Current options in the management of tree nut allergy. A systematic review and narrative synthesis.

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Abstract

Background: Tree nut allergy is usually life-long and potentially life-threatening. Standard of care consists of strict avoidance of the culprit nut and symptomatic treatment of accidental reactions. **Objective:** To evaluate the potential therapeutic options for desensitization of patients with IgE-mediated tree nut allergy, focusing on, but not limited to, immunotherapy. **Methods:** We systematically searched three bibliographic databases for studies published until July 2022 for active treatments of IgE-mediated allergy to tree nuts (walnut, hazelnut, pistachio, cashew, and almond) with allergen-specific immunotherapy (AIT) using oral (OIT), sublingual (SLIT), epicutaneous (EPIT) or subcutaneous (SCIT) delivery, or with other disease-modifying treatments. **Results:** We included 17 studies (three randomized, double-blinded, placebo-controlled, five quasi-experimental prospective cohorts, five prospective cohorts, two retrospective cohorts, and two case reports. Three studies investigated sublingual immunotherapy, five investigated oral immunotherapy to a single tree nut, and six used multi-food oral immunotherapy with (four) or without (two) omalizumab. The remaining studies investigated the effectiveness of monoclonal antibodies in multi-food allergic patients, including patients with a tree nut allergy. The heterogeneity of the studies prevented pooling and meta-analysis. **Conclusion:** Even though strict avoidance remains the standard of care for patients with tree nut allergy, alternative approaches have been tested in clinical trials and real-life studies. These new concepts require further investigation with more well-designed studies including well-characterized nut allergic patients before implementing them in daily clinical practice.

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Short Title: Tree Nut Immunotherapy

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ABSTRACT

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Objective: To evaluate the potential therapeutic options for desensitization of patients with IgE-mediated tree nut allergy, focusing on, but not limited to, immunotherapy.

Methods: We systematically searched three bibliographic databases for studies published until July 2022 for active treatments of IgE-mediated allergy to tree nuts (walnut, hazelnut, pistachio, cashew, and almond) with allergen-specific immunotherapy (AIT) using oral (OIT), sublingual (SLIT), epicutaneous (EPIT) or subcutaneous (SCIT) delivery, or with other disease-modifying treatments.

Results: We included 17 studies (three randomized, double-blinded, placebo-controlled, five quasi-experimental prospective cohorts, five prospective cohorts, two retrospective cohorts, and two case reports. Three studies investigated sublingual immunotherapy, five investigated oral immunotherapy to a single tree nut, and six used multi-food oral immunotherapy with (four) or without (two) omalizumab. The remaining studies investigated the effectiveness of monoclonal antibodies in multi-food allergic patients, including patients with a tree nut allergy. The heterogeneity of the studies prevented pooling and meta-analysis.

Conclusion: Even though strict avoidance remains the standard of care for patients with tree nut allergy, alternative approaches have been tested in clinical trials and real-life studies. These new concepts require further investigation with more well-designed studies including well-characterized nut allergic patients before implementing them in daily clinical practice.

KEYWORDS: Allergy treatment, food allergy, immunotherapy, management, tree nuts

MAIN TEXT

INTRODUCTION

Botanically, a tree nut is a dry hard fruit that grows in trees and does not open to release its seed, such as chestnut, hazelnut, and acorn. In everyday language, the term is used to describe a variety of edible seeds of drupe fruits like walnuts, almonds, and pistachios[1]. The most commonly consumed tree nuts in Europe

include almonds, hazelnuts, walnuts, pecan nuts, cashews, pistachio nuts, Brazil nuts, and macadamia nuts[2]. Peanut, although a legume, is often referred to together with tree nuts due to their similar culinary use.

Tree nuts belong to the group of the eight major allergenic foods and, along with peanuts, have been implicated in severe fatal or near-fatal allergic reactions[3]. However, allergic manifestations to nuts vary substantially, depending on several factors, such as the implicated nut[4], the sensitization to distinct allergen components and the presence of co-factors[5,6], and even the process of the nuts before consumption[7]. Almond, for example, rarely causes significant clinical allergy[8]. Furthermore, allergy to different allergen components influences the predicted severity of a reaction, ranging from benign oropharyngeal symptoms to life-threatening anaphylaxis[9,10]. Unlike peanut allergy, allergy to tree nuts has been under-investigated. Evidence on the prevalence, clinical manifestation, and natural history of tree nut allergy is generally sparse, as has been recently reviewed[5,6,11]. Recent studies[12,13] suggest that allergy to tree nuts is more common than peanut, in many countries, and poses a substantial burden to patients and families. As with other food allergens, the management relies on strict avoidance of the culprit nut (and often of potentially cross-reacting foods) and symptomatic treatment of accidental consumption. Food oral immunotherapy (OIT) is actively investigated for the management of milk, egg, wheat, and peanut allergy[14]. FDA (U.S. Food and Drug Administration), EMA (European Medicines Agency), and NICE (U.K. National Institute for Health and Care Excellence) have recently approved peanut OIT for clinical practice. On the contrary, there is a lack of data on desensitization approaches in managing tree nut allergy. This systematic review aims to evaluate potential therapeutic options for the desensitization of patients with IgE-mediated tree nut allergy.

The primary question was, "Which are the therapeutic options for the desensitization of patients with IgE-mediated walnut or cashew or pistachio or hazelnut, or almond allergy? What is the effectiveness and safety of these options?".

METHODS:

We systematically searched PUBMED, SCOPUS, and the COCHRANE LIBRARY [search terms (WALNUT OR CASHEW OR PISTACHIO OR HAZELNUT OR ALMOND OR TREENUT OR TREE NUT OR TREE NUTS OR TREENUTS) AND (ALLERGY OR HYPERSENSITIVITY OR ANAPHYLAXIS) AND (MANAGEMENT OR THERAPY OR TREATMENT OR IMMUNOTHERAPY)] for active treatments of IgE-mediated allergy to tree nuts (walnut, hazelnut, pistachio, cashew, and almond) with allergen-specific immunotherapy (AIT) using oral (OIT), sublingual (SLIT), epicutaneous (EPIT) or subcutaneous (SCIT) delivery or with other disease-modifying treatments (PROSPERO registration number: CRD42021248763). More details can be found in the Appendix S1.

This review's main outcomes were desensitization, through the change in the threshold of the tree nut in question required to elicit an allergic reaction while on treatment, and sustained unresponsiveness, defined as the ability to consume foods containing the tree nut in question after discontinuing treatment.

The search was performed on 10/02/2020 for PUBMED and SCOPUS databases and on 09/12/2020 for COCHRANE LIBRARY. An alert was created for further PUBMED results.

A new search using the same terms and following the same methodology was conducted on 13/07/2022 to include any recent studies.

Title and abstract screening and study selection were performed by three authors (MP, PX, EE) independently. Relevant references of included articles were also screened. Data extraction to standardized Excel forms was performed by one investigator (MP).

The quality of included studies was assessed using the JBI Critical Appraisal tools [15,16], by MP and EE. Case-series check list was found more suitable than cohort check list for the assessment of the included cohorts. We decided to use that tool instead of other cohort studies' appraisal tools for consistency. Discrepancies were resolved by consensus.

RESULTS:

The original search retrieved 689 unique citations; six additional articles were found via references and three via Pubmed alerts, of which 52 were full-text screened. The final search retrieved 8 additional articles, which were full-text screened. Overall, 17 studies were included (Fig. 1 and 2, and Table 1). Of them, three were randomized, double-blinded, placebo-control (RDBPC) studies[17-19], five quasi-experimental prospective cohorts[20-24], five prospective cohorts[25-29], two retrospective cohorts[30,31], and two case reports[32,33].

Participants with hazelnut allergy were included in 14 studies, walnut in 1 [17,18,20,21,23-27,33], cashew in 9[17,18,20,21,23-27], pecan in 7[17,18,20,21,24-26], almond in 5[17,20,21,26,27], and pistachio in 5[17,18,23,27,32].

The population in question was adults in three studies[19,28,32], children in 5[14,17,27,31,33], and both in 9[18,20-26,29].

A detailed description of all the included studies, and studies that might appear to meet the inclusion criteria, but which were excluded, can be found in the Supplementary text.

Efficacy and safety

1.1 Sublingual immunotherapy (SLIT) (Table S1)

Three studies, a RDBPC[19] and a follow-up[28] conducted by the same team, and a prospective cohort[22], investigated SLIT for the treatment of PFA or LTP syndromes. The first two studies used hazelnut extract standardized in the major allergens Cor a 1 and Cor a 8 in 12 and 7 adults with hazelnut allergy, respectively. The third study investigated the effect of Pru p 3 SLIT in 29 children and adults with LTP syndrome, including 5 patients with almond allergy, 5 with walnut, 10 with hazelnut, and 1 with cashew allergy. Hazelnut studies required a DBPCFC at baseline, while the Pru p 3 study relied on history. The RDBPC study included 12 patients in placebo, the follow-up study used baseline assessment as the comparator, and the real-life cohort included 13 patients who followed the standard of care/avoidance (SOC). In all three studies, SLIT started with a build-up phase and gradual escalations until maintenance dose was reached (13,25 mg of total hazelnut protein, corresponding to 24,34 μg of Cor a 8 and 37,63 μg of Cor a 1 in the hazelnut-SLIT, and 12,5 μg of Pru p 3 in the Pru p 3-SLIT). The time of intervention varied from 8 weeks [19] to 1 year[22]. The primary outcome in all studies was the effectiveness of SLIT, and was assessed by the changes in Eliciting Dose (ED) during the exit DBPCFC[19,28], or by OFCs to unpeeled peach and nuts[22]. Hazelnut SLIT[19,28] was successful in increasing ED and induced immunological changes in a time-depended way. More than 50% of patients with PF- or LTP-allergy passed an exit DBPCFC to 20 gr of hazelnut after at least 8 weeks of treatment. On the contrary, the effectiveness of Pru p 3 SLIT for a year on LTP-allergy to hazelnut was assessed in only 3 of the 10 hazelnut allergic patients, and one of them passed an exit OFC to 14 gr of nut. This could be attributed to the lowest maintenance dose, or to the inability of Pru p 3 to cross-desensitize Cor a 8[22]. Regarding safety, SLIT was mainly associated with oral pruritus. No epinephrine administrations were reported.

Because of the favorable safety profile, more studies are needed to investigate if SLIT could represent an effective option for desensitizing patients with PFAS or LTPS to tree nuts.

1.2. Oral immunotherapy (OIT) (Table 2)

Single tree nut

Five studies[23,24,30,31,33] investigated OIT to a single tree nut in children. 58 children received walnut OIT in two studies[24,33], 170 received hazelnut OIT in two studies[30,31], and 50 children received cashew OIT in one[23]. Inclusion required a low dose positive oral food challenge in a case report of three children undergoing low dose walnut OIT[33], a positive DBPCFC in 70 children receiving hazelnut OIT[30], and a positive OFC or a history of a recent reaction in the rest of the studies[23,24,31]. In one hazelnut-OIT study, 4 children with no history of reaction, but a strong immunological suggestion of tree nut allergy, were also included[31]. One walnut and the cashew OIT-studies included a control group receiving standard of care (avoidance)[23,24], and the rests used baseline assessment as a comparator[30,31,33]. The primary outcome was desensitization in four studies[23,24,30,31]and sustained unresponsiveness in the case report study[33]. The oral immunotherapy

protocol included an initial escalation phase in four studies[23,24,33]. All included a build-up phase until maintenance dose, which varied from 75mg[33] to 1200mg[23,24] of nut protein, while the case report study used antihistamine premedication until the maintenance[33]. The time of intervention varied from 6 to 12 months. Overall, according to each study's primary outcome, OIT succeeded in 41% of treated patients for hazelnut, 88% for cashew and to 89% for walnut, and induced favorable immunological changes (Table 2 and Supplementary text). During OIT most participants reported at least one allergic adverse event. Epinephrine administration varied from 0 to 20% of participants, depending on the protocol. Studies with lower maintenance dose[30,33] report no epinephrine use. Eosinophilic esophagitis was reported in 2 out of 278 patients, while 4 patients developed symptoms compatible with oral immunotherapy-induced gastrointestinal and eosinophilic responses (OITGER), which subsided with temporary dose reduction.

Multiple food (multi-OIT)

Multi-OIT including tree nuts, was reported in six studies[17,18,20,21,25,26], all generated from the same group, addressed in children[17] or children and adults[18,20,21,25,26]. All studies required DBPCFC prior to intervention and included an initial escalation, followed by a build-up phase. The maintenance dose varied from 300[18]to 4000mg[21] of nut protein and the time of intervention from 9 to 72 months. Two studies used antihistamines as adjuvant[20,21], and four used omalizumab[17,18,25,26]. One study used baseline assessment as a comparator[21], one study compared multi OIT to single peanut OIT[21], one compared multi OIT with and without omalizumab with the standard of care[17], and three compared the efficacy of different maintenance doses (2000 or 1000 and 300mg) to sustain desensitization after reaching the initially maintenance dose[18,20,25]. Safety was the main outcome in two studies[21,26], efficacy in two[17,18], and both in two[20,25]. One study assessed sustained unresponsiveness[18] and three assessed cross-desensitization[17,18,25]. In total, 128 participants included cashew in their OIT and 91 of them were co-treated with omalizumab, 104 included walnut of which 39 with omalizumab, 57 hazelnut (44 with omalizumab), 33 almond (22 with omalizumab), and 30 pecan (15 with omalizumab). Collectively, desensitization achieved in 88% of treated nuts, 89% in omalizumab multi-OIT and 86% in multi-OIT alone, and tolerogenic immunological changes were noted. Hazelnut-OIT had the lowest (70%) and pecan-OIT the highest (100%) efficacy, regardless of omalizumab use. The use of omalizumab helped to accelerate the procedures[26]. Compared to single OIT, multi-OIT required more time to reach maintenance[21]. Of interest, all but one of the 104 patients who reduced the maintenance dose to 300mg of tree nut protein, retained their tolerance to a 2000mg challenge, regardless of the implicated tree nut or the use of omalizumab[18,20,25].

Regarding safety, multi- and single-OIT performed similarly when tested in the same protocol and population[21], with two reported uses of epinephrine in each group, while omalizumab reduced the frequency of adverse reactions during the initial phases of OIT[17]. Comparing all OIT studies, patients in single-OIT without omalizumab experienced more frequent and more severe adverse reactions than patients treated with multi-OIT, with or without omalizumab, but different protocols and different populations must be considered. The occurrence of allergic reactions tended to decrease over time in the long term follow up studies[20,25].

Other interventions

The remaining studies investigated the effectiveness of other interventions in multi-food allergic patients, including patients with tree nut allergy[27,29,32]. Two studies performed OFCs prior to intervention[29,32] and one required a recent history of allergic reaction[27]. All assessed changes in the quality of life through different questionnaires.

Two studies assessed omalizumab in food allergic children, including two children allergic to cashew, one to pistachio, four to walnut, six to hazelnut, and three to almond[27,29]. Administration of omalizumab for 4-6 months resulted in increasing ED[27]or tolerance[29] in approximately 60% of tree nuts reported, but reactivity or tolerance were not always tested with OFCs before treatment.

In a case report, a three-month treatment with dupilumab for atopic dermatitis in an adult with pistachio and corn allergy and sensitization to cashew, walnut, hazelnut, and almond, resulted in pistachio tolerance[32].

Sustained Unresponsiveness (SU)

Two studies, the case report of low walnut-OIT[33] and the RDBPC multi-OIT with omalizumab study[18], assessed the maintenance of tolerance after discontinuation of the intervention. In the walnut study the time on maintenance was 1 year on 75 mg of walnut protein and the discontinuation period was two weeks. All three participants retained SU to 450mg of walnut protein. The multi-OIT study assessed 6 weeks SU after 2.5 years on maintenance with 2000-4000mg of treenut protein. 53% of tree nuts OFC were successful at a cumulative dose of 2000 mg of nut protein, with walnut performing the highest (82%) and cashew the lowest (18%) SU. Of note, SU was not assessed in 26% of tested tree nuts.

Cross-desensitization

Five studies assessed cross-desensitization to another nut, one regarding walnut-OIT[24], one cashew-OIT[23], and three multi-OIT[17,18,25]. Walnut-OIT desensitized 8 out of 15 (53%) hazelnut allergic patients[24], 5 of 19 cashew (26%) allergic patients[24] , and 71 of 79 (90%) pecan allergic patients[17,18,24]. Additionally, in one omalizumab multi-OIT study[25], of the 8 participants with pecan in their OIT and 10 with walnut, 7 were desensitized to both foods. Cashew-OIT desensitized 4 of 11 (36%) walnut allergic patients[23] and 61 of 68 (90%) pistachio allergic patients[17,18,23]. Higher success rates were noted between nuts with similar phylogenetic origin (cashew and pistachio, and walnut and pecan).

Quality of life assessment

Changes in quality of life were assessed by three studies[24,27,29], of which, one concerned walnut-OIT[24], and two omalizumab only[27,29]. The questionnaires used were the age-appropriate "Food Allergy Quality of Life Questionnaire" (FAQLQ) in the walnut-OIT study[24], the FAQLQ-Parental Form (PF)[27], and the "Pediatric Quality of Life Inventory" (PedsQL) 4.0 questionnaire in the omalizumab studies[29].

Walnut-OIT resulted in a clinical meaningful improvement only in participants desensitized to all nuts they were allergic to.

Omalizumab's effect on food allergy collectively resulted in a significant improvement in the health status, reduced stress associated with the allergy, and a significant decrease in the limitations of activities in daily life[27]. The PedsQL questionnaire scores were significantly increased by the treatment in both parents and patients, with greater improvement in the physical health summary score and the psychosocial health summary score[29].

Additionally, a hazelnut-OIT study[31] used a non-validated Likert questionnaire, addressed to children and their caregivers, to assess children's acceptance of hazelnut-OIT. The questionnaire was completed at a median of 47.5 months after the initial consultation. Children considered OIT effective and would recommend it to another child, but daily consumption was considered as a strain and as a medication.

DISCUSSION

i. Main findings

We identify three main strategies addressing the modification of tree nut allergy: the sublingual immunotherapy, the oral immunotherapy, single or multiple, with or without omalizumab, and the use of monoclonal antibodies interfering with allergic responses.

Sublingual immunotherapy was investigated in a small number of patients with LTP hazelnut allergy, with moderate efficacy but a favorable safety profile[19,22,28]. Single OIT was investigated for hazelnut, walnut and cashew allergy. Efficacy and safety varied according to protocol, population, and tree nut tested[23,24,30,31,33]. Multi-OIT studies included participants with variable tree nut allergy profile[17,18,20,21,25,26]. Multi-OIT was not significantly more or less effective than single-nut OIT[21]. The use of omalizumab appeared to allow for faster desensitization with fewer adverse reactions, especially during the build-up phase, and does not affect efficacy[17]. Overall, the efficacy and the safety of tree nut OIT was found to be similar to that demonstrated

by peanut OIT trials[34,35]. Omalizumab and dupilumab were investigated in a case report and two small cohort studies of multi-food allergic children and adults, with favorable outcomes[27,29,32].

Cross-desensitization between cashew and pistachio, or walnut and pecan, was described[17,18,20,23,24], attributed to the close phylogenetic affinity of the respective nuts[36]. Interestingly, cross desensitization to distant phylogenetic nuts through walnut and cashew OIT was also documented[23,24]. Linear and structural homologies of vicilin, legumin, and 2S albumin epitopes of tree nuts belonging to different botanical families[36] could contribute to the observed cross-desensitization, which, additionally to multi-OIT results, straightly affects the management options for multi-nut allergic patients.

Sustained unresponsiveness depended on the length of avoidance, with fewer participants maintaining their desensitization over time[18,33].

Managing tree nut allergy had a positive effect on the quality of life of patients and families, especially when desensitization to more nuts was achieved[24,27,29].

ii. Strengths and weaknesses

Although there are recent reviews on the management and diagnosis of tree nut allergy[5,6,37-39] this is the first systematic review thoroughly investigating the available information on therapeutic options for the desensitization of patients with IgE-mediated tree nut allergy, other than peanut. Studies addressing the management of tree nut allergy which did not fulfill the prespecified inclusion criteria of this review can be found in Supplementary text.

Unfortunately, the heterogeneity of the studies included in this review prevented pooling and meta-analysis (Supplementary Tables S2 and S3). Only a small number of studies assessed interventions specifically for tree nut allergy, while the majority referred to multi-food allergic individuals, including subgroups with a co-existing tree nut allergy. To overcome this, we had to extrapolate the participants and the outcomes in interest, although they were not fully characterized. Caution should also be taken when reviewing the numbers of patients treated with multi-OIT, with or without omalizumab, as most studies are originated by the same team, thus, the population might have specific demographic characteristics or might have been recycled.

iii. Implications for research

The management options of patients with tree nut allergy need to be further investigated by researchers. Regarding specific immunotherapy, SLIT or OIT, more studies are needed, with well characterized participants by means of molecular allergens, which are better predictors of severity of tree nut allergy[40-42].

In OIT more studies are needed to determine the optimal build-up phase, with or without adjuvant, and maintenance dose, which balance efficacy, safety, and compliance. The current knowledge of immune modulation during OIT[43] does not support the acquisition of a permanent tolerance phenotype (SU). The frequency and the dose required to maintain desensitization are probably dependent on individual biomarkers, still not fully elucidated.

The use of biologics is an appealing option, especially for patients with allergic comorbidities, and they deserve further research.

iv. Implications for clinical practice

Although large studies are lacking, there are reports about implementing tree nut immunotherapy in clinical practice[27,31,44-46]. The effectiveness of lower doses (300mg protein) to maintain desensitization to higher doses, along with the cross-desensitization effect and the possibility of multi-OIT, can be translated into clinical practice with simultaneously desensitization to multiple nuts with properly designed oligo nut mixtures. Furthermore, a maintenance dose as low as 75 mg protein per day may confer protection from traces' exposures, but this should be interpreted with caution, as only three cases are reported[33].

Finally, tree nut allergic patients currently on biologics for other allergic comorbidities, might benefit from a re-evaluation, including OFCs, of the activity of their tree nut allergy.

v. Conclusion

Even though strict avoidance is currently the standard of care for patients with tree nut allergy, alternative approaches have been tested in clinical trials and real-life studies. These new concepts require further investigation with more well-designed studies including well-characterized nut allergic patients before implementing in daily clinical practice.

IMPACT STATEMENT

HIGHLIGHTS BOX

This systematic review comprehensively describes current and exploratory therapeutic options for the desensitization of patients with IgE-mediated tree nut allergy. Several approaches that have been tested in clinical trials and real-life studies to ameliorate the burden of tree nut allergy on patients' health and quality of life, may be considered as a therapeutic option by future guidelines.

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FIGURE 1: PRISMA flow diagram

FIGURE 2: Quality assessment of included studies

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