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Current developments in the treatment of peanut allergy

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Abstract Peanut allergy is a potentially life-threatening disease because it leads to severe allergic reactions, especially in children but also in adults. So far, allergen avoidance is the most effective therapy for treating peanut allergy. In this article, current developments of peanut allergy specific immunotherapy are critically discussed based on the existing literature. These include sublingual, epicutaneous and oral peanut immunotherapy. Nonspecific treatment approaches with new-targeted antibodies such as anti-IgE (omalizumab) or anti-IL-4/IL-13 receptor antibodies (dupilumab) can also be used to treat peanut allergy with regard to the mode of action of these antibodies. Multiple studies are already available for omalizumab and are currently performed with dupilumab. Whether and which therapies for the treatment of peanut allergy will be available on the market in the future is not only relevant in terms of clinical effectiveness in the sense of a long-term stable increase in the threshold level, but also in terms of the tolerability in everyday life of affected patients.

Keywords Peanut allergy · Anaphylaxis · Immunotherapy · Anti-immunoglobulin E · Dupilumab

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Introduction

Peanuts belong to the legume family (pulses) and are the most common triggers of severe allergic reactions in children [1]. Studies on the prevalence of sensitization to peanuts have shown a rate of 10.9% for children and adolescents and 8% for adults [2]. A distinction needs to be made here from the prevalence of peanut allergy, i.e., clinically relevant sensitization. Data from Europe show that this prevalence varies according to age and is approximately 1.1% for children aged between 2 and 5 years, 0.1–1.7% for children and adolescents, and 1.3% for individuals aged over 18 years [3, 4]. While allergies to food allergens, such as cow's milk and hen's egg, show a strong to moderate tendency to develop tolerance in childhood, peanut allergy is often known to persist into adulthood [5–7]. Recent analyses of clinical profiles of peanut allergy patients show that anaphylactic reactions due to peanut allergy are more likely to be particularly severe and result in hospitalization [8]. The peanut allergens clinically relevant for severe reactions are heat-stable and belong to the family of storage proteins. They include the 7S globulins (Ara h 1), the 11S globulins (Ara h 3), and the 2S albumins (Ara h 2/6). Of these, Ara h 2 is reported to be a marker allergen for severe reactions in many patients [9, 10]. Ara h 9 is a lipid transfer protein [11] and oleosins (Ara h 10 and Ara h 11) were also recently described in the peanut [12]. In the case of strong sensitization to Bet v 1, specific immunoglobulin (IgE) antibodies to Ara h 8, the Bet-v-1 homolog, may be detectable in the setting of pollen-related cross-reactivity [13]. Profilins (Ara h 5) have also been described in peanut [14].

In addition to acute measures in the event of a reaction, the treatment of peanut allergy includes dietary counselling and strict allergen avoidance [9]. This reduces quality of life for those affected and places re-

Table 1 Overview of published clinical studies

Working group	Journal (year)	Clinical study design	OFC for inclusion	Cohort size, age (years)	Intervention	Duration, maintenance dose	Efficacy data
Oral Immunotherapy							
Anagnostou et al. (STOP II) [18]	Lancet (2014)	Phase 2a, monocentric, RCT	DBPCFC	99, 7–16	Phase 1: pOIT versus avoidance (control group) Phase 2: pOIT (control group)	26 Weeks, 800 mg	Phase 1: 24/39 (62%) of the pOIT group tolerated ≥ 1400 mg peanut protein (versus 0/46 in the control group)
Tang et al. (PPOIT) [19]	J Allergy Clin Immunol (2015)	DBPC/RCT	DBPCFC	62, 1–10	Probiotics + pOIT versus placebo	18 Months, 2000 mg	ppOIT: 23/28 (82.1%) tolerated ≥ 4000 mg peanut protein (2–5 weeks after therapy) Placebo: 1/28 (3.6%) tolerated ≥ 4000 mg peanut protein (2–5 weeks after therapy)
Bird et al. (ARC001) [20]	J Allergy Clin Immunol (2018)	Phase 2, multicenter, DBPC/RCT	DBPCFC	55, 4–21	AR101 versus placebo	20–36 Weeks, 300 mg	AR101: 23/29 (79%) tolerated ≥ 443 mg peanut protein and 18/29 (62%) tolerated ≥ 1043 mg peanut protein Placebo: 5/26 (19%) tolerated ≥ 443 mg peanut protein and 0/26 (0%) tolerated ≥ 1043 mg peanut protein
Vickery, PALISADE Group (PALISADE) [21]	NEJM (2018)	Phase 3, multicenter, DBPC/RCT	DBPCFC	551, 4–55	AR101 versus placebo	12 Months, 300 mg	4–17 Years: AR101: 76.6% tolerated 300 mg, 67.2% tolerated 600 mg, 50.3% tolerated 1000 mg peanut protein in a single dose Placebo: 8.1% tolerated 300 mg, 4% tolerated 600 mg, 2.4% tolerated 1000 mg peanut protein in a single dose
							18–55 Years: no statistical significance AR101: 41.5% tolerated 600 mg peanut protein in a single dose Placebo: 14.3% tolerated 600 mg peanut protein in a single dose
Soller et al. [22]	J Allergy Clin Immunol Pract (2019)	Peanut OIT in real-world setting, multicenter	DBPCFC (optional)	270, 9–71 (months old)	pOIT	Three protocols, 300–320 mg	No DBPCFC control
Blümchen et al. [23]	J Allergy Clin Immunol (2019)	Multicenter, DBPC/RCT	DBPCFC	62, 3–17	Low-dose pOIT versus placebo	13 Months, 125 mg, 250 mg	Low-dose pOIT: 23/31 (74.2%) tolerated ≥ 300 mg peanut protein, 13/31 (41.9%) tolerated 4.5 g peanut protein Placebo: 5/31 (16.1%) tolerated ≥ 300 mg peanut protein, 1/31 (3.2%) tolerated 4.5 g peanut protein
Epicutaneous immunotherapy							
Dupont et al. (ARACHILD) [24]	J Allergy Clin Immunol (2014)	Phase 2, multicenter, DBPC/RCT	DBPCFC	54, 5–17	EPIT versus placebo	18 Months, 100 µg	10-Fold increase in tolerated dose in 40% of the SLIT group
Sampson et al. (VIPES) [25, 26]	J Allergy Clin Immunol (2015)	Phase 2b, multicenter, DBPC RCT	DBPCFC	221, 6–55	EPIT versus placebo	12 Months, 50 µg, 100 µg, 250 µg	10-Fold increase in cumulative threshold dose or ≥ 1000 mg peanut protein in 50% of the 250 µg treatment group (versus 25% in the placebo group)
Sampson et al. (OLFUS-VIPES) [27]	J Allergy Clin Immunol (2016)	Open-label, follow-up study (VIPES)	DBPCFC	173 (83% VIPES participants)	EPIT	24 Months, 250 µg	Results of the interim analysis (treatment duration, 24 months): 10-fold increase in cumulative threshold dose or ≥ 1000 mg peanut protein in 69.7% of participants. 10-Fold increase in the cumulative threshold dose or ≥ 1000 mg peanut protein in 80% of participants in the 6- to 11-year age group
Jones et al. (CoFAR 6) [29]	J Allergy Clin Immunol (2017)	Phase 2, multicenter, DBPC/RCT	DBPCFC	74, 4–25	EPIT versus placebo	52 Weeks, 100 µg, 250 µg	10-Fold increase in cumulative threshold dose in 46% with 100 µg treatment, 48% with 250 µg treatment, 12% with placebo
Fleischer et al. (PEPITES) [30]	JAMA (2019)	Phase 3, multicenter, DBPC/RCT	DBPCFC	356, 4–11	EPIT versus placebo	12 Months, 250 µg	Increase in threshold dose (from < 10 to ≥ 300 mg and from 10–300 mg to ≥ 1000 mg) in 35.3% with 250 µg treatment and 13.6% with placebo
Fleischer et al. (PEOPLE) [31]	J Allergy Clin Immunol (2020)	Open-label, follow-up study (PEPITES)	No OFC for inclusion	198, 4–11	EPIT	36 Months, 250 µg	12-Month therapy: increase in the threshold dose to ≥ 1000 mg in 40.4% (57/141) 36-Month therapy: increase in threshold dose to ≥ 1000 mg in 51.8% (73/141) Increase in threshold dose in 75.9% (107/141) 13.5% (19/141) tolerated 5444 mg peanut protein in the DBPCFC

Table 1 (Continued)

Working group	Journal (year)	Clinical study design	OFC for inclusion	Cohort size, age (years)	Intervention	Duration, maintenance dose	Efficacy data
Sublingual immunotherapy							
Kim et al. [32]	J Allergy Clin Immunol (2011)	Monocentric, DBPC/RCT	No OFC for inclusion	18, 1–11	SLIT versus placebo	12 Months, 2000 µg	Median cumulative tolerated dose: SLIT: 1710 mg peanut protein Placebo: 85 mg
Fleischer et al. [33]	J Allergy Clin Immunol (2013)	Multicenter, DBPC/RCT	DBPCFC	40, 12–37	SLIT versus placebo	44 Weeks, 1386 µg	SLIT group: increase in median cumulative tolerated dose in 70% (4/20): from 3 to 496 mg Placebo group: increase in median cumulative tolerated dose in 15% (3/20)
Narisety et al. [34]	J Allergy Clin Immunol (2015)	Monocentric, DBPC/RCT	DBPCFC	21, 7–13	SLIT versus OIT (active SLIT/placebo OIT versus placebo SLIT/active OIT)	12 Months, 3.7 mg (SLIT), 2000 mg (OIT)	141-Fold increase in threshold dose (OIT group) versus 22-fold increase in threshold dose (SLIT group)
Burks et al. [35]	J Allergy Clin Immunol (2015)	Follow-up study (Fleischer DM, et al.)	No OFC for inclusion	37, 12–36	Open-label (follow-up)	36 Months, 1386–3696 µg	4/37 (10.8%) Desensitized for 10 g peanut protein >50% Dropout

DBPC double blind placebo controlled, *DBPCFC* double blind placebo controlled food challenge, *EPIT* epicutaneous immunotherapy, *OFC* oral food challenge, *OIT* oral immunotherapy, *pOIT* peanut oral immunotherapy, *ppOIT* peanut OIT plus probiotics, *RCT* randomized controlled trial, *SLIT* sublingual immunotherapy

strictions on everyday life. Although food allergies are rarely fatal, deaths are frequently reported, particularly in childhood [15]. In summary, there is a pressing need for effective therapies to be developed and made available for the treatment of a clinically relevant peanut allergy involving recurrent systemic reactions.

In contrast to inhalation allergies, specific immunotherapy is not yet established for the treatment of peanut allergies. The fact that the initial studies using subcutaneous administration frequently reported systemic reactions during the course of treatment is of importance in this context [16, 17]. The current article presents and critically discusses novel therapeutic approaches for the treatment of peanut allergy, with a differentiation being made between specific and nonspecific treatment. The specific forms of treatment can also be differentiated on the basis of route of administration. Numerous studies have been published to date on epicutaneous, sublingual, as well as oral immunotherapy (Table 1; [18–35]) and are discussed below.

Epicutaneous peanut immunotherapy

Epicutaneous immunotherapy involves the administration of the allergen by means of a skin patch. The clinical evidence shows efficacy for epicutaneous immunotherapy as it increases the oral threshold dose in provocation testing after a treatment phase of several months with very good tolerability [31]. A recently published phase-2 placebo-controlled dose-finding study showed statistically significant results with a 10-fold increase in dose in 48% of patients receiving epicutaneous therapy with a patch containing 250 µg peanut protein [29]. In the subsequent phase-3 study (PEPITES), the eliciting dose was increased after 1 year from less than 10 mg to more than 300 mg and from 10–300 mg to over 1000 mg peanut protein before and after therapy in 35.3% of patients compared to 13.6% in the placebo group [30]. Despite this highly significant threshold increase in the active group, the statistical efficacy goals were not met. The evaluation of these results has not been completed as yet [30]. After 3 years of treatment, efficacy further increased to 51.8% [31]. Interestingly, the safety data were comparatively satisfactory: only three subjects dropped out due to anaphylactic reactions (1.3%), and systemic allergic reactions occurred in eight patients (3.4%) [30].

Oral peanut immunotherapy

Oral immunotherapy with peanut protein has been performed for decades in selected patients at allergy centers [22]. The literature describes a number of protocols with both low and higher doses of peanut protein. Essentially, these case reports and case series show that oral immunotherapy can result in an increase in threshold doses, and, as such, offer a certain level of protection against accidental reactions. A recently published paper showed that low-dose oral peanut immunotherapy (maintenance dose, 125–250 mg) resulted in 23 of 31 treated patients (74.2%) tolerating ≥300 mg peanut protein and 13 of 31 patients (41.9%) tolerating 4.5 g peanut protein versus one of 31 patients in the placebo group [23]. Data on specific oral peanut immunotherapy in phase-2 and -3 clinical trials have recently been published [20, 21]. Here again, an efficacy in terms of an increased tolerance to up to 1 g peanut protein was observed [20, 21]. Studies have shown that systemic reactions

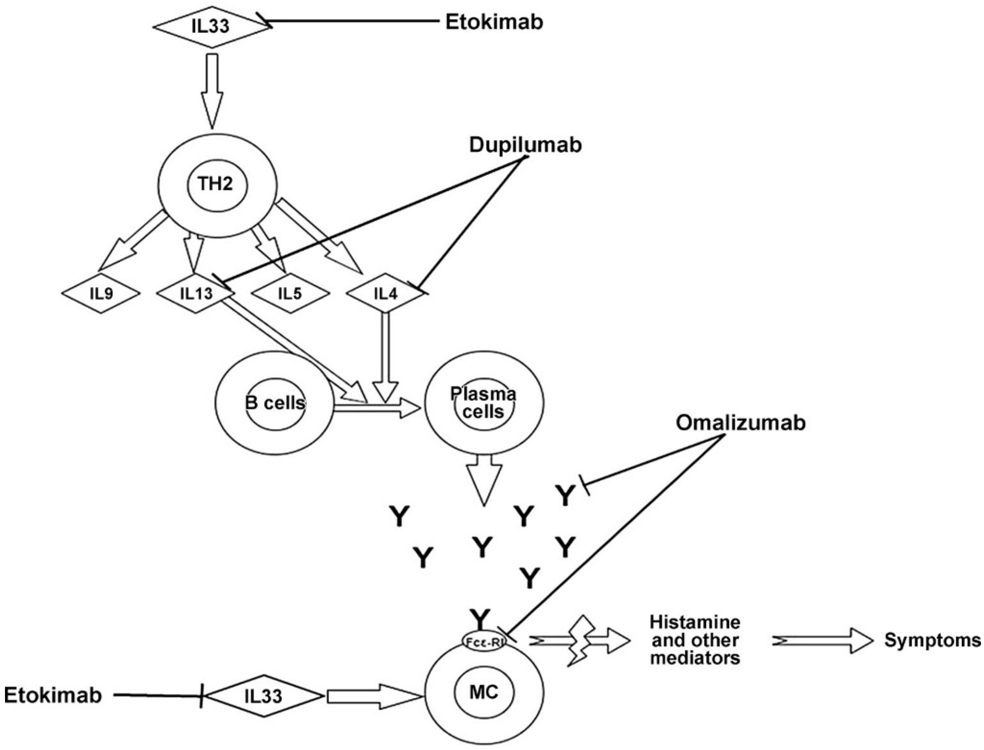

Fig. 1 The use of biologicals in food allergy. *Y* immunoglobulin E , *Fcε-RI* Fc epsilon receptor, *MC* mast cells, *IL* interleukin, *TH2* T helper 2

as side effects of treatment occur in up to 10% of patients, particularly during the dose escalation phase of therapy [20, 21, 36]. Therefore, this type of treatment should primarily be performed in specialized centers under close medical supervision in the future. It is particularly important that patients and family members are well trained in the emergency management in the case of a reaction.

Approval procedures for both epicutaneous and oral immunotherapy are currently underway in Europe. Since the phase-3 studies were conducted predominantly in children, one can expect approval to be granted primarily for this age group.

Another study examined whether the use of probiotics in addition to oral immunotherapy is beneficial. A double-blind placebo-controlled study evaluated the effect of *Lactobacillus famosos* in combination with oral peanut immunotherapy in 62 children [19]. Although the results showed a degree of superiority for the probiotic group, further studies are required in the future to confirm this result. Moreover, side effects were also not uncommon, with oropharyngeal and gastrointestinal symptoms, as well as systemic reactions, being described. Gastrointestinal symptoms led to treatment discontinuation in up to 30% of patients [37].

In principle, it has not yet been clearly proven whether oral immunotherapy actually leads to long-term tolerance, or instead results in a temporary deactivation. Only a handful of patients exhibit long-term stable tolerance to the food in question, if not regularly consumed, following discontinuation of oral tolerance induction [38]. Most studies show maximum long-term data at between 1 and 3 years after treatment discontinuation. The rate of patients developing real tolerance is presumably higher among young children. For example, a study by Soller et al. showed that 29 of 32 patients who received oral immunotherapy at preschool age developed tolerance [22]. Therefore, in principle, it is possible to achieve long-term tolerance with oral as well as with epicutaneous immunotherapy. Further investigations are needed in the future to identify the time of long-term tolerance and relevant patient groups.

Sublingual peanut immunotherapy

Sublingual immunotherapy (SLIT) with peanut also results in clinical effects with a good safety profile. However, sublingual peanut immunotherapy achieves only a minimal increase in tolerated protein quantities and the dosages are limited in relation to the volume to be administered. In a study by Kim et al., a 20-fold increase in tolerated dose (1710 mg, median) was observed in the context of SLIT [32]. Although no anaphylactic reactions occurred, oropharyngeal events represented the adverse side effects predominantly observed [32]. Another study conducted by Fleischer et al., has shown an increase of the median cumulative dose tolerated increased from 3 to 496 mg after 44 weeks of treatment in the SLIT group [33].

Table 2 Omalizumab in food allergy[a]

Mechanism	
Omalizumab binds to IgE and prevents binding to the FcεRI receptor on basophils and mast cells. Free IgE and the release of mediators are reduced	
Concepts	
Omalizumab as monotherapy	
Omalizumab as adjuvant therapy	Oral immunotherapy for one food allergen (peanut or cow's milk)
	Oral immunotherapy for multiple food allergens
Potential advantages	
Reduction in treatment duration	
Better efficacy	
Better tolerance at higher dosages	
Acceleration of the dose escalation phase of immunotherapy	
Increased tolerance	
Reduction in the rate of side effects	

Fcε-RI Fc epsilon receptor, *Ig* immunoglobulin
[a]Omalizumab in food allergy and potential benefits (based on data from [42–46])

Use of biologics to treat of peanut allergy

The biological agent that has been the longest in use in the field of allergies is anti-IgE, which has been approved for the treatment of steroid-resistant allergic asthma in Germany since 2005. In addition, omalizumab has been approved for the treatment of chronic spontaneous urticaria since 2014. Omalizumab (Fig. 1) is a recombinant DNA-produced human IgG1 antibody that selectively binds IgE and prevents it from binding to the high-affinity IgE receptor (FCεR1) on the surface of mast cells and basophils [39, 40]. The first study on the use of anti-IgE in the context of specific immunotherapy was carried out using a grass pollen extract [41]. Although the data did not show improved efficacy, the findings pointed to better tolerability of the grass-specific immunotherapy. The first study on the use of omalizumab in food allergy was published many years ago [42]. Unfortunately, the development program that was underway at that time was not pursued due to the risk of severe reactions during treatment in patients with severe food allergy. Studies on the use of omalizumab for the treatment of food allergy were resumed around 10 years ago. The concept pursued here was to combine potentially effective oral immunotherapy with anti-IgE treatment to reduce the rate of side effects.

Indeed, the evidence on peanut-allergic children shows that it is possible to successfully perform oral desensitization with peanut and a significantly reduced side effect profile. For example, in a study of 37 children treated with anti-IgE for 12 weeks, 1-day desensitization with up to 250 mg peanut protein, followed by weekly increments in peanut protein up to 2000 mg, was shown to be successful. Of the 29 patients treated with anti-IgE, 23 (79%) tolerated 2000 mg peanut protein 6 weeks after completion of omalizumab treatment, while only one in eight patients (12%) in the placebo group achieved this. The rate of side effects was also significantly lower in the omalizumab-treated group [43]. Anti-IgE can also be successfully used in food allergy even when not combined with oral immunotherapy, as reported in numerous studies and case reports [44, 45]. These studies reported an improved tolerance of 500–6500 mg peanut protein, but there are also patients in whom the treatment was ineffective, meaning that efficacy needs to be proven by oral provocation tests.

Ultimately, the concept of omalizumab monotherapy is to achieve long-term treatment, while a combined use with oral immunotherapy aims to provide temporary anti-IgE treatment. This would reduce not only costs, but also the repeated use of injections.

Another recent study investigated the efficacy of anti-IgE treatment in children allergic to several foods [2–5]. That particular study also showed that, at week 36, the omalizumab-treated group (30/36, 83%) was significantly more likely to tolerate 2 g protein of more than two of the relevant food allergens compared to placebo (4/12, 33%) [46]. These data show that omalizumab can improve the efficacy of oral immunotherapy even in patients with multiple food allergies (Table 2).

Another antibody of great interest with regard to the treatment of food allergies is dupilumab. This antibody is directed against the IL-4 receptor α chain and interferes not only with IL-4 but also the IL-13 signal transduction pathway (Fig. 1). Dupilumab has been approved for the treatment of atopic dermatitis in Germany since 2017 and for the treatment of Th2-mediated bronchial asthma since 2019. In addition to extremely good clinical efficacy and tolerability, a reduction in both total and specific IgE was observed in patients during treatment. As such, one can also assume efficacy in food allergy [47]. Clinical studies on this are currently underway, suggesting that this interesting approach may lead to new therapeutic options in the future.

Etokimab is another antibody that has been evaluated as a monotherapy for peanut allergy in a randomized phase-2a placebo-controlled study. This is an anti-IL-33 antibody that may be effective in treating peanut allergy [48]. A recently published study showed that the etokimab-treated group (11/15, 73%) tolerated at least 275 mg peanut protein at day 15 using double-blind placebo-controlled food challenge (DBPCFC). Further 4 of 7 patients (57%) tolerated at least 275 mg peanut protein at day 45 with DBPCFC [48].

Conclusion

Peanut allergy is common and can cause severe, and in very rare cases even fatal, allergic reactions. Since there is no causal therapy for this disease as yet, avoidance of the triggering allergens remains the standard therapy [9]. However, this often leads to a significant reduction in quality of life for those affected, meaning that new therapies are urgently required from a medical perspective. Although specific immunotherapy with food allergens (oral immunotherapy [OIT], epicutaneous immunotherapy [EPIT], and sublingual immunotherapy [SLIT]) is potentially effective, it carries the risk of side effects. Deployment of these forms of treatments, which are currently being tested for children with peanut allergy, requires optimal collaboration between patients receiving treatment in allergy centers and pediatricians. Therefore, biologics such as anti-IgE and the anti-IL-4/IL-13 receptor antibody dupilumab hold a great potential for the treatment of peanut and other food allergies in children and adults. These biologics modulate the IgE-dependent reactions that occur in food allergies and can be used alone or in combination with allergen-specific approaches. Studies are currently underway worldwide and will hopefully contribute to a sustainable and, above all, safe treatment concept for patients in all age groups in the future.

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