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Research Article

Examining the Use and Outcomes of Peanut Oral Immunotherapy in Peanut-Allergic Children: A Systematic Review of the Literature

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ABSTRACT

Peanut allergy is one of the most common allergies in children, affecting 1% to 4.5% of the population with a rise in prevalence over the past decade. It is a major public health concern as it significantly diminishes the quality of life of those who are allergic, their families and their caregivers. Peanut allergy is an IgE-mediated Type I hypersensitivity response to peanuts and Peanut Oral Immunotherapy (P-OIT) is a treatment which attempts to mediate this over reactive response to peanuts by repeating and increasing administration of peanut protein doses.

The specific objectives of this review are as follows:

1. To characterize the dosing regimens used for P-OIT in peanut-allergic children.
2. To examine the efficacy and effectiveness of P-OIT in peanut-allergic children.
3. To assess treatment experience of patients during P-OIT in peanut-allergic children.

An electronic search was performed on MEDLINE through EBSCOhost and PubMed databases, yielding 515 articles. After application of filters and duplicate removal, 189 articles remained for screening. After inclusion and exclusion criteria were applied, 36 articles remained. Based on the objectives, 10 articles were selected for this literature review. Which were quantitative in nature and were all valid. Three key themes emerged from the articles. First, by examining the various dosing protocols of P-OIT RCTs (randomised control trials), there is a clear lack of universal recommendations and standardization on up dosing protocols and further research is needed to substantiate standardized dosing regimen recommendations. Secondly, although there is strong evidence for efficacy of the P-OIT RCTs, there is currently no avenue to evaluate whether the P-OIT would be as effective in the community. Finally, there is need for more primary research on the quality of life and treatment experience of participants. As this has shown to be beneficial to facilitating treatment outcomes and will give more insight into alternative methods of increasing the efficacy of P-OIT.

Keywords: Peanut allergy; Peanut oral immunotherapy; Food allergy; Children; Quality of Life

Abbreviations: OIT: Oral Immunotherapy; P-OIT: Peanut Oral Immunotherapy; DBPCFC: Double-Blind Placebo-Controlled Food Challenge; NOAEL: No Observed Adverse Effect Level; AE: Adverse Event; QoL: Quality of Life; LOAEL: Lowest Observed Adverse Effect Level.

INTRODUCTION

Peanut allergies are an IgE-mediated Type I hypersensitivity reaction and are of the most common allergies in childhood, affecting 1% to 4.5% of the population with increasing prevalence over the past decade [1,2]. It is a major public health issue as it

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significantly diminishes the quality of life of those who are allergic, their families and their caregivers. In addition to affecting physical health, peanut allergy influences mental health and emotional functioning of peanut allergic individuals [3]. Due to its life-threatening nature, the allergy can instill constant fear and anxiety in those who are allergic and those around them. There is no current cure for peanut allergy, and those affected opt for avoidance and rescue medications to remain safe [1]. Methods to mitigate an allergic reaction are needed, in order to allow those suffering from the serious life-threatening allergy an opportunity to navigate their daily life with less fear and anxiety. Peanut allergy pathophysiology

The first stage of an allergic reaction to peanuts involves the sensitization which comes after contact of peanut with skin epithelium or gastrointestinal tract (*via* oral route) [2]. After this first encounter, pro-inflammatory cytokines drive dendritic cells and immune cells towards T-helper lymphocyte type 2 (TH2) cells, this TH2 cell mediated immune response produces an accumulation of basophils and eosinophils that leads to activation of B cells which mature into peanut specific-immunoglobulin E (IgE) [2].

On re-introduction to peanuts, the allergen will bind to the peanut specific-IgE and activate the mast cells to release different inflammatory cells that include histamine, leukotrienes, platelet activating factor, cytokines which are all involved in the allergic reaction (Figure 1) [2].

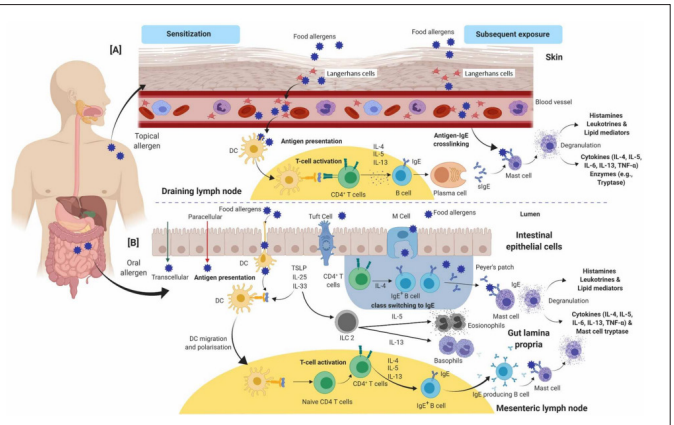

Figure 1: An overview of the immunological events occurring during allergic sensitization and effector phase upon exposure to food allergens *via* (A) skin and (B) gut. (A) In the epidermis, allergens are sampled by Langerhans cells and the adaptive immune response is developed in draining lymph nodes. (B) In the gut lumen, allergens are taken up by DCs and the subsequent events take place in Peyer's patches/ mesenteric lymph nodes. Antigen-presenting cells (Langerhans cells in A or dendritic cells in B) present allergen-derived peptides to naïve CD4+T-cells *via* MHC-class II complex.

In healthy individuals, a tolerogenic immune response develops, mediated by regulatory T-cells and IL-10. In susceptible individuals, naïve CD4+T-cells polarize toward a Th-2 phenotype and produce IL-4, IL-5, and IL-13. IL-4 and IL-13 induces production of allergen specific IgE antibody by B cells and clonal expansion. Allergen-specific IgE binds to FcεRI receptors on the surface of basophils and mast cells. This entire process is called allergic sensitization. On subsequent exposure to the same allergen (*via* contact or ingestion), the allergens bind and crosslink cell-bound IgE antibodies, which triggers degranulation and release of chemical mediators such as histamine, cytokines and prostaglandins. These mediators are responsible for the manifestation of an allergic reaction. Cytokines including IL-4, IL-5, IL-6, IL-13, and TNF-αare further released which leads to cell-mediated late-phase allergic reactions through recruitment of eosinophils and Th-2-cells. CD, Cluster of differentiation; DC's, Dendritic cells; FcεRI, High affinity immunoglobulin E receptor; MHC, Major histocompatibility complex; Th-2, T-helper-2; IL, Interleukin; IFN-γ, Interferonγ; TNF-α, Tumor necrosis factor-α. Reproduced from Pratap et al [4] .

Tolerance/Desensitization

The physiological pathway of tolerance and desensitization are connecting in many ways. However, the difference between both is seen clinically, as desensitization will only confer protection of an allergic response if the patient continues to stay in a maintenance treatment of the allergen. On the other hand, tolerance will involve a normal reaction of the body after an exposure of such allergen even if the patient had no maintenance treatment. The definition of those term forms the immune-physiology point are described here:

Tolerance: An allergen like peanut is digested by the gut and macrophages transfers it to dendritic cells. It will then be presented to naïve T cells which differentiate into regulatory T (Treg) cells which exert tolerance by inhibiting TH2 cells [2].

Desensitization: Is a decrease in activation of effector cells and TH2 cells shift to regulatory T cells [2]. Allergen specific B cells switch from IgE to IgG4 cells which compete with IgE for binding to allergen which downregulates TH2 cells [2].

With this knowledge allergen immunotherapy utilizes the immune system to treat an allergic condition [2] by attempting to establish immune tolerance or sustained unresponsiveness so there is no overactive immune response to the allergen [2].

Peanut Oral Immunotherapy (P-OIT) involves the repeated and increasing administration of peanut protein doses to reduce sensitivity towards it [2]. The allergen is given in the up-dosing phase with increasing amounts until the therapeutic dose is attained. Once reached, the maintenance phase begins, which entails daily ingestion of peanuts for a specific amount of time. The goal is to desensitize the abnormal immune response to peanuts by repeated and increasing administration of the peanut allergen [4-6].

The aim of this study is to systematically review the published literature on the use of P-OIT on peanut-allergic children and the outcomes of the therapy.

The specific objectives of this review are as follows:

1. To characterize the dosing regimens used for P-OIT in peanut-allergic children

2. To examine the efficacy and effectiveness of P-OIT in peanut-allergic children

3. To assess patient treatment experience during P-OIT in peanut-allergic children

METHODOLOGY

Search strategy

An electronic search was performed on MEDLINE through EBSCOhost and PubMed databases to identify the relevant literature on this topic and to address the objectives of this review.

The following search strategy was used for MEDLINE through

EBSCOhost:

1. "Peanut oral immunotherapy"

2. "Children" OR "child" OR "paediatric" OR "kids"

The follow search strategy was used on PubMed:

3. "Peanut oral immunotherapy"

4. "Children" OR "child" OR "paediatric" OR "kids"

Inclusion and exclusion criteria

The initial inclusion criteria of filtering out articles published more than 10 years ago was switched to no publications of more than 8 years ago to gain more access to more relevant and recent articles (Table 1 and Figure 2).

Table 1: Inclusion and exclusion criteria.

	Inclusion	Exclusion
Language	English	Not available in English
Species	Human studies	Non-human studies
Subject age	Jan-18	Less than 1 or over 18
Date	Initially: Publication between 2011 and 2021 End selection: 2013-2021	Publication of more than 10 years ago initially then publication of more than 8 years ago.
Text availability	Articles available with full text online	No full text available
Type of study	Randomized controlled trials (RCTs), clinical trials	Systematic review, meta-analysis, case control study, cross-sectional study, case report
Outcomes	Efficacy and safety of P-OIT	Studies examining sublingual or epicutaneous immunotherapy
	Outcomes of P-OIT (sustained unresponsiveness)	Antibody focused studies
	Quality of life during and burden after P-OIT	Any studies that don't align with literature review outcomes

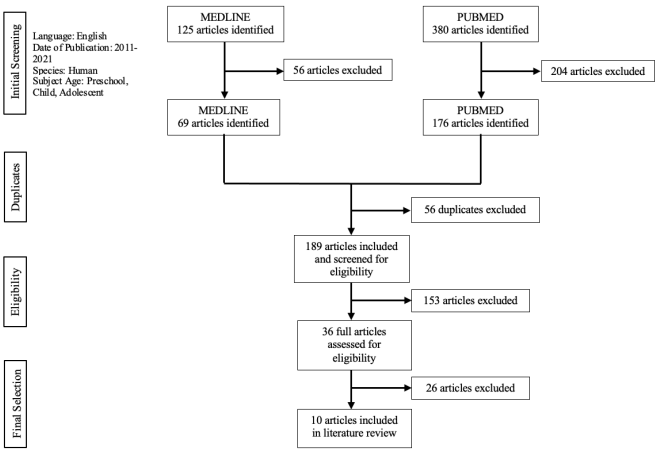

Figure 2: Search strategy for selecting relevant articles for inclusion in this review.

Selection criteria

The initial search strategy yielded 125 articles from MEDLINE through EBSCOhost and 390 from PubMed. The MEDLINE articles were then narrowed down to 69 after the initial filters were applied and the PubMed articles were narrowed down to 176 articles. After removal of duplicates, 189 articles remained. The abstracts of the 189 articles were read and 153 articles were not eligible. The remaining 36 articles were read in full and 26 were excluded for not reaching the inclusion and exclusion criteria. Finally, 10 articles were selected for the literature review.

Article validity

The 10 articles included in this review were critically evaluated using the Evidence-Based Librarianship (EBL) Critical Appraisal Checklist (Appendix A). All the articles had an overall validity score greater than 75% (Table 2).

Table 2: EBL critical appraisal summary.

Study	Validity Score (%)				
	Population	Data collection	Study design	Results	Overall
Anagnostou et al. (2014)	87.50%	100%	100%	83.30%	92%
Vickery et al. (2018), USA	100%	100%	100%	83.30%	92%
Blumchen et al. (2019)	87.50%	83.30%	100%	83.30%	88%
Hourihane et al. (2020)	100%	83.30%	100%	83.30%	92%
Vickery et al. (2021)	87.50%	80%	100%	83.30%	87.50%
Reier-Nilsen et al. (2018)	71.40%	83.30%	100%	66.70%	80%

RESULTS

Characterize the dosing regimens used for P-OIT in peanut-allergic children

Four of the 10 articles in this review outlined clear dosing regimens in P-OIT RCTs ranging from 6 to 16 months. All four studies followed a gradual up-dosing regimen where patients would ingest increasing amounts of peanut protein every two weeks [7-10]. Two studies escalated their doses from 3 mg to 300 mg respectively, while Anagnostou et al. escalated doses from 2 mg-800 mg. Low dose P-OIT was examined in Blumchen et al. and doses were determined based on each patient's eliciting dose (dose at which clinical symptoms are observed) and had a maximum target dose of 250 mg [8,9].

Following the up-dosing phase, each study had a maintenance phase where the same dose is taken over a period of time. Two studies had a set maintenance dose of 300 mg peanut protein daily [8,9]. One study had patients take their highest dose tolerated (target of 800 mg) daily [7]. Blumchen et al. had a maintenance phase at the patients' target maintenance dose ranging from 125 mg to 250 mg [10,11]. Maintenance phases for these studies lasted from 2 to 6 months.

All four studies had an exit Double-Blind-Placebo-Controlled Food Challenge (DBPCFC) at the end of the up-dosing and maintenance phases to examine efficacy.

One additional article was a follow up study to the PALISADE study and explored daily and non-daily dosing regimens to comparatively determine if a difference in desensitization existed [8,12-14].

Examine the efficacy and effectiveness of P-OIT in peanut-allergic children

Seven articles in this literature review analyzed the efficacy of P-OIT using DBPCFCs [7-11,15,16]. Five of these articles examined patients' tolerance to peanuts right after the maintenance phase ended while the other two [7-11,15,16] analyzed sustained unresponsiveness, measuring tolerance 4 weeks to a year after P-OIT.

A single dose of 1000 mg to 4500 mg in four of the five studies was tolerated by significantly more participants in the active P-OIT groups than the placebo groups-ranging from 41.9% to 62% of active group subjects (compared to 2%-4% of placebo groups) – with no dose-limiting symptoms [7-10]. Reier-Nilsen et al. reported 21.1% of active P-OIT subjects reaching 5000 mg [11]. Three studies reported that a single dose of 300 mg or more was tolerated by a range of 74% to 76.6% active group participants compared to 8.1% to 16.1% of placebo subjects [8-10]. Two studies also reported a significant increase in peanut threshold for active P-OIT participants [7,8].

Two studies analyzed sustained unresponsiveness, defined as the ability of a subject to pass an oral food challenge after stopping P-OIT and introduce the allergen into their diet [15,16]. One study reported that 50% of active P-OIT participants were able to tolerate 5000 mg of peanut protein without symptoms 4 weeks after a 5-year P-OIT treatment [16]. Nagakura et al. reported that 58% were able to tolerate 795 mg peanut protein 1 year after P-OIT [15].

Assess patient treatment experience during P-OIT in peanut-allergic children

Two studies sought to evaluate patient quality of life and treatment experience during P-OIT treatment as primary outcomes to their studies [12,13]. Reier-Nilsen et al. used the Paediatric Quality of Life Inventory Version 4.0 (5-point Likert scale) to evaluate child self-reports and parental proxy on psychosocial functioning during P-OIT treatment [13]. A non-significant mean change of 4.4 was reported for child self-reports and a significant mean change of 9.3 was attained for the parental proxy reports [13].

Howe et al. reported that for families and patients that were taught to view side effects as a sign of desensitization (Symptoms as Positive Signals, SAPS), there was less anxiety about symptoms (p=0.003), decreased likelihood to report that dosing had not gone well when experiencing symptoms (p=0.05) and decreased likelihood to experience non-life-threatening symptoms at high peanut doses (p=0.007) [12].

Two other studies measured the Quality of Life (QoL) of subjects through the Food Allergy Quality of Life Questionnaire (FAQLQ). Anagnostou reported a clinically meaningful improvement in QoL of both the control and active groups (p=0.32) on the parent FAQLQ [7]. O'Hourihane et al. reported a significant difference between placebo and active group "allergen avoidance and dietary restrictions" (p=0.011) and active group "risk of accidental exposure" (p=0.026) for 8–12-year-olds [9]. Summarises the populations, methods, findings and strengths and limitations of the ten studies in this review (Supplementary Table 1).

DISCUSSION

Five of the P-OIT RCTs in this literature review have a similar structure in the dosing regimen: an up-dosing phase followed by a maintenance phase with a final exit Oral Food Challenge (OFC) [7-10,14]. This general structure, despite the substantial differences between protocols regarding peanut protein doses, phase length and exit OFC doses, is followed by most clinical trials performing P-OIT [5]. Some studies do outline their rationale for utilizing a certain protocol. Anagnostou et al. based their 800 mg maintenance dose on their pilot study that demonstrated that this amount was tolerated by subjects daily, suggesting efficacy [7]. Blumchen et al. had the slowest up-dosing scale, spanning over 14 months, which may have been an attempt to reduce the number of adverse events experienced by subjects [10]. Regardless, as P-OIT continues to be an investigational therapy for those with peanut allergies, the articles in this review suggest that there is a clear lack of universal recommendations and standardization on updosing protocol. Further research is needed to substantiate standardized dosing regimen recommendations.

The results of the studies examining efficacy of P-OIT [7-11, 14-16] report an increase in reaction threshold to peanuts in peanut-allergic children compared to the placebo groups. By the end of the clinical treatment three of the seven studies [8-10] reported that a significantly greater percentage of patients in the active P-OIT group were able to tolerate a minimum of 3 peanuts (1000 mg), with Blumchen et al. reporting that 41.9% patients were able to tolerate up to 15 peanuts (4500 mg) [10]. This suggests desensitization and therefore efficacy in P-OIT, however, these strategies did not come without adverse events. The majority of patients in the active P-OIT groups had adverse events during the up-dosing phase but was mostly mild in nature [9,10]. However, moderate or severe events such as upper airway angioedema or bronchospasm can occur, rendering it unclear if the efficacy seen in the clinical trials can be efficacious long-term and effective in the community.

Five of the RCTs above don't address whether the desensitization observed is sustained past the end of the trial [7-11]. Consequently, Nagakura et al. and Vickery et al. attempted to explore if sustained unresponsiveness can be achieved after the P-OIT trials. As outlined in the results, sustained unresponsiveness was reported for children without and with a history of anaphylaxis, suggesting that the desensitization achieved from P-OIT trials could lead to children adding the allergen to their diet [15,16].

While the efficacy of these trials is clear and valid, there are limited long term studies on introduction to peanuts and P-OIT in the community [2]. This gap in knowledge of whether P-OIT can be effective in the community requires extensive research to establish its use and safety.

The attitude or mindset that one might have towards a particular experience can profoundly shape how they feel and respond to it. In turn, this can influence one's health and healing in the medical environment [17]. Howe et al. adopted this strategy to determine whether changing the patients' mindset on how to interpret side effects from P-OIT treatment would influence treatment experience and outcome. This study found that attributing the side effects experienced to the process of desensitization at work. Patients in this treatment group had less anxiety and experienced less non-life-threatening symptoms as the dose increased, improving both treatment experience and outcome [12]. This is an important aspect to the effectiveness of P-OIT desensitization and the small size of

this study and tediousness of the intervention protocol suggests more research is needed to maximise this approach.

QoL was measured in several studies, two of the studies demonstrated that parents of the children involved in the study reported significant improvements in the quality of life of their child while the data was less significant from the child self-reports [7,9,11,12]. Potentially due to the small sample size or the parents' overestimation of the improvement experienced by their child. QoL is diminished in those with food allergies and the purpose of desensitization is to improve QoL of those with allergies, allowing them to navigate their daily lives with less fear and anxiety. However, due to the lack in research, it is unclear if P-OIT alters QoL positively or negatively. This highlights the importance and need to extend the research of P-OIT trials with QoL and patient experience as primary outcomes.

Outlines the overall validity scores of all 10 articles included in this study, all of which were over 75% and valid (Table 2). Appendix A provides the whole EBL Appraisal Checklist. While all the RCTs were valid in study design and most had reduced bias, the biggest limitation was their external validity. Seven studies had reduced results validity due to no or uncertain external validity as the robust nature of the clinical trials does not generalize to the real world and to real world encounters of peanuts. Furthermore, Howe et al., which changed the mindset of patients about side effects, reached a 66.7% data collection validity due to the uncertainty of whether the data collection instrument (survey) was validated or not. Additionally, due to the nature of the literature sought out, it was never clear if those collecting the data were providing a service to the subjects unless otherwise stated, as many participants were recruited from allergy clinics that could have a research team (Supplementary Table 2).

The strengths of this literature review are the comprehensive search strategy utilized to obtain articles and the fact many of the studies are more recent publications, providing relevant and up-to-date findings.

CONCLUSION

This literature review highlights three themes regarding the use of P-OIT and its effectiveness on peanut-allergic children. By examining the various dosing protocols of P-OIT RCTs, it has been shown that there is a lack of universal recommendations and standardization regarding up-dosing protocols and additional research is needed to substantiate standardized dosing regimen recommendations. This will allow for safer and more robustly researched P-OIT to be delivered to peanut-allergic children. Secondly, although there is strong evidence for efficacy of the P-OIT RCTs, there is currently a lack of research examining whether the P-OIT would be as effective in the community. Finally, there is need for more research on the quality of life and treatment experience of participants as this will give more insight into alternative methods of increasing the efficacy of P-OIT.

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