Review

Food Allergen Immunotherapy in the Treatment of Patients with IgE-Mediated Food Allergy

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Review

Food Allergen Immunotherapy in the Treatment of Patients with IgE-Mediated Food Allergy

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Abstract: The prevalence of allergic diseases, including food allergy, is increasing, especially in developed countries. Implementation of an elimination diet is not a sufficient therapeutic strategy in patients with food allergy, whose quality of life is significantly impaired. In recent years, new effective therapeutic strategies have been developed, such as the application of oral, sublingual, and epicutenous immunotherapy. Oral immunotherapy is the most often applied strategy because of its effectiveness and ease of application, with an acceptable safety profile. The effectiveness of oral immunotherapy in patients with egg, cow's milk and peanut allergy has been proven both in terms of raising of the threshold and the development of tolerance, and in some patients, the development of sustainable unresponsiveness. Although oral immunotherapy is an effective treatment for food allergy, several limitations, including long duration and a significant rate of reported adverse events, reduces its success. Therefore, new therapeutic options, such as treatment with biologicals, either as combinations with food allergen immunotherapy or as monotherapy with the aim of improving the efficacy and safety of treatment are being investigated.

Keywords: food allergy; IgE mediated food allergy; oral immunotherapy; OIT; sublingual immunotherapy; SLIT; epicutaneous immunotherapy; EPIT; biologics

1. Introduction

Food allergen immunotherapy (FAIT) has been used in recent years as a novel and sustainable treatment strategy for patients with clinically relevant IgE- mediated food allergy [1–3]. As in the treatment of other allergic diseases, food allergen immunotherapy is the only etiological therapy. Unlike traditional approaches in which a patient with a proven food allergy is recommended keeping a strict elimination diet and using symptomatic drugs such as adrenalin in case of anaphylaxis, allergen immunotherapy is a new approach in the treatment of food allergy [3,4]. Complete elimination of the food allergen in question from the patient`s diet and avoidance of any contact with the food by ingestion, skin contact, inhalation is difficult to implement in practice due to the risk of cross-contamination or accidental exposure [2,3]. It is undoubtfulthat patients with food allergies have a significantly impaired quality of life, both because of the constant fear of a life-threatening reaction as well as of demanding diets that can affect their nutritional status and a balanced diet if important nutrients are avoided. Because of that, the introduction of allergen immunotherapy in patients with clinically relevant food allergies has offered a significant improvement in the management of such patients [5].

Certain specificities in the immune response during FAIT related to the different application routes (oral, sublingual, epicutaneous), type of food allergen, protocols (doses and frequency of administration) appear to be associated with the effectiveness but also with the risk of side effects [5–7].

The primary goal of FAIT is to increase the response threshold and achieve desensitization or tolerance, and in some patients, sustained unresponsiveness (SU) even after discontinuing the regular use of allergens. This increase in the threshold is achieved after a variable period of application of increasing food allergen doses. The challenge of FAIT is to achieve SU to a food allergen, after the

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discontinuation of immunotherapy. Gaps persist in our understanding of the immune mechanisms of food allergy and how FAIT can lead to SU, especially since the number of patients with relapse increases over time after discontinuation of treatment [6,7].

The aim of FAIT is not only achieving SU or reduction of food allergen reactivity, but to attenuate life-threatening allergic reactions and reduce visits to the emergency department and hospitalization, as well. Furthermore, it is not enough to achieve and prove effectiveness of FAIT, it is necessary to carry out treatment with an acceptable risk of side effects [8,9]. In selected patients in whom the protocols are adapted or in whom the allergen is applied sublingually or epicutaneously, the risk and frequency of side effects can be reduced. Unfortunately, with such routes of application, overall lower maintenance doses are reached than with oral immunotherapy. Therefore, the risk of adverse events (AE) during food immunotherapy is likely dependent on the route, maintenance doses, processing and allergenicity of the food allergen, as well [7–9].

2. Mechanisms of Food Allergen Immunotherapy

FAIT is considered as an effective method for treating patients with IgE-mediated food allergies [10]. The mechanisms involved in the development of tolerance and immune modulation during FAIT are not fully understood. Development of immune tolerance and T and B cell responses changes were found in patients during FAIT [11,12]. A switch in immune responses from Th2 to Th1 cell polarization with an increase of INF-γ and a decrease of Th2 related cytokines (IL-4, IL-13) were reported. During immunotherapy exposure to continuous high doses of food allergens leads to Th2 and Th2A anergy and/or deletion and an increase in T regulatory cells which leads to the suppression of downstream allergic responses.

FAIT incompletely targets subsets of Type 2 immune cells which is a transient and non-permanent shifting [13]. Additionally, studies show that the function and number of Treg cells increase during FAIT [11,14]. In the development of peripheral tolerance Treg cells have a critical role, including the activation of specific cell subpopulationssuch as: inducible T regulatory (iTreg) cells, natural T regulatory (nTreg) cells and Tr1 cells and TGF-γ producing Th3 cells [15]. However, the impact of FAIT on the differentiation Treg subpopulations is not well understood. Certain studies showed an association between increased Tregs and improved outcomes in immunotherapy [16,17] while others did not prove the same effect [18,19]. A significant suppression in T follicular helper cells (Tfh) cells and transformation of follicular regulatory T (Tfr) cells following FAIT were found. Tfr cells may have important roles during FAIT and the development of immune tolerance which results in a significant decrease in Th2 responses. Modification of the Th2-mediated immune response appears to be essential for the achievement of tolerance to a particular food allergen, i.e. in the prediction and efficacy of the efficacy of FAIT [20]. In FAIT with egg, high baseline levels of of egg specific CD4+ Th2 cells strongly predicted failure of FAIT treatment [21]. In a study focusing on FAIT to peanut the failure to suppress Th2 response was associated with treatment failure [19].

Generally, every form of FAIT i.e., oral, sublingual and epicutaneous immunotherapy is characterized by decrease in basophil and mast cell activation [22,23]. Peanut oral immunotherapy (OIT) and milk sublingual immunotherapy (SLIT) have shown early but transient decreases in basophil activation with the loss of tolerance after the discontinuation of the immunotherapy [24,25]. During the up-dosing phase of FAIT, there is an initial rise of allergen-specific IgE levels, which is a consequence of the proliferation of allergen-specific memory B cells, followed by a gradual decrease of allergen sIgE at the end of the therapy [26].

Changes in the humoral response during FAIT are manifested by an increase in food protein specific immunoglobulin G, subclass 4 (IgG4) and specific immunoglobulin A (IgA) as well [27,28]. The increase of food specific IgA may play a role in the induction of tolerance [29]. Increased levels of specific IgG4 [30] are supposed to facilitate desensitization through its binding to the inhibitory IgG receptor (FcγRIIb), thus suppressing IgE signaling pathways [30,31]. The induction of allergen specific IgG4 during FAIT seems to be a result of the IL-10 producing subpopulations of regulatory T or B lymphocytes in desensitized patients [32,33].

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Decreased activation of basophils and mast cell are observed during the desensitization phase of FAIT measured by the suppression of the allergen-specific skin prick test and basophil activation test [34].

Modulation in the response of CD8+ T lymphocytes can be a predictor of response to OIT as well. The POISED study with peanut OIT showed that baseline levels of naïve CD8+ T cells and peanut -and Ara h 2-specific IgE were in positive correlation with treatment efficacy [35]. The role of dendritic cells during FAIT is not well established. An association between positive response to therapy and decreased TNF-α producing myeloid dendritic cells (mDCs) was also reported [36].

Although numerous studies have been published in recent years on the mechanisms action in FAIT, it has not yet been clarified which key changes in the immune response are related to the effectiveness of the treatment. Additional research is needed to pinpoint potential predictive biomarkers of treatment success and failure [37].

3. Oral Immunotherapy (OIT)

OIT represents the most common route of administration of FAIT where the allergen applied orally is immediately swallowed. It consists of daily ingestion of the food allergen dose starting below a patient's threshold and increasing the dose over time to increase tolerance to that food [38]. The first report of OIT dates back in 1908 when Schofield successfully desensitized a 13 year old boy with a history of anaphylactic reactions to egg by consuming gradually increasing amounts of egg, while otherwise avoiding egg completely. Although this early success has been promising, OIT was disregarded for the most part of the 20th century. However, given the several fold increase in the prevalence of food allergy in the last 30 years, OIT has has very much come to focus again [39].

3.1. Efficacy of OIT

OIT is currently the most studied type of FAIT but due to the heterogeneity of studies (trial design, sample size, participant's age and their baseline allergy status, dose-increase schedule, maintenance dose and therapy duration) it is difficult to compare them. This review included randomized controlled trials (RCT) on milk, egg and peanut, freely available on PUBMED (Tables 1–3)

Table 1. Review of efficacy and safety of OIT to milk.

reference	design	sample	participants characteristic	Form of allergen	duration	Maintenance dose	Efficacy	safety
milk								
Skripak et al. (2008) [40]	Double-blind, placebo-RCT	n=20 (6-17 y) OIT: n= 12 Placebo: n= 7	Positive DBPCFC to 2,5g MP. Baseline median threshold: 40mg MP	Milk powder	5-6 months	500mg MP (15 ml of milk)	Median threshold after OIT: OIT: 5140mg Placebo: 40mg (P=0,003)	AE/total doses: OIT 45,4%, placebo: 11,2% AE/each participant: OIT 35%, placebo group 1%. AAR: OIT 1%, placebo 0%
Narisety et al. (2009) [41]	Extension of previous p study[40]	N=15 (6-16y)	Negative DBPCFC to 2,5g MP	Dairy products	3-17 months	Daily diary intake at home	OFC to 16g MP: Negative for 33%	AE/total doses: 17% Epinephrine: 0,2% reaction

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Inuo et al. (2018) [46]	Double-blind, placebo-RCT, 2 phase: 8 weeks pHF or eHF, then 8 weeks all on eHF	n= 25 (1-9y) 2 group: active: pHF-pHF (n=13) placebo: eHF-eHF (n=12)	History of systemic reactions to milk. Positive OFC to 20ml rCMF	pHF	16 weeks	0,5-20ml of pHF	OFC with rCMF: Threshold at the end of first phase: Significantly elevated in pHF.pHF (P=0,048)	AE: not severe reaction 2 participants in active group mild reaction
Nagakura et al (2021) [44]	Open-label RCT	n=33, >5y HM-OIT: (n=17) UM-OIT (n=16)	Positive DBPCFC on 3-ml HM, History of milk anaphylaxis	HM vs. UM	1 year	3 ml milk	Desensitization to 3ml and 25ml: HM-OIT: 35%, 18% UM-OIT; 50%, 31% (P=0,34, P=0,43)	AE at home dose: HM: OIT: 8,1%; UM-OIT: 9,6% AE moderate/severe at home: HM-OIT: 0,7%; UM-OIT: 1,4% (P=0,0002)
Maeda et al. (2021) [42]	Open-label RCT	n= 28, 3-12y OIT: n=14 Control: n=14	Positive OFC to 10 ml milk	Liquid milk	1 year	100ml milk	OFC to 100ml milk: OIT: 50% Control: 0% (P< 0,01)	AE required adrenaline: OIT: 43% participants Control: 0% participants
Van Boven et al. (2023) [45]	RCT follow-up study	n=18 (6-36 months) OIT: n= 11 control: n=7	Milk allergy diagnosed by allergist)	iAGE	24 months	5% total protein intake/ day	DBPCFC (4,3g MP): OIT vs. placebo: T1 (8 months); 73 vs 57% T3 (24 months): 82 vs 71%	AE: no product related

RCT- randomized controlled trial; y- years; OIT- oral immunotherapy; DBPCFC- doble-blind placebo-controlled food challenge; MP: milk protein; AE- adverse events; anaphylactic adverse reactions; OFC- oral fool challenge; pHF- partially hydrolyzed formula; eHF- extensively hydrolyzed formula; rCMF- regular caw's milk formula; HM- heated milk, UM: unheated milk; iAGE- heated milk protein standard product.

Table 2. Review of efficacy and safety of OIT to egg.

reference	design	sample	participants characteristic	Form of allergen	duration	Maintenance dose	Efficacy	safety
Burks et al. (2012) [47]	Double-blind, placebo-RCT	n=55 (5-11y) OIT: 40 Placebo: 15	Clinical history of egg-allergy	EWP	24 months	2g EPW	At 10 and 22 months:	AE: % participants OIT: 78%; Placebo: 20%

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							Desensitization to 5 and 10g of EPW: OIT: 55% and 75% Placebo: 0% and 0% (P<0,00, P<0,0011) At 24 months: SU to 10g EPW + whole cooked egg: OIT: 11%, placebo: 0% (P<0,03)	(P<0,01) Severe AE: no
Jones et al. (2016) [7]	Extension of previous study[47] at 4y	n=55 (5-11y) OIT: 40 Placebo: 15	Clinical history of egg-allergy	EWP	2y	2g EPW	SU to 10g EPW + whole cooked egg by 3 and 4 y: OIT: 45% and 50%	AE during OIT dosing: 54% OIT participants, mostly mild symptoms
Itoh-Nogato et al. (2018) [50]	Randomized, parallel-group, delayed-start study. 1st stage: early-start group on rush OIT. 2nd stage: all participants on OIT	n=45 (5-15y) early start: n= 23 (received rush OIT for 3 months) late-group: n=22 (continue egg elimination for 3 months before OIT)	positive DBPCFC to ≤ 500 mg dried raw EPW	EWP	1y	60g of cooked egg ~ 1 medium size egg or 1g EPW	Desensitization to 1000mg EPW after 3 months: Early star: 87% Late start: 22% (p< 0,001).	AE during first stage: Early-star: 80% Late-star: 0% AE requiring adrenaline; 11,6%
Kim et al. (2020) [48]	Extension of previous published study[47] at 5y	n=55 (5-11x) OIT: 40 Placebo: 15	Clinical history of egg-allergy, Completed previous OIT study		1y	Unlimited consumption all form of egg	Ingestion all form of egg: SU-OIT: 100% Desensitized OIT: 43% Non-desensitized OIT: 17% Placebo: 36%	AE: no OIT participants reported symptoms to any baked egg consumption
Kim et al.	Open label	n= 50 (3-36y) BE-R): n=27	Negative	BE vs. EWP	2y	2000 mg egg	SU to 7,444 mg white egg protein:	AE: % participants: BE-R: 2,8%

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(2020) [6]	randomized trial	OIT-R): n=23. OIT-assigned (OIT-A) comparison: 39	DBPCFC to BE Positive DBPCFC to unbaked egg (1444mg of egg white protein)			white protein	BE-R= 11,1% OIT-R: 43,15% OIT-A 17,9%	OIT-R: 3,9% OIT-A: 12,6% Severe AE: only in OIT groups
Palosuo et al. (2021) [49]	Open-label randomized trial	n= 50 (6-17y) OIT: 32 Control: 18	Positive DBPCFC to heated egg white	EWP	8 months	1g egg-white protein	Desensitization to 1g of egg white protein: OIT: 44% Control: 4,8%	AE: 82% participants during build-up phase No severe reactions

RCT- randomized controlled trial; y- years; OIT- oral immunotherapy; EWP- egg white powder; SU- sustain unresponsiveness; AE: adverse events; DBPCFC- double-blind placebo-controlled food challenge; BE-R- baked egg randomized. OIT-R- OIT randomized, OIT-A- OIT assigned.

Table 3. Review of efficacy and safety of OIT to peanut.

reference	design	sample	participants characteristic	Form of allergen	duration	Maintenance dose	Efficacy	safety
Varshney et al. (2011) [56]	Double-blind placebo RCT	n=25 (1-16 y) OIT= 16 Placebo= 9	Clinical history of reaction to peanut (<60 min after ingestion)	Peanut flour	1y	4000 mg PP ~ 15-16 peanuts	Desensitization to 5g PP: OFC: 100%, placebo: 0%	AE/dose: 1,2% in OIT participants during build-up phase Epinephrine: no
Anagnostou et al. (2014) [57]	Crossover 2- phase-RCT (STOP II)	n= 85 (7-16y) OIT: 46 Control: 39 2.phase: Control -> OIT	Immediate reaction after peanut ingestion, positive DBPCFC	Peanut flour	6 months	800mg PP	Desensitization to 1400mg PP: First phase: OIT: 62%, control: 0% (p<0,001) Second phase: Control after OIT: 54%	AE per OIT dose: 6,3%- mild reaction Adrenaline: 0,01% dose

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Vickery et al. (2017) [58]	Double-blind placebo RCT	n= 37 (9-36 months) Low dose (LD): 20 High dose (HD): 17	Positive OFC to 4g PP	Peanut-flour	22-36 months	PP: LD: 300 mg HD: 3000 mg	SU to 5g PP: 29/37 (78%) LD: 85%; HD: 71%, p=0,43 Control: 4%	AE: % participants: LD: 90%, HD 100%
Bird et al. (2017) [60]	Double-blind placebo RCT Phase 2 (ARC001)	n= 55 (4-26y) AR101: 29 Placebo: 26	Positive DBPCFC to 143 mg PP	AR101-comercial product	20-34 weeks	300mg PP	Desensitization to 300mg PP AR101: 79% placebo: 19% (p<0,001) Desensitization to 600mg PP: AR101: 62% placebo: 0% (p<0,001)	AE: % participants during treatment: AR101: 93%, placebo: 46%. No severe AE
Vickery et al (2018) [61]	Double-blind placebo-RCT Phase 3 (PALISADE)	n= 496 (4-17y) AR101: 372 Placebo: 124	Positive DBPCFC to 100 mg PP (1/3 peanut)	AR101-comercial product	1y	300mg PP	Desensitization to 600mg PP: AR101: 67,2%, placebo: 4% (p<0,001)	AE: % participants: AR101: 98,7%, placebo: 95,2% Severe AR: AR101: 4,3%, placebo: 0,8%
Chintrajah et al. (2019) [35]	Double-blind placebo-RCT 2 phase study Peanut-0: no peanut after OIT Peanut-300: 300mg PP daily after OIT Placebo: received placebo (POISED study)	n= 120 (7-55y) Peanut -0: 60 Peanut-300: 35 placebo: 25	Positive DBPCFC to 500 mg PP	Peanut flour	3y	4mg od PP	Negative DBPCFC to 4g PP at week 104 (desensitization) and 117 (SU): Peanut-0: 85%, 35% Peanut-300: 83%. 54% Placebo: 4%, 4% SU to 4 g PP at week 156: Peanut-0: 13 Peanut-300-37%	AE: % participants through 1st to 3rd years: Peanut-0: 95%-2% Peanut-300: 91%-20% Placebo: 64%-5%
reference	design	sample	participants	Form of allergen	duration	Maintenance dose	Efficacy	safety

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			characteristic					
Vickery et al. (2020) [62]	Open-label follow-on study of previous study[61] (ARC004) PTAH= formerly AR101	n=358 (4-17y) PTAH: 256 A) PTAH: daily dosing: 300mg daily B) PTAH: non- daily dosing 300mg (e.g. biweekly) C) PTAH-naive: 102	PTAH: negative DBPCFC to 300mg PP PTAH naïve: placebo arm from PALISADE	PTAH (Palforzia commercial product)	1-2y	300mg of PTAH	Desensitization to 2g PP Daily dosing> non-daily dosing	AE: almost all PTAH participants Daily dosing< non-daily dosing
Jones et al (2022) [59]	Double-blind placebo RCT (IMPACT trial)	n= 146 (12-48 months) OIT: 96 Placebo=50	Positive DBPCFC to 500mg PP	Peanut flour	160 weeks	2000mg PP	Desensitization to 5g PP OIT: 71%, placebo: 2% (p<0,0001) SU to 5g PP: OIT: 21%, placebo: 2% (p=0,0021)	AE: % participants: OIT: 98%, placebo: 80% Epinephrine: OIT 22%, placebo 0%
Fernandez-Rivas et al (2022) [63]	Open label follow-on study of previous study[62]	n= 130 (4-17y) A: 104 (1,5y) B: 26 (2y)	negative DBPCFC to 300mg PP	PTAH (Palforzia-commercial product)	1,5-2y	300mg of PTAH	DBPCFC to 2g PP: A: 48,1%; B: 80,8%	AE: decreased throughout the intervention period in both groups

RCT- randomized controlled trial; y- years; OIT- oral immunotherapy; PP- peanut protein; AE: adverse events; DBPCFC- double-blind placebo-controlled food challenge; LD- low dose; HD- high dose; SU- sustain unresponsiveness; PTAH- peanut (*Arachis hypogaea*) allergen powder-dnfp (Palforzia®, Aimmune Therapeutics).

3.1.1. Milk OIT

The first milk OIT double-blind RCT was carried out in 2008 by Skripak et al. involving 20 children with cow's milk allergy (CMA) [40]. All children were desensitized with median increasing reactivity threshold from baseline 40 mg to cumulative dose of 5140 mg milk protein on the end of OIT, with no change in threshold in the placebo group. AE were frequent in the OIT group, but nearly 90% were mild to moderate with no treatment requirement. OIT followed by measured dairy intake at home on daily basis led to a continuous threshold improvement, however accompanied by AE, sometimes to the previously tolerated dose [41]. In a more recent ORIMA study carried out in children with severe CMA, 50% OIT participants were desensitized with significant increase in milk threshold, but the incidence of AE, including those requiring adrenaline administration, were high [42]. In general, milk OIT carries a high risk for AE development, so efforts were made to find strategies to increase protocol safety through different, less allergenic forms of milk.

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There is emerging evidence that heat-processing and food matrix could change the allergenicity of milk protein. Baking milk within a wheat matrix reduces the potential of milk protein to cause allergic reactions. Heating processes induce conformational changes of certain cow's milk epitopes, especially whey proteins such as β-lactoglobulin, whose allergenicity significantly decreases above 90°C, while caseins are stable to heat-treatment [43]. Nagacura et al. compared the safety and efficacy of low-dose OIT with heated milk (HM) or unheated milk (UM) in children with anaphylaxis [44]. HM includes milk powder prepared by heating cow`s milk at 125°C for 30 seconds and spray-drying for 3 seconds, while UM refers to unheated cow`s milk sterilized at 125°C for 2 seconds (UHT milk). Although the treatment efficacy was a bit lower in the HM group, the frequencies of total AE, moderate as well as severe , were significantly lower in the HM than in the UM group. Interestingly, whereas casein-specific IgG4 levels significantly increased from baseline in both groups, β-lactoglobulin-sIgG4 levels significantly increased only in the UM group. It is assumed that β-lactoglobulin-sIgG4 may require exposure to unheated β-lactoglobulin and this may be related to differences in treatment efficacy among HM and UM group.

Although OIT with baked milk is promising, the amount of proteins in such products is not standardized which has created the need for a safe product with a standard amount of protein. The iAGE-product is well defined standardized heated and glycated milk protein product whose tolerance has been investigated in a small pilot study and showed that this product could be safe for ordinary OIT treatment in a infants and young children suffering from CMA, but future studies should confirm these results and assess the effectiveness of tolerance induction acceleration in larger samples [45].

Allergenicity of cow's milk protein could be decreased or lost by breaking down cow's milk proteins into short peptides by enzymatic hydrolysis, and the effect of allergenicity depend on the final peptide fragment size [43]. Partially hydrolyzed formulas (pHF) consists of peptides with molecular weights of approximately < 5,000 Da while extensively hydrolyzed formula (eHF) contains only peptides with molecular weights < 3,000 Da. In contrast to eHF, pHF is not intended for use with infants with CMA but possesses low allergenicity. OIT involving the ingestion of pHF improved tolerance to cow's milk in children suffering from severe CMA, compared to those consuming eHF , in a safe manner [46].

3.1.2. Egg OIT

The first egg OIT double-blind RCT dates from 2012. Burks et al. [47] reported that 78% children in OIT group were desensitized after 22 months, while 28% children in same group achieved SU after 24 months. At the same time, no child in the placebo group has passed the (oral food challenge) OFC test. AE occurred most frequently in the OIT group, but less than 1% were considered moderate. However, some allergic reactions were of sufficient clinical significance that approximately 15% of the children from the OIT group did not finish the treatment, mostly due to allergic reactions [47]. In the long-term OIT follow-up study the same participants were followed up for 4 years. Half of OIT-treated subjects achieved SU by year 4 with mild symptoms reported throughout the study which demonstrated that the probability of achieving SU after OIT increases with longer duration of therapy, [7]. Furthermore, possibility to unlimited egg consumption lasting up to 5 years after completion of therapy in the majority of egg-allergic children [48]. In more recent OIT studies on children with severe egg allergy, despite frequent AE, most participants in the OIT group were desensitized or partially desensitized compared to the avoidance group, which enables them to incorporateegg products into their daily diet or has improved their quality of life [49,50]. It seems that polysensitization to all 4 egg allergen molecules Gal d 1-4 is associated with poor de-sensitization responses [49]. Like with milk, allergenicity of egg proteins could be changed during processing due to protein unfolding which leads to conformational changes that can hide or destruct specific IgE binding epitopes. Generally, heating decreases the allergenicity of egg proteins, especially within a wheat matrix like cakes or biscuits [51]. The majority of egg allergic patients are tolerant to a certain amount of baked egg (BE) products, but it is questionable whether ingestion of low levels of BE boosts tolerance development, or this allergy phenotype is simply predictive of tolerance development

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[52,53]. It appears that in children allergic to unbaked egg but tolerant to BE, egg OIT was preferable to BE ingestion for inducing SU [6]. Egg OIT may also be safer and more effective in BE tolerant than in BE reactive children [6]. Sensitization to heat resistant egg white allergen Gal d 1 (ovomucoid) may be a useful predictor of clinically reactive BE allergy phenotype [54].

3.1.3. Peanut OIT

The prevalence rate of peanut allergy has increased several folds during the past decades, especially in Westernized nations where it currently affects 1-4,5% children. It is one of the most frequent trigger for fatal anaphylaxis and generally persists to adulthood, which is why response management is crucial [55]. For this reason, most OIT studies have been carried out with the peanut allergen. The first peanut OIT double-blind RCT was conducted by Varshney in 2011 on a small sample of 25 children younger than 16 years of age with peanut allergy. All OIT treated subjects, but no one in placebo group, were desensitized to the cumulative dose of 5 g peanut protein (equivalent of approximately 20 peanuts). This regimen was well-tolerated, accompanied with only mild clinically relevant symptoms during the build-up phase, but the trial did not include patients with a history of severe anaphylaxis [56]. The STOP II study reported that OIT to peanut was successful in the induction of desensitization in most children suffering from peanut allergy of any severity, raising the reactive threshold at least 25 times so that nearly 90% of participants can tolerate daily ingestion of 800 mg of protein (5 peanuts) which significantly improved their quality of life. Side-effects were mild in most participants [57]. The POISED study has shown that OIT induces desensitization to 4 g of peanut protein in most peanut-allergic individuals, but discontinuation, or even reduction to 300 mg per day, decreases the probability of tolerating peanut at previously achieved thresholds indicating the importance of continuing daily allergen ingesting. Biomarkers associated with SU were higher baseline peanut specific IgG4/ IgE ratio and lower Ara h 2 IgE and basophil activation responses [35].

Most OIT trials included school age children, but the hypothesis that early immunotherapy interventions potentially disrupt peanut allergy due to the plasticity of a relatively immature immune response, encouraged Vickery et al. to treat peanut allergic children under 3 years of age. They reported that 78% of subjects receiving OIT demonstrated SU to peanut. Interestingly, low-target maintenance dose of peanut protein (300 mg per day) was as effective as high-target maintenance dose (3000 mg per day) suggesting that low-dose therapy achieved immunoregulation and a high rate of SU in young children [58]. They also reported that SU was clearly associated with low baseline peanut sIgE levels. Children who completed OIT were approximately 19-fold more likely to begin eating peanut-containing foods than matching peanut-allergic controls practicing avoidance. The IMPACT trial confirmed that starting the peanut OIT in children younger than 4 years was associated with an increase in both desensitization and SU. The majority (71%) OIT-treated children were desensitized to 5 g of peanut protein, while fewer patients (21%) achieved SU. Nevertheless, in OIT treated participants, there was substantial increase in peanut tolerability compared to baseline 25 mg peanut protein at study entry and this was not seen in the placebo group. An inverse relationship between the age at screening and SU was also observed in OIT participants with the best outcome noted in the youngest children under 2 years (71% SU). The trial concluded that SU was predicted by younger age and lower baseline peanut- specific IgE [59]. In both trials most participants had at least one OIT dosing reaction, mostly mild to moderate.

Apart from the conventional food form usually used for OIT, commercial standardized products could also be used for this purpose. The ARC001 study has been the first phase 2 double-blind placebo RCT peanut OIT trial assessed the efficacy and safety of AR101, oral biologic drug product with defined peanut protein profile, intended to reduce clinical reactivity to peanut in children and young adults with peanut allergy. AR101 has met its primary endpoint, demonstrating desensitization to 300 mg peanut protein in 79% of the AR101 group compared with 19% in placebo group, which is more than the amount of peanut typically triggering a reaction with accidental ingestion (approximately one and a half peanuts). AE occurred in nearly all AR101 subjects, but more than 95% were mild [60]. In a phase 3double-blind placebo-RCT called PALISADE which has been

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carried out on children and adolescents who were highly allergic to peanut, AR101 demonstrated higher efficacy compared to placebo in children and adolescents aged 4 to 17 years, but this effect in adult participants was not significant [61]. An open-label follow-on study to PALISADE, called ARC004, explored long-term treatment beyond 1 year using 300 mg of Peanut [*Arachis Hypogaea*] allergen powder-dnfp (PTAH), formerly AR101. The ARC004 trial reported that daily dosing cohorts appeared to have higher desensitization and lower AE rates than non-daily dosing cohorts, indicating that, in children and adolescents, continued daily treatment with PTAH beyond 1 year is associated with continued and improved efficacy and safety [62]. Peanut-allergic participants evaluated after ~1.5 and ~2 years of daily PTAH demonstrated an increased tolerance to peanut protein with a potential for lower frequency of AEs, which,over time, positively affected the quality of life in c children and adolescents with peanut allergy, as well as their caregivers [63].

3.1.4. OIT to Other Food Allergens

OIT studies with other food allergens are scarce, especially those of RCT design. In one of the rare double-blind RCT with wheat, high-dose wheat OIT induced desensitization in most participants after 1 year and SU in 13% of subjects after 2 years. Compared to egg OIT, efficacy of wheat OIT was lower, but the safety was similar [64].

In generally, OIT is carried out to one food allergen at a time, but a multifood OIT study reported that desensitization to 1 food or multiple foods simultaneously through OIT appears to be safe and feasible using the OIT protocol that has been established [65].

3.2. Safety of OIT

OIT studies for food allergy are promising, but treatment is frequently complicated by AE including severe reaction requiring epinephrin. Although AEs are mainly related to the build-up phase, they also appear in the maintenance phase, sometimes to a previously tolerating dose, usually accompanied by certain risk cofactors like exercise, viral infection, or menses. This often causes anxiety and fear and is one of the main reasons for withdrawing from the study. Therefore, interventions to improve OIT for patients are needed. Changing patient mindsets about treatments and symptoms, encouraging the mindset that symptoms can signal desensitization, is a potential route to help patients cope with challenging medical treatments and may benefit both patient experience and physiological treatment outcomes [66]. Even when successful, OIT has limited long-term efficacy as benefits usually decrease when treatment is discontinued.

4. Sublingual Immunotherapy (SLIT)

Sublingual immunotherapy (SLIT) for food allergy involves placement of allergen solution (µg to mg) under the tongue on daily basis. The main aim is to achieve allergen-specific desensitization [67]. SLIT can represent a promising method in clinical use because of its simple administration, very low doses of allergen that are used and its overall safety profile. Its efficacy and safety profile are reviewed in this paper (Table 4).

Table 4. Review of efficacy and safety in SLIT.

Author (year)	Type of study	Allergen	Participants	Duration	Efficacy	Safety
Kim et al. (2011) [74]	Double-blind placebo-RCT	peanut	n=18 (1-11 y) Peanut SLIT n=11 Placebo n=7	12 months (6 months build-up and 6 months MD)	Median SCD peanut SLIT vs placebo p=0.011	Transient oropharyngeal itching most common AE 0.26% antihistamine treatment

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						0.02% doses required albuterol for mild wheezing
Fleischer et al. (2013) [79]	Multicenter placebo-RCT	peanut	n=40 (12-40, median age 15 y) Placebo group n=20 Intervention group n=20	The first phase 44 weeks (68 weeks data)	Week 44: RR intervention group vs placebo p<0.001 median SCD week 44 vs baseline in intervention group p<0.01 Week 68: median SCD week 68 vs 48 p=0.05, week 68 vs baseline p=0.009 Week 44 Crossover: median SCD p=0.02	Week 44: transient oropharyngeal itching most common AE 1.1% of total doses required treatment. Crossover High Dose subjects: 2.9% doses required treatment 1 subject had anaphylaxis
Burks et al. (2015) [80]	Long-term follow-up RCT	peanut	n=40 (12-40 y)	From week 68 to 164	4/37 (10.8%) of SLIT participants fully desensitized to 10 g of peanut powder and SU	98% of the doses were tolerated without AE no severe symptoms no epinephrine
Kim et.al (2019) [76]	Open-label extension RCT	peanut	n=48 (1-11 y) 2-mg peanut SLIT MD	5 years	67% SCD ≥ 750 mg on DBPCFCs. median SCD 1750 mg 25% (12/48) 5000-mg DBPCFC; 10/12 SU after 2 to 4 weeks	AE 4.78%; transient oropharyngeal itching most common Antihistamine use 0.21% No epinephrine
Kim et al. (2023) [78]	Open-label, prospective RCT	peanut	n=54 (1-11 y) 4 mg peanut SLIT MD	48 weeks	Mean SCD (0-48 month) p<0.0001 36% SCD of 5000 mg 70.2% SCD ≥ 800 mg	Dosing AE 4% of doses
Enriquez et al. (2005) [70]	Double-blind placebo-RCT	standardized hazelnut extract	n=23 (19-53 y) Active group n=12 Placebo group n=11	12 weeks	Median SCD hazelnut SLIT p=0.02 50% active group reached highest dose (20 g)	AE Mild; Systemic reactions 0.2%
Keet et al. (2012) [72]	Open-label exploratory RCT	milk	n=30 (6-17 y)	60 weeks	1/10 SLIT/SLIT group, 6/10 SLIT/OITB group, 8/10 SLIT/OITA group – SCD DBPCFC 8-g (p=0.002, SLIT vs OIT) End of study: p=0.09 SLIT vs OIT	Symptoms 29% of SLIT doses and 23% of OIT doses. no significant differences in the rate of total AE SLIT and OIT p=0.73, 0.70, and 0.50, respectively

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						Multisystem symptoms OIT vs SLIT p < 0.001
Garrido-Fernández et al. (2014) [71]	Double-blind placebo-RCT	peach extract	n=31 (18-65 y) Treatment group: placebo=2:1	6 months	Median SCD p=0.002 3-fold improvement in tolerance in active group p=0.065	No data. All subjects that started treatment also have finished it
Author (year)	**Type of study**	**Allergen**	**Participants**	**Duration**	**Efficacy**	**Safety**
Kinaciyan et.al (2018) [69]	Double-blind, placebo-explorative RCT	Apple protein	n=60 (aged 18-65 y) 1:1:1=placebo: rMal d 1: rBet v 1	16 weeks	rMal d 1 vs placebo and rBet v 1 (p=0.001 and p=0.038) SLIT rMal d 1 enhanced IgG4/IgE ratios (p=0.012).	Mainly local AE to both formulations

RCT- randomized controlled trial; SLIT- sublingual immunotherapy; y- years; MD- maintenance dose; SCD- successfully consumed dose; RR- response rates; AE- adverse events; SU- sustain unresponsiveness; DBPCFC- double-blind placebo-controlled food challenge; OIT- oral immunotherapy.

4.1. Efficacy of SLIT

SLIT, as a method of immunotherapy has been studied in the treatment of kiwi, apple, peach, hazelnut, peanut and milk allergies. SLIT for food allergy treatment was first described in 2003 [68] where a subject underwent SLIT with kiwi extract and was successfully desensitized. Birch pollen–related apple allergy (BPRFA) represents one of the most prevalent food allergies in adult patients. Symptoms appear due to birch pollen allergen Bet v 1 which is highly cross-reactive with Mal d 1 (apple protein). Study of Kinaciyan et al. [69] demonstrated that equal doses of Bet v 1 and Mal d 1 allergens induce different clinical and immunologic outcomes. SLIT with specific Bet v 1 did not result with significant desensitization outcomes in patients with Mal d 1 allergy. This study showed efficacy in treatment of BPRFA with SLIT using the Mal d 1 (apple allergen) but not using the Bet v 1 (birch allergen). Double-blind, placebo RCT for hazelnut from 2005. and peach allergy from 2014. found a significant increases in tolerance to hazelnut and peach extract after sublingual immunotherapy [70,71].

In RCT of Keet et al. [72] children with CMA underwent SLIT or SLIT escalation followed by OIT. After initial DBPCFC and SLIT escalation, participants either continued SLIT to 7 mg daily or began OIT (1000 mg allergen OITB group or 2000 mg the OITA group) using milk protein. After maintenance period at week 12 and week 60 participants underwent DBPCFC with 8 g of milk protein. 1/10 participants in the SLIT group, 6/10 participants in the SLIT/OITB group, and 8/10 participants in the OITA group passed the 8 g milk protein DBPCFC after maintenance period (p=0.002). This trial has found that 6 of the 15 participants who passed 60 week DBPCFC lost desensitization to milk in less than 6 weeks. They did not completely lose desensitization to milk and they were still able to consume at least 2.5 oz of milk (at the beginning of trial it was just a teaspoon of milk). OIT was much more effective than SLIT, but with more systemic AEs.

In study of SLIT versus OIT for the treatment of peanut allergy results shown that pre-treatment with SLIT before OIT led to significant reduction in overall AE [73].

Kim et al. [74,76,78] conducted 3 significant clinical trials with SLIT in subjects with peanut allergy. All three studies included participants ages 1-11 years and they investigated efficacy and safety of SLIT for peanut allergy desensitization. The first study of SLIT treatment in children that

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have peanut allergy was the study of Kim et al. from 2011 [74]. It is a double-blind placebo RCT of 18 subjects with 6 months escalation plus 6 months of dose maintenance. During the DBPCFC median successfully consumed dose (SCD) for the treatment group was 1710 mg and for placebo group 85 mg, which represents significant difference between groups p=0,011. These results represent potential protection from accidental peanut ingestion through everyday life situations and accidental exposure (often less than 100 mg peanut protein) [75]. Kim et al study from 2019 was a RCT long-term SLIT for peanut allergy with 5 years total duration [76]. SLIT maintenance dose was 2 mg/d. Median SCD was 1750 mg peanut protein. After maintenance period and DBPCFC participants were without peanut protein exposure for 2-4 weeks and 10 of 12 participants reached SU. This results suggest that SLIT can enable safety through food exposure for most patients because tolerability of 300 mg peanut protein has 95% risk reduction [77] and in this study clinical threshold was greater than 1000 mg peanut protein. SU in this study was assessed after 2 to 4 weeks without any peanut exposure and that period of time might be too short for determination of real SU after therapy with SLIT. Another study from 2023 aimed to determinate the efficacy and safety of SLIT with 4 mg/d of peanut protein and durability of desensitization after SLIT. Their results suggest that SLIT can give great results in desensitization even for a longer period of time without of exposure (more than 17 weeks) [78]. First study from 2013. is a double-blind placebo RCT that lasted for 44 weeks (data available for 68 weeks), and second study from 2015. is a open-label long-term follow-up study [79,80]. After 44 weeks of SLIT there was a statistically significant difference between intervention (14/20) and placebo group (3/20) $p<0.001$. The study fulfilled its primary efficacy end point plus it showed great outcomes in those participants on higher maintenance dose (originally placebo group until week 44). Burks et al. [80] in their trial wanted to investigate the long-term (3-year) clinical and immunologic efficacy of peanut SLIT. This study showed modest desensitization and only 10.8% participants reached SU after SLIT therapy most likely because of a high participant drop out rate.

Immunological parameters were analyzed in most of the reviewed studies, and they had statistical significance but none of them could reliably determine the best choice of immunotherapy or predict the level of therapy success.

4.2. Safety of SLIT

Majority of all AE in every trial were described as local oropharyngeal itching with no need for epinephrine use. SLIT is considerable as a very safe treatment with very good tolerance and very low rate of rate of side effects.

All studies with SLIT and peanut allergy to date excluded patients with anaphylaxis history although it is extremely important to help such patients find an effective and safe treatment that would certainly have a positive effect on their quality of life.

5. Epicutaneous Immunotherapy (EPIT)

Epicutaneous immunptherapy (EPIT) is currently under investigation as a new type of immunotherapy for food allergy. Preclinical studies indicate that allergen applied via the epicutaneous route to intact skin does not cross into the circulation but rather activates dendritic cells in the dermal layer of the skin to affect immune activation [81]. EPIT is considered as a simple and safe method which does not interfere with everyday life and activities. Evidence showsthat patients easily follow the immunotherapy protocol and tolerate this type of immunotherapy very well [82]. All studies reviewed in this paper used the Viaskin® patch. Sweat effects on dissolution of the allergen in the patch and after the opening of skin pores allergen can be transferred to skin-based Langerhans cells with minimal risk of systemic absorption. Difference from other immunotherapy approaches is that EPIT delivers μg doses (rather than mg) of allergen, avoids oral route, and may have less AEs and better compliance than other types of immunotherapies [83]. The efficacy and safety of EPIT (in food allergy) with Viaskin patches has been investigated in several phase 2 and 3 controlled clinical trials, mostly on subjects with peanut allergy (Table 5).

Table 5. Review of efficacy and safety in EPIT.

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Author (year)	Type of study	Allergen	Participants	Duration	Efficacy	Safety
Dupont et al. (2010) [93]	Double - blind placebo - RCT	Milk	n=19 (3 months-15 y) n=10 active group n=9 placebo group	3 months	PP population CTD (0-90 day) p=0.18	AE mild
Spergel et al. (2020) SMILEE [94]	pilot double-blind placebo - RCT (+ open-label extension study)	Milk	n=20 (Age: 4-11 y) n=15 active group, n=5 placebo group	11 months + 11 months open label	VM500 group mean eos/hpf 50.1 ± 43.97 vs the placebo group 48.20 ± 56.98 eos/hpf VM500 group lower mean eos/hpf count p= 0.038 Open label phase: 47% response mean values of fewer than 15 eos/hpf	Improvement in endoscopy scores in treatment group AE mild
Sampson et al. (2017) VIPES [82]	multicenter double-blind placebo - RCT + 2-year, open-label extension study	peanut	n= 221 (6-55 y) randomization 1:1:1:1 Open Label Extension Study, n=171	12 months + 2-year, open-label extension study	RR month 12 VP250-µg vs placebo p = 0.01; %responders only significant for the VP250 p =0.04 RR in children VP250 vs placebo p =0.008; Open-label Extension study: RR at months 12 and 24 in the overall population 59.7% (89/149) and 64.5% (80/124)	AEs largely local skin reactions
Jones et al. (2017) CoFAR6 [87]	Multicenter Double-blind placebo - RCT	peanut	n=74 (4–25 y), median age 8,2 n=25 placebo n_{VP100}=24 or n_{VP250}=25	52 weeks	Treatment success: VP100 vs PLB p = 0.005;VP250 vs PLB p=0.003; VP100 vs VP250, p=0.48 -medium change SCD: Among 3 groups p=0.003; Placebo vs VP100 p=0.014; Placebo vs VP250 p=0.003; VP100 vs VP25 p=0.41 -success better in younger participants (6-11 y) p=0.006	AEs largely mild Non–patch-site AE: 0.2% of placebo and VP100 doses and 0.1% of VP250 doses
Scurlock et al. (2021) Follow-up [88]	Open-label RCT	peanut	n=74 (4-25 y)	130 weeks	Desensitization: 5% PLB-VP250, 20.8% VP100-VP250, 36% VP250 median SCD change from baseline of 11.5 mg, 141.5 mg, and 400 mg, respectively.	most dosing AE mild

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CoFAR				post hoc analysis of change in SCD week 52-130: overall p=0.29, within treatment groups PLB-VP250 p=0.32; VP100-VP250 p=0.32; VP250 p=0.10.	
Fleischer et al. (2019)[89] PEPITES	multicenter Double-blind placebo - RCT	peanut	n=356 (4-11 y) n=238 peanut protein 250 µg; n=118 placebo	12 months	The percentage difference in responders VP250-µg vs placebo p<0.001 The lower bound of the 95% CI of the difference 12.4% crossed the prespecified lower limit of 15%	AE mostly mild 4 of 238 participants (1.7%) in the active group discontinued treatment due to AEs.
Author (year)	**Type of study**	**Allergen**	**Participants**	**Duration**	**Efficacy**	**Safety**
Fleischer et al. (2020)[90] PEOPLE	Open-label follow-up RCT	peanut	n=198 (4-11)	5 years (4-5 y still in progress)	141 (71%) subjects DBPCFC at month 36 At month 36: 51.8% subjects ED>1000 mg, At month 12: 40.4%; 75.9% increased ED compared with baseline; 13.5% tolerated DBPCFC of 5444 mg. Median CRD from 144 to 944 mg; SU 14 of 18 subjects	AEs mild or moderate
Pongracic et al. (2022)[95] REALISE	multicenter Double-blind placebo - RCT + ongoing open-label active treatment	peanut	n=393, (4-11 y) 3:1= VP250: placebo for 6 months; 72.3% participants with history of peanut anaphylaxis	3 years (6 months double blind placebo control)	REALISE was without a DBPCFC and therefore had no efficacy assessment.	82.7% mild AE; 36.9% moderate AE 1.3% severe AE overall
Greenhawt et al. (2023)[91] EPITOPE	multicenter Double-blind placebo - RCT	peanut	n=362 (1-3 y), the median age: 2.5 y intervention :placebo 244:118 ED<300 mg	12 months	Intervention group 67.0% vs. placebo group 33.5%, p<0.001) the mean change in CRD intervention vs placebo group 3.13 (p<0.001) ED intervention vs placebo group 2.96 (p<0.001)	AE mostly mild Serious AE 8.6% intervention group 2.5% placebo group; anaphylaxis 7.8% and 3.4%;

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							Serious treatment-related AE 0.4% intervention group, no placebo group. Treatment-related anaphylaxis 1.6% intervention group, none placebo group.

RCT- randomized controlled trial; y- years; EPIT- epicutaneus immunotherapy; PP- per protocol; AE-adverse events; CTD- cumulative tolerated dose; VM500-Viaskin milk 500 μg; eos/hpf- eosinophils/high power fields; CRD-cumulative reactive dose; VP250-Viaskin peanut 250 μg; VP100-Viaskin peanut100 μg; SCD- successfully consumed dose; RR-response rates; PLB-placebo; DBPCFC- double-blind placebo-controlled food challenge; ED-eliciting dose; SU- sustain unresponsiveness.PEOPLE demonstrated durable efficient clinical outcomes of EPIT treatment in children with peanut allergy (4-11 years old). Results of PEOPLE showed persistent desensitization to allergen with EPIT treatment over longer periods of time. After 36 months ¾ participants had better ED compared to the beginning of the trial and more than 1/2 of participants at 36 month had ED of >1000 mg. Those participants with ED>1000 mg underwent complete elimination of peanut for 2 months to determine a SU. SU was reached in 77.8% of participants (14 of 18). Conclusions about EPIT efficacy in establishment of SU cannot be made because of a small number of people that could participate in the SU assessment.

5.1. Efficacy of EPIT

Prevalence of anaphylaxis and severe reactions to food in the pediatric population is the highest and most common in peanut food allergy [84]. It is very hard to avoid peanut consumption because of its widespread presence in various foods and dishes and unintentional exposure rates are high. There is a great need and longing for new and safe types of treatment for food allergies, especially peanuts so that patients and their families can have better overall quality of life [85]. It is estimated that most of peanut allergic children will have allergic reactions to <1 peanut kernel (300 mg of peanut protein) [86]. So, one of the aims of this paper is to review efficacy and safety of EPIT as a treatment option in food allergy.

Efficacy represents the success of the implemented therapy, a treatment that safely and feasibly results in desensitization. The primary efficacy end point of most reviewed trials was the difference in response rates between intervention and placebo groups after a period of time (patients underwent a DBPCFC to establish changes in eliciting dose (ED)).

The "Viaskin® Peanut's Efficacy and Safety" (VIPES) 2b double-blind placebo RCT looked at 3 doses of a peanut protein patch (50, 100, and 250 μg) doses across 221 subjects (6 to 55 years) at 22 centers for 12 months of treatment. After 12 months of treatment patients underwent a DBPCFC to establish changes in ED. Statistically significant difference in response rates (RR) was observed between the Viaskin peanut 250-μg (VP250) and placebo group $p = 0.01$. EPIT gave statistically better results in participants 6-11 years old with VP250 ($p = 0.008$) but not in participants older than 11 years[82]. Similar findings regarding age were found in the CoFAR6 study, also finding that participants younger than 11 years yield more benefit from EPIT than older participants [87]. CoFAR6 trial was conducted for 52 weeks and after that participants underwent to new open-label clinical trial for 130 weeks in total. In this study all participants were in the VP250 group [88]. 79.7% participants completed the 130 weeks of active treatment. This extended EPIT with VP250 was safe, well tolerated with persistent desensitization during trial period. This study confirmed that treatment response was better in younger children (ages 4-11 years) receiving VP250. These three studies show better EPIT outcomes in younger participants which means that food allergy treatment should begin

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as early as possible in order to expect better treatment results. Another randomized trial PEPITES (Peanut EPIT Efficacy and Safety) [89] used these findings and had 356 peanut-allergic children participants aged 4-11 years and used only VP250 patches on the intervention group. Intervention group had significantly better treatment outcomes than the placebo group p<0,001 but the lower bound of the 95% CI of the difference (12.4%) crossed the prespecified lower limit of 15%, and thus the trial could not be considered positive. Participants who completed PEPITES were offered enrollment in another study PEOPLE (PEPITES Open-Label Extension) [90]. In this study all participants were in the intervention group with VP250 for 24 or 36 months. After that period of time all participants had the opportunity to enroll in another 24-month treatment, totalling in 5 years of study in the same participants.

A recently published RCT (EPITOPE) [91] made a step forward in efficiency research of EPIT in peanut allergic children age range 1-3 years. The primary efficacy end point in the active group was significant greater compared to the placebo group (p<0.001). Participant in the active VP250 group had a median change in ED (from start of the trial to month 12) of 900 mg vs 0 mg in the placebo group participants (p<0.001). This showed that EPIT can be a useful tool in treatment of peanut allergy in children younger than 4 years. Open-label extension of the EPITOPE trial is ongoing and we hope that those results will provide significant information regarding the efficacy of EPIT and its potential use in everyday clinical work.

Children with peanut allergy have high rates of comorbidities such as atopic dermatitis, asthma or other allergies especially food allergies. Davis et al. [92] conducted the study (data from PEPITES and REALISE study) of the safety and efficacy of EPIT in peanut-allergic children with these comorbidities. Peanut EPIT showed statistically significant efficiency of the therapy, regardless of the mentioned comorbidities.

There are a few clinical trials related to EPIT and other food allergens that are available. Here we will highlight studies that show promising results regarding EPIT and effectiveness of the method.

A pilot study from 2010 evaluates the safety of EPIT in children (age range 3 months- 15 years) for 3 months under therapy (active or placebo). Active patches contained 1 mg skimmed cow's milk powder. In this preliminary study cumulative tolerated dose (CTD) failed to demonstrate a statistically significant improvement, most likely due to very the short duration of the trial. Results suggested that EPIT with milk protein is well tolerated [93].

SMILEE [94] is RCT study with aim to determine efficacy and safety of EPIT with Viaskin milk (500 µg milk proteins, VM500) in children with milk-induced EoE. Seven participants that were on VM500 treatment vs 2 placebo participants had a significantly lower mean eos/hpf count p=0.038. At the end of the open-label phase 47% participants had mean values of fewer than 15 eos/hpf which means that EPIT might not be effective just for IgE mediated food allergy but also for non-IgE mediated food allergies.

All clinical trials reviewed in this paper indicate that EPIT has promising effect in desensitization and that it can be a useful tool for treatment food allergy.

5.2. Safety of EPIT

EPIT is consider as a safe treatment, especially compared to other types of immunotherapies. All studies reviewed in this paper highlight EPIT as a highly safe method. Symptoms are mostly application site related, and mostly mild to moderate [82,87–91,93–95]. Adherence in most studies is very good, except SMILEE [94] where a high rate of protocol violations was reported (nonadherence to diet therapy, noncompliance with PPI dosing).

The only trial that included participants with a history of anaphylaxis and exclude DBPCFC as a part of trial procedure is REALISE (Real Life Use and Safety of EPIT) RCT [95] which gives more reliable results in regards of safety, closer to real life for people with food allergy. Participants were highly atopic and 72,3% participants had a history of anaphylaxis to peanut protein. Compliance to treatment was very high, most of reported AEs were mild (82.7%) or moderate (36.9%). Findings from REALISE suggest that EPIT is a safe and well-tolerated method of immunotherapy for food allergy

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regardless of the possibility of developing severe symptoms and anaphylaxis.Given all the above, it can be concluded that EPIT has a potential impact on substantial reduction of allergic reactions to peanut. These findings are essential for people with food allergies and their families, especially in regards of improving their quality of life. This could also lay a basis for the implementation of food allergy related immunotherapy in routine clinical use.

6. Food Allergen Immunotherapy and Biologics

There are many novel therapeutic approaches being investigated for the treatment of food allergy such as micobiome modulating drugs and biologicals. Biologicals are promising therapeutics which target the underlying immune response driving food allergy. Among these biological drugs, omalizumab, or anti-IgE antibody, is most commonly used, both in clinical studies and in clinical practice, as monotherapy in patients with severe IgE mediated food allergy or in combination with FAIT [96,97]. It has shown favorable effects for improving the safety and efficacy of oral immunotherapy as well as its potential use in the management of food allergies independently of oral immunotherapy. Therapy with omalizumab increases the threshold of reactivity to foods and increases the tolerated dose of foods when given as monotherapy or in combination with oral immunotherapy. Omalizumab administered during the up-dosing phase of OIT shortens the time required to reach the maintenance dose. Furthermore, omalizumab can also prevent systemic allergic reactions including anaphylaxis when given as an adjunct to immunotherapy [96–98].

There are many other upcoming biologicals that are currently under investigation in ongoing clinical trials such as the anti-IL4 receptor ◎ antibody or dupilumab, and ligelizumab or the next generation of anti-IgE antibody, and tezepelumab that blocks the activity of TSLP and etokimab or the anti-interleukin 33 antibody [99].

7. Conclusions

FAIT is the only disease-modifying treatment option for individuals with IgE-mediated food allergy. It has been shown that FAIT is a clinically effective and safe treatment option for patients with clinically relevant food allergy. Although FAIT is generally an effective treatment option, some patients do not respond well. The understanding of underlying mechanisms in FAIT is lacking, but most are related to the modulation of the innate and adaptive immune responses, which are also related to the effectiveness of the treatment. There has been no clear relationship between the immunological changes observed and the level of response to FAIT. Further research is needed to confirm and interpret these associations with different route, doses, duration, frequency of application and clinical response to FAIT. On the other hand, the occurrence offside effects, including anaphylactic reactions, during OIT are still significant, and further narrow the indications for use, which calls for additional research as well.

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