector for which he or she has been trained. A prescribing of two epinephrine auto-injectors at the same time might be reasonable; for example, if there is a history of a particularly severe anaphylactic reaction, the patient weighs >100 kg, suffers from uncontrolled bronchial asthma or mastocytosis, if

there is predictably poor accessibility to the nearest emergency medical care, or a second set is needed for childcare centers/schools or if the parents are separated [6].

### Antihistamines and glucocorticoids

Mild allergic reactions with isolated skin symptoms (urticaria/angioedema) or isolated gastrointestinal symptoms (abdominal pain, diarrhea, vomiting) should be treated with an antihistamine in combination with a glucocorticoid [6]. H1-antihistamines of the second generation (e.g., cetirizine, levocetirizine,

# Anaphylaxis Action Plan

Photo	Name:	_____
	Date of birth:	_____
Confirmed allergens, that cause <b>anaphylaxis</b>		
_____		
Asthma?		
<input type="checkbox"/> Yes (higher risk for a severe reaction)		
<input type="checkbox"/> No		
Family emergency contact: name / phone		
_____		
Where is emergency medication stored?		
_____		
Plan prepared by (physician):		
_____		
Date / Signature		
How to administer the adrenaline autoinjector		
_____		
<p style="text-align: center;">Sticker with instructions how to use prescribed adrenaline autoinjector</p>		

## Mild to moderate allergic reaction

### Signs and symptoms

- Tingling mouth and throat
- Itching on palms, soles or genital area
- Redness of the skin
- Wheals, hives
- Swelling of lips and face
- Nausea, vomiting
- Feeling of impending doom

### First Aid Action

1. Stay with the patient/ child. **Call for help: 112** (ambulance and inform emergency contact)
2. Give **antihistamine and corticosteroid**

\_\_\_\_\_

Name and dose of antihistamine

\_\_\_\_\_

Name and dose of corticosteroid

3. Locate **adrenaline autoinjector** and **watch patient** for further signs and symptoms of anaphylaxis

## Severe reaction

### Signs and symptoms

- Sudden hoarseness
- Shortness of breath
- Wheezing
- Loss of consciousness
- Combination of two or more symptoms from different body areas (skin, gastrointestinal tract, respiratory system, cardiovascular system) e.g. abdominal pain and skin-reaction
- Any (even mild) reaction, after definite allergen contact (e.g. eating allergenic food or being stung by bee or wasp)

### First Aid Action

1. **Administer adrenaline autoinjector** into outer mid-thigh

\_\_\_\_\_

Name of adrenaline autoinjector

2. **Position of patient:**
  - with respiratory symptoms: sit or position of comfort
  - with cardiovascular symptoms while conscious: lay flat
  - unconscious: recovery position
3. **If short of breath** (airway symptoms) administer asthma reliever (blue inhaler) in addition

\_\_\_\_\_

Name of asthma reliever

4. **Call for help: 112** (ambulance and ask for emergency physician)
5. Inform **emergency** contact (see left)
6. Give **antihistamine and corticosteroid** in addition (see above)

**Fig. 1** Anaphylaxis action plan (reprinted with kind permission by Deutscher Allergie- und Asthmabund [DAAB])



**Table 2** Placebo-controlled studies on peanut oral immunotherapy (OIT)

First author	Varshney et al.	Bird et al.	Blumchen et al.	Chinthrajah et al.	Vickery et al.	Houriha et al.	Jones et al.
Year of publication	2011 [35]	2018 [37]	2019 [36]	2019 [38]	2018 [39]	2020 [40]	2022 [41]
Country	USA	USA	Germany	USA	USA, Canada, Europe	Europe	USA
Phase	Ila	Ila	Ila	Ila	III	III	III
N=	19 OIT 9 Placebo	29 OIT 26 Placebo	31 OIT 31 Placebo	95 OIT 25 Placebo	372 OIT 124 Placebo	132 OIT 43 Placebo	96 OIT 50 Placebo
Age (years)	1–16 years	4–26 y	3–17 years	7–55 years	4–17 years	4–17 years	1–3 years
Maintenance dose (mg peanut protein)	4000	300	125–250	4000	300	300	2000
N= X of the active group reaching maintenance dose	16/19 (84%)	23/29 (79%)	16/31 (52%)	27/95 (28%)	294/372 (79%)	106/132 (80%)	90/96 (94%)
Length of the study for endpoint “Desensitization”	12 months	9 months	16 months	26 months	12 months	9 months	31 months
≥ X mg single dose peanut protein tolerated at EXIT/final oral challenge	5000 mg	300 mg (cumulative dose 443 mg)	300 mg	1050 mg (cumulative dose 4000)	600 mg	1000 mg	5000 mg
Number of patients (%) who reached endpoint “Desensitization”	OIT: 84% Placebo: 0%	OIT: 79% Placebo: 19%	OIT: 74% Placebo: 16%	OIT: 84% Placebo: 4%	OIT: 67% Placebo: 4%	OIT: 58% Placebo: 2%	OIT: 71% Placebo: 2%

desloratadine) are not approved for the treatment of anaphylaxis, but are recommended for oral emergency therapy because of rapid bioavailability as well as few side effects (such as sedation; Table 1, [6]). Only first-generation H1-antihistamines (dimetindene and clemastine) have official drug licensing for the treatment of anaphylaxis but have sedating side effects. Glucocorticoids play only a minor role in the acute therapy due to their slow onset of action and unclear efficacy in acute anaphylaxis [29]. The German guideline recommends them as part of an emergency kit despite sparse evidence [6].

### Beta-2-adrenoceptor agonists

In cases of known bronchial asthma or previous reaction with bronchospasm, an inhaled  $\beta_2$ -adrenoceptor agonist should also be prescribed for the emergency kit (Table 1; [6]). In children, for administration of the  $\beta_2$ -adrenoceptor agonist via a metered-dose inhaler a spacer should be used or, for example, administered via an autohaler.

### Anaphylaxis group training

Furthermore, patients, their families and possibly other carers should be instructed in detail in the technique regarding the use of the epinephrine auto-injector and the indications for its use. For this purpose, a structured patient education program (anaphylaxis group training) is offered in Germany for adult patients, children, their parents, adolescents and also partly for teachers and educators according to the curriculum (<https://www.anaphylaxieschulung.de>) established by AGATE (Arbeitsgruppe Anaphylaxie Training und Edukation e.V.). It includes a 2-day sequential training on triggers, diagnosis, symptoms, medications, practical training and safety in the use of the auto-injector, practical action plan, prevention and reduction of anxiety. The effectiveness of

this training was demonstrated in a randomized controlled trial [30].

### Pillar 3: oral immunotherapy

As a third pillar, oral immunotherapy (OIT) for children and adolescents with primary peanut allergy provided by peanut protein as defatted powder of *Arachis hypogaea L., semen* (peanuts) has now been drug licensed in the European Union since 2020. In Germany, this therapy is available for children and adolescents from 4–17 years of age since fall 2021.

The principle of OIT for peanut allergic patients is the daily oral administration of initially very small amounts of peanut protein, which are slowly increased over a defined period of time. The goal is to gradually increase the amounts of peanut allergen without exceeding the reaction threshold, and then continue to increase the threshold level while maintaining a daily dose. The intention is that the patient is better protected from allergic reactions in case of accidental peanut consumption in everyday life while maintaining peanut avoidance (desensitization). More than 10 years ago, the first pilot studies in small numbers of patients were able to confirm for the first time the hypothesis of a possible desensitization after OIT performed in peanut allergic children [31–34]. This was followed by several placebo-controlled phase II trials [35–38], which verified significant efficacy of peanut OIT in contrast to placebo treatment with a relatively good safety profile (Table 2).

Efficacy or primary endpoint in these studies was defined as the number of patients who tolerated a given amount of peanut protein during oral peanut provocation after a certain duration of therapy. Studies differed in duration of intervention (9–26 months), selected maintenance dose of OIT (125–4000 mg peanut protein, equivalent to less than approximately  $\frac{1}{2}$  to 13 peanuts daily), and definition of primary

endpoint (maximum tolerated dose of 300 mg peanut protein single dose to 5000 mg cumulative dose at final provocation). In all, 74–84% of patients receiving OIT versus 0–19% of placebo patients met the primary endpoint, respectively.

A probability calculation could show that raising the reaction threshold to, for example, 300 mg (before therapy  $\leq 100$  mg) or 1000 mg (before therapy  $\leq 300$  mg) peanut protein leads to  $>95\%$  and  $>99\%$  risk reduction of allergic reaction after accidental consumption of foods such as cookies, doughnuts, ice cream or savory snacks in peanut allergic patients, respectively [12, 42]. One of the phase II studies of OIT also demonstrated an absolute risk reduction in allergic reaction during accidental consumption of peanut with OIT performed in the verum group (8 accidental reactions in 5/30 patients) in contrast to the placebo group (24 accidental reactions in 14/31 patients) [43].

A randomized controlled trial in forty 9- to 36-month-old peanut-allergic children receiving either OIT with a maintenance dose of 300 mg or 3 g of peanut protein demonstrated that there was no significant difference in efficacy or safety profile when comparing the two groups [44]. Thus, a maintenance dose of 300 mg peanut protein was selected in subsequent pivotal phase III trials.

### Pivotal phase III studies on oral immunotherapy with peanut protein

The recently approved product for OIT contains peanut protein as defatted powder of *Arachis hypogaea L., semen*. It is a standardized, defatted, lightly roasted peanut flour containing the allergens Ara h 1, Ara h 2, and Ara h 6 in defined amounts [37]. These are heat-stable storage proteins from the cupin superfamily and prolamin superfamily, which are recognized by more than 50% of the allergic population by specific IgE antibodies (major allergens).

Two large pivotal phase III studies in the USA and Europe (PALISADE [39]; ARTEMIS [40]) have confirmed the efficacy of this therapy for 4- to 17-year-old children. The international, randomized, placebo-controlled PALISADE trial included 551 4- to 55-year-old patients with peanut allergy. All patients initially received a double-blind placebo-controlled peanut challenge (DBPCFC) and could only be included if they were reacting to a maximum dose of  $\leq 100$  mg peanut protein (approximately 1/3 of a peanut kernel). The primary endpoint of this study was defined as the proportion of children (4–17 years,  $n=496$ ) who tolerated a single dose of  $\geq 600$  mg peanut protein (approximately 2 peanuts, endpoint for North America) with no or only very mild symptoms at the exit DBPCFC. After inclusion, patients were randomized 3:1 to AR101 (name of the peanut protein during drug development) vs. placebo. In an initial dose escalation on day one, five doses of peanut protein/placebo were given in ascending doses (0.5 to 6 mg)

every 20–30 min under medical supervision. If these doses were tolerated, a single dose of 3 mg peanut protein/placebo was given again the next day under medical supervision. Thereafter, study subjects took this dose once daily at home. The dose was increased every 2 weeks under medical supervision for 6 months (20–40 weeks) up to a maintenance dose of 300 mg peanut protein (equivalent to about one peanut kernel) or placebo, which was taken daily for another 6 months. Finally, DBPCFC was repeated, and 67.2% of AR101-treated 4–17 year olds tolerated  $\geq 600$  mg peanut protein in the exit food challenge after approximately 1 year of therapy compared to only 4% of placebo-treated patients (intention-to-treat (ITT) data; 95% confidence interval [CI]: 53.0, 73.3;  $p < 0.0001$ ). Furthermore, 50.3% of AR101-treated children tolerated even a single dose of 1000 mg peanut protein compared to 2.4% in the placebo group (95% CI: 38.0, 57.7;  $p < 0.0001$ ). Thus, the primary endpoint for the age group 4–17 years was met.

Of the 55 adult participants, only 33 completed the study. In the verum group, 41.5% tolerated  $\geq 600$  mg peanut protein in the exit food challenge after therapy compared to 14.3% in the placebo group. The difference between the two groups was not statistically significant.

The safety profile was consistent with that of previously published preliminary studies. Almost every patient experienced mild to moderate symptoms (94.4% AR101, 94.4% placebo) after receiving AR101 or placebo. In descending frequency, symptoms included abdominal pain, vomiting, pruritus, upper abdominal pain, cough, scratchy throat, itching mouth, nausea, urticaria, sneezing, and globus sensation, which diminished or occurred less frequently during the course of therapy. Life-threatening events or deaths did not occur. Serious adverse events (SAEs) were rare overall (AR101 2.2% [9 events], placebo 0.8% [1 event]). Within these anaphylactic/systemic allergic reactions (anaphylaxis defined according to Sampson et al. [45] or systemic reactions beyond this definition) occurred in three cases in the verum group: one severe anaphylaxis with severity grade 3 as defined by Muraro et al. [46] (such as hypoxia, arterial hypotension, or neurologic impairment), one moderate, and one mild systemic allergic reaction (severity classification according to CoFAR, Burks et al. [47]). One case experienced a severe asthma exacerbation and one case experienced a moderate asthma exacerbation. Systemic allergic reactions (anaphylaxis defined according to Sampson et al. with any severity and regardless of association with therapy or systemic reactions beyond this definition) were generally otherwise mild (such as transient pruritus, exanthema/flush, abdominal pain) to moderate (such as prolonged symptoms of urticaria, wheezing without dyspnea, abdominal pain, repeated vomiting). They occurred in 14.2% of the verum group and 3.2% of the placebo group. Epinephrine was used by 14% of

AR101-treated patients and 6.5% of placebo-treated patients. The study was prematurely terminated by 11.6% of AR101-treated patients and 2.4% from the placebo group, mostly due to adverse events. Biopsy-proven eosinophilic esophagitis occurred in one case. In every case, symptoms completely resolved after discontinuation of OIT.

Immunologically, there was a significant increase in peanut-specific IgG4 titers as well as a reduction in peanut wheal size in the skin prick test after therapy [39]. However, there was no statistically significant change in specific peanut IgE levels between baseline and end of study.

The European ARTEMIS study confirmed the efficacy and safety of AR101 therapy [40]: 77 of 132 (58%) included children and adolescents who received AR101 versus 1 of 43 placebo subjects (2%) tolerated a single dose of 1000 mg peanut protein (approximately 3 peanuts kernels) in the exit food challenge after approximately 9 months of therapy. Patients were included only if they had experienced dose-limiting symptoms to  $\leq 300$  mg peanut protein at the screening DBPCFC. The safety profile was similar to that of the PALISADE study. With any allergen exposure (AR101/placebo or accidentally to peanut or other food allergens), systemic allergic reactions occurred in 12% of the verum group and 2% of the placebo group, similar to the PALISADE study. Epinephrine was used by 6.8% of AR101 patients and 2.3% of placebo patients. In the ARTEMIS study, the subjects' quality of life was also assessed, e.g., by means of the FAQLQ questionnaire. In the age group of 8- to 12-year-olds, a significant improvement in the quality of life of the verum group vs. the placebo group was observed with regard to the overall evaluation (total score) and the domains "allergen avoidance and dietary restriction" and "risk of an accidental reaction".

A follow-up study of the PALISADE trial showed a sustained response after the first year of treatment [48]. Patients treated with AR101 in the prestudy were assigned to different treatment arms with continued daily or nondaily dosing. The highest desensitization rate was seen in patients who continued to take the investigational drug daily [48].

OIT with peanut protein as defatted powder of *Arachis hypogaea L., semen* (peanuts) was approved in 2019 by the Food and Drug Administration (FDA) in the USA for 4- to 17-year-old children suffering from peanut allergy. Since October 2020, the European Medicines Agency (EMA) has approved the drug for Europe. The commercial launch in Germany and simultaneous dossier submission to the Joint Federal Committee (G-BA) took place in October 2021. This means that patients can now be treated in specialized health centers before the G-BA and the Institute for Quality and Efficiency in Health Care (IQWiG) have assessed in detail the added value of the drug for people with statutory health insurance. At the same time as submitting the dossier to the G-BA, the company

also plans to apply for a new procedure code, as the therapy effort is very high not only from the patient side, but also from the physician side.

### Implementation of OIT

As is stated in the German summary of product characteristics (SmPC) treatment is indicated for patients between 4–17 years of age and confirmed diagnosis of peanut allergy. Treatment can be continued in patients who turn 18 years within the course of the treatment. For the correct diagnosis of peanut allergy see part 2: Diagnosis of peanut allergy with special emphasis on molecular component diagnostics [3]. In case of unclear history and/or sensitization profile, a diagnostic oral provocation testing should be considered before starting therapy.

Treatment must NOT be performed in the following cases:

- Patients with severe or life-threatening anaphylaxis 60 days prior to initiation of therapy (e.g., severe respiratory, cardiovascular, consciousness, or dual organ system involvement)
- Severe or uncontrolled bronchial asthma
- Known or history of eosinophilic esophagitis or other eosinophilic gastrointestinal disorders
- Suspicion of eosinophilic esophagitis (e.g., dysphagia)
- Chronic, recurrent or severe gastroesophageal reflux disease (GERD)
- Existing or history of systemic mastocytosis
- Hypersensitivity to any of the other ingredients (microcrystalline cellulose, partially pregelatinized corn starch, colloidal anhydrous silicon dioxide, magnesium stearate).

The indication should be critically evaluated in the case of

- Known chronic urticaria; in this case, the safety assessment may be falsified
- Conditions in which severe allergic reactions/administration of epinephrine may impair survival or lead to increased adverse events (e.g., severe cystic fibrosis, unstable angina, recent myocardial infarction, arrhythmias, cyanotic congenital heart disease, uncontrolled hypertension, inherited metabolic diseases).

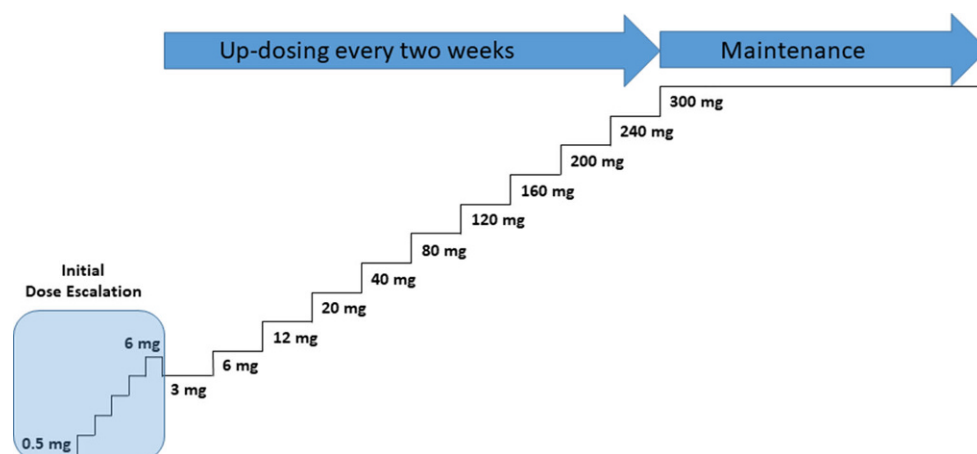
The treatment is carried out in three successive phases:

- Initial dose escalation
- Up dosing
- Maintenance

The medication must be taken orally with an age-appropriate creamy/mushy food that is well tolerated and readily consumed by the patient (either cool or maximum at room temperature). Each dose should be taken, if possible, at the same meal/time of the



**Fig. 2** Overview of the course of therapy of oral immunotherapy (OIT) with peanut protein as defatted powder of *Arachis hypogaea* L., *semen* (peanuts)



day. Peanut avoidance must be continued throughout therapy. Since anaphylactic reactions may occur during this therapy, patients must be very well informed about this and must continue to carry the emergency kit including the epinephrine auto-injector with them at all times.

The initial dose escalation and each first dose of a new dosage level must be taken under medical supervision. The dose may only be increased if the previously taken dose is tolerated. Initial dose escalation takes place on one day under medical supervision in a specialized healthcare facility starting with 0.5 mg (Fig. 2). Every 20–30 min the dose should be increased (subsequently 1 mg–1.5 mg–3 mg–6 mg). If at least 3 mg is tolerated without the need for medical intervention (e.g., administration of medication), the patient can enter the up-dosing phase (Fig. 2). This begins the next day (but no later than four days after initial dose escalation) with a dose of 3 mg, also under medical supervision. Subsequent doses are then taken daily at home. If the dose level is tolerated, the dose is increased to the next higher level after 2 weeks, again under medical supervision (Fig. 2). A total of 11 levels are provided up to a dose of 300 mg peanut protein (equivalent to about one peanut kernel). After each up-dosing, the patient is monitored for 60 min. In addition, an emergency kit including epinephrine for self-injection must be available to the patient at all times, and the patient or parents should be instructed in the recognition of allergic symptoms and the proper use of the medication. Once the dose of 300 mg is reached, maintenance therapy follows (Fig. 2). Here, the patient maintains the dose level of 300 mg daily for at least 24 months, whereby, based on current data, it will be necessary to continue therapy until a point in time not yet determined by current data. An overview of the course of therapy is shown in Fig. 2.

Temporary dose changes during the up-dosing or maintenance may be necessary due to side effects or for practical reasons. In this case, maintenance of the dose level for more than 2 weeks, dose reduction or dose suspension may be necessary according to the

physician's assessment. A reduction of the up-dosing interval of less than 2 weeks is not recommended.

To reduce the occurrence of potential side effects, it is important to consider avoidable and unavoidable cofactors:

- No hot shower/bath before and 3 h after ingestion
- No physical exertion before and 3 h after ingestion
- After physical exercise, signs of a hypermetabolic state (e.g., flushing, sweating, rapid breathing, rapid heart rate) must have resolved before taking the dose
- No alcohol 2 h before or 2 h after the dose
- No dose intake in case of fever/intercurrent illness or asthma exacerbation (in these cases, a physician at short notice should be consulted to discuss possible dose adjustments)
- Infections, asthma exacerbation, menstruation, stress, fatigue, nonsteroidal anti-inflammatory drug use and open mouth sores can lead to increased allergic reactions.

If the dose is missed for a maximum of 2 days, the therapy can be continued at home at same dose level. In case of a longer break, the intake should be under medical supervision for safety reasons. In case of a break/missed dose of at least 5 days, the dose must be reduced to at least 50% of the last tolerated dose and the intake must take place under medical supervision. At a break of at least 14 days, therapy adherence must be assessed and either a restart of therapy or a complete discontinuation of therapy must be considered.

Serious side effects such as difficulty swallowing, difficulty breathing, voice changes or tightness in the throat, dizziness or fainting, severe stomach cramps or pain, vomiting, diarrhea, or severe redness or severe itching of the skin require immediate treatment, including intramuscular administration of epinephrine by means of an auto-injector, also an immediate medical evaluation must be carried out. The appropriate contacts and the emergency plan must be handed out by the attending physician(s)

at the start of therapy adapted to local conditions. No further intake should be made at home and the attending physician should be consulted. Also in case of asthma worsening or signs of an eosinophilic esophagitis, a therapy adjustment including a stop of therapy should be considered. Typical symptoms of a developing eosinophilic esophagitis are heartburn, difficulty swallowing, pain on swallowing, stomach pain or chest pain—not being transient, but occurring recurrently, daily or getting worse. A resumption of therapy should only take place after consulting the attending physician.

### Other, not yet approved therapy concepts

Several other therapeutic concepts are under investigation but are not yet in the approval process. For example, epicutaneous immunotherapy is being investigated in peanut allergic children. In this therapy, allergen exposure is initially controlled by increasing wearing time of the patch which is applied to the back. After 2 weeks, the child eventually wears the patch continuously. The patch as well as the application site is changed daily. The efficacy of this type of desensitization was demonstrated in a phase III trial in 4- to 11-year-old peanut-allergic children [49]. The primary endpoint was defined as the number of study participants who had a reaction at  $\leq 10$  mg peanut protein at screening DBPCFC and a reaction dose of  $\geq 300$  mg peanut protein at the exit food challenge after 1 year of therapy, or number of participants who had a dose-limiting reaction between 10 and 300 mg at screening DBPCFC and a reaction at  $\geq 1000$  mg peanut protein at the exit food challenge. 35% of the active group vs. 14% of the placebo group had met this primary endpoint (ITT population). However, the lower limit of the confidence interval of the difference between placebo and the active group, which was set before the start of the study, was not reached. The most common side effects of this therapy were seen within the patch application area and were reported as itching, redness, urticaria, and worsening of eczema. Mild to moderate anaphylactic reactions (anaphylaxis defined by Sampson et al. [45], severity defined by Muraro et al. [46]) occurred in 3.4% of children in the active group and 0.8% in the placebo group. The company has now modified its product and plans to test the optimized adhesion of the patch in vivo by means of a new phase III study (press release 20 December 2021, DBV Technologies).

Several other therapeutic options are under investigation in clinical trials, such as multiple OIT under simultaneous omalizumab therapy (NCT03881696; NCT04045301), the simultaneous use of OIT and dupilumab (NCT03682770), or hypoallergenic peanut extract for subcutaneous administration (NCT02991885) and the oral mucosal immunotherapy (OMIT) via toothpaste peanut protein administration (NCT04603300). Peanut immunization using the virus-

like particle platform is close to the clinical phase. Recently a double-blind placebo-controlled trial in the USA with 146 1- to 3-year old peanut allergic children could demonstrate the efficacy of an oral immunotherapy in this age group for the end point desensitization [41]. After 134 weeks of OIT, 71% of the verum group and only 1 patient (2%) in the placebo group tolerated 5 g peanut protein during oral challenge testing. After a treatment gap of 6.5 months, a sustained unresponsiveness to 5 g peanut protein was diagnosed in 21% of the active group and only in 1 patient (2%) of the placebo group [41]. Both oral immunotherapy with AR101 (NCT03736447) and epicutaneous immunotherapy (NCT03211247) are now being investigated in phase III trials in 1–3 year olds. Thus, multiple therapeutic options for peanut allergic patients at different ages will likely be available in the next few years.

### Conclusion

With the newly approved drug for oral immunotherapy (OIT; defatted powder of *Arachis hypogaea* L., *semen*), a causal therapy for peanut-allergic children is now available for the first time. The previous management concept of strict allergen avoidance and therapy of accidental reactions has thus been qualitatively significantly expanded by the option of desensitization. This option will not be the right one for all peanut-allergic children. Systemic allergic reactions under OIT are a relatively common side effect. However, they occur in a controlled setting since they are expected by patients and parents as a possible side effect. Based on the data published to date, they can therefore be classified as manageable. Furthermore, the risk of a systemic allergic reaction after accidental peanut consumption in an uncontrolled setting seems to be reduced by desensitization. An exact consideration of the burden of peanut allergy for the family and a potential therapy with its advantages but also disadvantages such as the daily burden of therapy in everyday life and potential risks must be made with each patient and their family individually. This should be done in a detailed educational discussion in the sense of a “shared decision making”. If an OIT is not an option for the patient, it will have to be determined in the coming years which other therapeutic option can be chosen as an alternative.

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