Title: Current options in the management of tree nut allergy, focusing on, but not limited to immunotherapy: A systematic review.

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October 28, 2022

Abstract

This systematic review evaluates the potential therapeutic options for desensitization of patients with IgE-mediated tree nut allergy, focusing, but not limited to, on immunotherapy. We 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. We included 26 studies, but the heterogeneity of the studies prevented pooling and meta-analysis. Immunotherapy with hazel pollen extracts might benefit patients with a secondary nut allergy due to cross-reactivity with PR-10 or profilin panallergens but is unlikely to be beneficial in patients with a severe nut allergy caused by seed storage proteins. Sublingual immunotherapy has a moderate efficacy but a favorable safety profile. Oral immunotherapy (OIT), single, or multi-nut, with or without omalizumab, is the most studied approach. In general, tree nut OIT is effective in conferring protection from accidental exposures, with safety similar to that demonstrated by peanut OIT. The observed cross-desensitization between tree nuts straightly affects the management options for multi-nut allergic patients.

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Short Title: Tree Nut Immunotherapy

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Conflict of Interest: MP, PX, AGM, JL, EE, and NGP declare no conflicts of interest.

Acknowledgments: This work was supported by grants from the Hellenic Society of Allergology and Clinical Immunology and was co-financed by Greece and the European Union (European Social Fund-ESF) through the Operational Programme "Human Resources Development, Education and Lifelong Learning" in the context of the Act "Enhancing Human Resources Research Potential by undertaking a Doctoral Research" Sub-action 2: IKY Scholarship Programme for PhD candidates in the Greek Universities. AGM was supported by the National Institute for Health and Care Research Manchester Biomedical Research Centre (NIHR Manchester BRC) and by an NIHR Clinical Lectureship in Respiratory Medicine.

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

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Main Text

Word Count: 4425

INTRODUCTION/BACKGROUND

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[1]. However, allergic manifestations to nuts vary substantially, ranging from benign oropharyngeal symptoms to life-threatening anaphylaxis, depending on several factors, such as the implicated nut[2,3], the sensitization to distinct allergen components, the presence of co-factors[4-7], and even the process of the nuts before consumption[8]. 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[4,5,9]. Recent studies[10,11]suggest that, in many countries, allergy to tree nuts is more common than peanut. As with other foods, the management of tree nut allergy involves 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. FDA, EMA, and NICE 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 desensitization of patients with IgE-mediated tree nut allergy.

Materials and Methods

To answer the question "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?" we systematically searched three electronic databases for active treatments of IgE-mediated allergy to tree nuts (Appendix 1).

RESULTS:

The original search retrieved 689 unique citations, six additional articles were found via references and three via Pubmed alerts, of which 44 were full-text screened. The final search retrieved 8 additional articles which were full-text screened. Overall, 26 studies were included (Fig. 1 and Table 1). Of them, five were randomized, double-blinded, placebo-controlled (RDBPC) studies[12-16], one non-randomized, placebo-controlled[17], eight prospective cohorts, including two conference abstracts[18-25], five observational studies[26-30], three retrospective studies[31-33], one follow-up study[34], and three case reports[35-37].

Participants with hazelnut allergy were included in 19 studies, walnut 18, cashew 16, pecan 13, almond 12, and pistachio 8 (Appendix 2).

Efficacy and Safety

Effect of Pollen-Specific Subcutaneous Immunotherapy (SCIT) on Tree nut allergy (Table 2)

Van Hoffen et al.[15] contacted a DBPC study in adults with birch pollen and hazelnut allergy. After a year on birch- pollen-SCIT, no changes in eliciting dose (ED) and symptom score during the exit double-blinded placebo-controlled food challenge (DBPCFC) were noted.

Alonso et al.[26] investigated the effect of 1 year of plane-pollen-SCIT in 16 adults, including six with walnut allergy and six with hazelnut allergy. Three walnut-allergic patients completed the study, of which one increased the ED, and two reached the highest dose of 25g at the exit oral food challenge (OFC). Five hazelnut allergic patients underwent exit OFC; in one the ED decreased from 20 to 0,1gr, in one remained unchanged, and the rest reached the highest dose.

Tree Nut Specific Immunotherapy

Sublingual Immunotherapy (SLIT) (Table 3)

Initially, Enrique et al.[14] investigated the efficacy of hazelnut-SLIT in 12 allergic patients. After 2-3 months of therapy, the ED increased from 2,29g to 11,56g, and 5 participants reached the highest dose (20g of hazelnut), compared with 1 in placebo. Systemic reactions occurred in 0,2% of doses (3 reactions in 2 patients, one of each group), only during the build-up phase. Local reactions, mainly immediate oral itching, were observed in 7,4% doses. Four patients in treatment reported abdominal pain during the build-up phase. All reactions during the maintenance phase were oral itching, in the same patient.

In the follow-up study[34], seven patients were reassessed after a year with hazelnut-SLIT. Three discontinued after 4 to 6 months. There was a further increase in ED to 14,57g, and five patients reached the highest dose. One patient, who had tolerated the highest dose at the original study, lost protection one year after. Less than 2% of patients reported oral itching. No systemic or gastrointestinal reactions were reported.

Recently, Beitia et al[24] prospectively assessed the effect of 1-year Pru p 3-SLIT on 29 patients with LTP-syndrome, including 5 patients with allergy to almond, 5 to walnut, 10 to hazelnut, and 1 to cashew. Of them, 4 discontinued treatment before the first year. Authors reported the results of three final OFCs with hazelnut; 1 was successful. Of the overall 29 participants, 10,3% discontinued due to adverse reactions and 72,4% reported mild oral pruritus during the first weeks, which required no treatment.

Oral Immunotherapy (Table 4)

Single Tree Nut

Bradatan et al.[21] reported the results of 37 children treated with tree nut/peanut-OIT for up to two years, to reach a target daily dose of 4gr of nut/peanut. At 18 months 25 passed an OFC to their respective tree nut. Three peanuts-, two cashew- and one hazelnut-OIT children withdrew early because of allergic side effects. Most of the reactions reported during the maintenance phase were transient and required no treatment.

The NutCRACKER study[22] described the results of walnut OIT in 55 walnut allergic children; 49 reached maintenance (4000mg of walnut protein) and were considered desensitized, three increased their ED and were considered partially desensitized, and three did not complete treatment (one due to anaphylactic reactions). At least one adverse reaction was reported by 47 children at the hospital up-dosing, and by 40 at the home-dosing, mostly mild, with respiratory and gastrointestinal symptoms. Epinephrine was administered to 11 children at the hospital and 8 at home. Three had symptoms compatible with oral immunotherapy-induced gastrointestinal-and-eosinophilic responses (OITGER), which subsided with temporary dose reduction. Nine children of the control group began OIT, seven were desensitized and were included in the subsequent analysis. After achieving walnut desensitization at 4000mg the maintenance dose decreased to 1200mg daily. 45 participants followed up for at least six months, 11 reported mild allergic reactions requiring antihistamines, and one required epinephrine. After six months, all successfully consumed a single dose of 4000mg of walnut protein.

The results of a low-dose walnut-OIT in 3 children were recently reported by Sasamoto et al.[37]. Children received an individualized home starting dose and gradually reached the maintenance dose of 75mg of walnut protein after 3, 4, and 3 months respectively. The overall adverse reaction rate per intake at home dosing was 3.1%, including two anaphylactic reactions. No epinephrine use was required.

Hazelnut-OIT was first described by Morally et al.[32]in a retrospective study of 100 children. After six months on an individualized up-dosing protocol to a low maintenance dose (half of baseline ED), 34 were desensitized to a cumulative dose of 1635mg hazelnut. Median ED increased by 417mg. The remaining 66 children had at least doubled their baseline ED at six months. Side effects were retrospectively reported by 76 children; 30 reported at least one non-severe reaction. Symptoms suggesting eosinophilic esophagitis (EoE) or serious side effects were not reported.

Sabouraud et al.[33] reviewed the medical records of 70 children undergoing hazelnut-OIT, including four children with hazelnut sensitization, but no history of ingestion. At baseline, a low-dose OFC with hazelnut was used to establish an individualized, intermediate, 6-months target dose. The procedure was repeated every 6 months until a final individualized dose was reached. At 1 year, 16 children had reached maintenance, and 36 ingesting >120mg of hazelnut protein. The cumulative reaction dose increased from 13mg to 741mg. 40 children had at least 1 adverse effect at home, of which half were mild, 17 developed hazelnut aversion, and 14 reported recurrent abdominal pain. Severe systemic reactions were reported by two children, one of whom required epinephrine. Among 212 OFCs performed, seven severe systemic reactions were recorded, with four requiring epinephrine. One child developed EoE.

Cashew-OIT was described by Elizur et al.[25] in 50 cashew-allergic patients. At a median time of 12 months, 44 reached the target dose of 4000mg cashew protein and were considered fully desensitized, three tolerated 1200mg and considered partially desensitized, and three discontinued. The 44 desensitized participants were instructed to consume daily 1200mg of cashew protein. After 6 months they were all successfully challenged to 4000mg. At the in-hospital build-up 44 participants experienced at least one allergic reaction, mainly mild to moderate, while epinephrine was required in 9 participants. At home dosing, 26 participants reported allergic reactions, mostly mild, and three reported epinephrine administration. One patient developed OITGER symptoms and one developed EoE.

Multi-OIT

Begin et al.[20] first investigated the safety of the approach in 25 children in comparison to peanut-only-OIT. After an initial escalation day (IED), the dose was increased every two weeks until maintenance (2gr protein

per food). In the multi-OIT group, 13 participants included cashew in their regimen, 14 walnut, 7 pecan, 3 hazelnut, and 5 almond. There was no statistical difference in dose progression comparing the number or the combinations of foods in the OIT mix. All participants reached a 10-fold increase in their ED. Adverse reactions did not differ between peanut-only and multi-OIT groups. Most reactions were mild, regarding mainly abdominal pain. Epinephrine was required during home dosing for two participants in each group.

In the follow-up study by Andorf et al.[28], 46 participants, on a maintenance dose of 2gr per food, were followed up for up to 72 months to evaluate the feasibility of SU on lowering the dose from 2gr to 300mg and/or altering the frequency of dosing. In the "high" maintenance group, cashew was included in 13 participants; walnut in 3, pecan in 3, none had hazelnut, and 2 had almond. In the "low" maintenance group none had cashew, 10 had walnut, 5 had pecan, 3 had hazelnut, and 3 almond. Of the 25 participants with more than one food in their OIT, 10 were on a low, and 10 were on a high maintenance dose for all foods at the end of the follow-up. At the end of the study, the proportion of participants per allergen on the low dose was 66,6% for walnut, 62,5% for pecan, 100% for hazelnut, 60% for almond, and 46,2% for cashew. Each participant could tolerate [?] 2g protein in an OFC of his respective food allergens, independent of the high or the low dose. During the study, 1207 reactions were observed, with a median of 25 reactions per participant. The reactions were mainly mild, 129 were moderate, and 5 were severe, with nasal congestion and skin symptoms only. Neither fatal nor serious adverse events nor epinephrine administration were described. The frequency of allergic adverse events decreased over time. Safety did not differ between groups.

Eapen et al.[31] reported their two years' experience with multi-food OIT in 45 children. OIT protocol and maintenance dose were individualized. The multi-OIT regimen contained cashew/pistachio in 34 children, walnut/pecan in 25, hazelnut in 13, and almond in 8. At 18 months, 35 children were on daily maintenance, four were on three times per week after 6, 8, 10, and 24 months on daily maintenance, and six had discontinued. Allergic reactions occurred in 22 children during the up-dosing or in the first three months of maintenance. Most reactions were of grade 1, according to Sampson's grading, 9% were grade 2, and none was grade 3. The reactions resolved with no medication in 29 children and with antihistamines in 22. One child needed albuterol, and three epinephrine administrations were reported, all at home. Four children visited the Emergency Department for food allergy reactions, compared to 7 out of 44 children on a waiting list to start OIT during a similar period of 18 months.

Multi OIT with Omalizumab

In 2014 Begin et al.[19] first described a rush OIT protocol for up to five foods using omalizumab in 25 children. Cashew was included in 14 children, walnut in 9, pecan in 7, hazelnut in 3, and almond in 6. All children reached a 10-fold increase in their ED by two months on OIT and the maintenance dose (4000gm per food allergen) by nine months. During IED 13 children developed mild reactions. At hospital escalations, 13 mild reactions occurred per 227 doses. At-home dosing, 401 reactions were reported per 7530 doses, of which 385 were mild, 15 were moderate, and 1 was severe and required epinephrine. Home reactions occurred more frequently in the first months of therapy.

In a subsequent follow-up [27], 34 children were followed for over five years. After reaching maintenance with 2g protein for each food, the dose was reduced to 300mg for some participants based on a team-based decision. Participants were followed every 6-12 months, up to 62 months, through standard oral food challenges (OFCs), SPTs, and blood tests. Of the 18 children with cashew in OIT, 17 reduced the maintenance dose to 300mg. The corresponding numbers for walnut and hazelnut were 8/10 and 6/7 respectively. All children with pecan in their OIT continued the high dose, and all six children with almond in OIT changed to the low dose. At the end of the follow-up, each child was able to tolerate at least 2g protein during an OFC of their respective allergens, independent of the high or low dose. During the study, 1126 reactions were recorded. Of those most were mild, 40 were moderate, and 5 were severe. All severe reactions occurred in the high dose within the first 19 months of maintenance and involved skin and nasal symptoms. There were no serious adverse events or anaphylactic reactions. Epinephrine was used for mild-moderate reactions. The number of allergic reactions decreased over time. Safety did not differ between the low and the high-dose groups.

In a RDBPC multi-OIT study by Andorf et al.[12], cashew was included in the OIT of 36 children, walnut in 25, hazelnut in 24, and almond in 7. After 36 weeks of OIT, a DBPCFC to implicated food was performed. In the omalizumab group, the proportion of children who passed a 2gr food protein per allergen was 20/25 for cashew, 17/20 for walnut, 16/17 for hazelnut, and 4/6 for almond. The corresponding numbers for the placebo group were 4/11 for cashew, 0/5 for walnut, 3/7 for hazelnut, and 0/1 for almond. Maintenance was achieved at 12 weeks in the omalizumab group versus 20 weeks in the placebo group. Throughout the study, there were no serious or severe adverse events. All patients in both groups experienced at least one adverse reaction during weeks 8-16. The omalizumab group had a significantly lower median per-participant percentage of OIT doses associated with any adverse events and a significantly lower median per-participant percentage of OIT doses associated with gastrointestinal and respiratory adverse events. There were 11 epinephrine uses, 5 in the omalizumab group and 6 in the placebo group.

Subsequently, the same group compared the efficacy of alternative maintenance dosing for six weeks on SU[13]. Having completed 30 months of omalizumab-facilitated multi-OIT and passed an OFC to at least 2gr per allergen, 60 participants were randomized to blindly receive 1g, 300mg, or 0mg per allergen as the maintenance dose for six weeks, followed by OFC to at least 2gr per allergen. In the 1gr group, desensitization was documented for 9/10 participants treated for cashew, 11/ 11 for walnut, 6/7 for hazelnut, and 2/2 for almond. The corresponding numbers for the 300mg group were 12/13 for cashew, 9/9 for walnut, 3/4 for hazelnut, and 1/1 for almond. During weeks 8-16, where OIT was co-administered with omalizumab, 42 participants reported at least one adverse event. Thereafter, all 60 participants had at least one adverse event, all but one classified as grade 1 or 2. Epinephrine was used eight times by six participants. No cases of life-threatening anaphylaxis or EoE were reported.

Other treatments

The effect of a 4-month treatment with omalizumab for severe asthma on the thresholds of food allergic reactions was investigated in a real-life study of 15 children with asthma and food allergies[30]. Among participants, there was a child with allergies to walnut, hazelnut allergies, peanut, peach, and apricot. Omalizumab administration for four months resulted in an elevation in hazelnut ED from 13,8 to 35,3mg of protein. Walnut was not evaluated.

In a similar study[29] of 5 children with multiple food allergies, administration of omalizumab for at least six months resulted in tolerance for hazelnut in 3/5 children, for walnut in 1/3, for cashew in 1/2, and for almond in 2/3. One child with pistachio allergy remained allergic.

Rial et al.[36] reported a case of a 30-year-old woman with severe atopic dermatitis and LTP-syndrome with multiple food allergies, including almond, pistachio, hazelnut, and walnut, and a positive OFC to pistachio. Three months after initiating treatment with dupilumab for atopic dermatitis, she reported accidental ingestion of pistachio without reaction. Tolerability was confirmed by an OFC to 50 gr pistachio.

Traditional Chinese Medicine[35], and Chinese Herbal Medicine [Food Allergy Herbal Formula-2 (FAHF-2)][16], have been investigated in multi-allergic children, with inconclusive results.

Sustained Unresponsiveness

In a conference abstract, Scurlock et al.[23] reported the results of 8 children with walnut and another tree nut allergy undergoing walnut-OIT for approximately three years. SU at four weeks off therapy to both walnut and another tested Tree Nut (tTN) was achieved by four subjects, to walnut only by six, and to a tTN only by five.

In the case series of Sasamoto et al.[37], all children achieved two weeks SU to 450 mg after 24, 14, and 12 months on daily maintenance with 75 mg walnut.

In the study of Andorf et al.[13], in the group which discontinued OIT (0 gr protein) for six weeks, SU was documented in 2/11 participants treated for cashew allergy, 8/11 for walnut, 3/6 for hazelnut, and 1/1 for almond.

Finally, in the study of Wang et al.[16], three months of discontinuation of FAHF-2 retained unresponsiveness in 5/8 active-treated participants and in 3/10 placebo-treated participants.

Cross-desensitization

In the study of Scurlock et al.[23], three years of walnut-OIT resulted in desensitization to both walnut and another tree nut for 7/8 children.

In the walnut-OIT study of Elizur et al.[22], after walnut desensitization, all 46 children co-allergic to pecan, eight of fifteen co-allergic to hazelnut, and four of nineteen co-allergic to cashew were also fully desensitized, while six and one children with co-allergy to hazelnut and cashew respectively, were partially desensitized.

In the cashew-OIT[25], 35 participants fully desensitized to cashew were also allergic to pistachio and were successfully challenged to 2500mg of pistachio protein. Ten participants were co-allergic to walnut and offered an OFC to 4000mg of walnut. Two refused the procedure. Of the eight challenged, four succeeded.

In multi-OIT studies, cross-desensitization has been assessed for walnut and pecan, and cashew and pistachio. In the omalizumab-facilitated multi-OIT study of Andorf et al.[27], of the 8 participants with pecan in their OIT and 10 with walnut, seven were desensitized to both nuts.

In the subsequent trial[12], 20/24 participants with cashew and pistachio allergy were desensitized to pistachio while treated with cashew, and all seventeen participants with walnut and pecan allergy were desensitized to pecan treated while treated with walnut.

In the latest study of this team[13], 3/4 of pecan-allergic participants and 8/8 of pistachio-allergic participants were desensitized. Six weeks after randomization to 1000mg, 300mg, and 0 mg maintenance dose all four pecan allergic participants (1-1gr, 1-300mg, 2-0mg) and seven of eight pistachio allergic participants (3-1gr, 3-300mg, 1/2-0mg) passed the food challenge.

Quality of life assessment

In the conference abstract by Bradatan et al[21] an improvement in QoL after OIT is reported without further information.

In the NutCRACKER study of walnut[22], age-appropriate FAQLQ from 52 patients were assessed. Children desensitized to all tested nuts reported significant improvement in the total FAQLQ and the sub-scores of emotional impact, food anxiety, and social and dietary limitation. In children remaining allergic to at least one nut, statistically, but not clinically, significant improvement was noted only for the social and dietary limitation scores.

Otani et al.[17] compared the effect of multi-OIT with and without omalizumab on Food Allergy Quality of Life-Parental Burden (FAQL-PB) Questionnaire against food avoidance. FAQL improved in active groups. In controls, FAQL worsened at six months and returned to baseline levels at 18 months of follow-up.

Arasi et al.[18] used the FAQL-PB questionnaire to assess the effect of peanut or multi-OIT on food allergy-specific health-related quality of life (HRQL) over a 24 month-follow-up in caregivers of children. Scores improved significantly; 42% of caregivers reported improvement at six months, 71% at 12 months, 76% at 18 months, and 92% at 24 months. Changes in the HRQL between baseline and 24 months were associated with older age, the absence of asthma, the absence of dose-related respiratory allergic reactions, and the greater number of foods in OIT.

Fiocchi et al.[30], used the "Pediatric Quality of Life Inventory" (PedsQL) 4.0 questionnaire in 15 children. The total score, the physical, emotional, social, and cognitive functioning, were improved in children and parents after four months on omalizumab.

The Parent Form of the "Food Allergy Quality of Life Questionnaire" (FAQLQ-PF) was used by Crespo et al.[29]. After two years on omalizumab, parents perceived an improvement in the health status of their

children. The stress associated with the allergy was reduced, and the limitations of the child's activities in their daily life decreased.

In the study of Lisann et al.[35], the "Food hypersensitivity family impact" (FLIP) questionnaire was improved in the three participating children after six months of Traditional Chinese Medicine.

Finally, Sabouraud et al.[33] used a non-validated Likert questionnaire (scale 1-7), addressed to 42 children >8 y.o. and their caregivers, to assess children's acceptance of OIT. The questionnaire was completed at a median of 47,5 months after the initial consultation. The median score for children's satisfaction was 5. Children considered OIT effective (6) and reported that would recommend it to another child with allergy (7). On the other hand, children did not enjoy eating hazelnut every day (3), and OIT was considered a strain (5) and medication (4).

DISCUSSION

Overall, although all included studies required food challenges or a recent convincing history of reaction for recruitment and an exit oral food challenge assessing outcomes, they were highly heterogenous regarding the population, interventions used, primary outcomes, and preferred methods of reporting results. While some studies aimed to recruit both children and adults, most of the included participants are children.

Besides that, one of the major drawbacks of all but three studies[22,25,37] is the lack of component resolved characterization of tree nut allergy. Some studies addressed this issue by requiring a low eliciting dose at the baseline food challenge, which is unlikely to occur when the allergy is due to panallergens.

Immunotherapy with pollen extracts[15,26] might benefit patients with secondary nut allergy due to cross-reactivity with PR-10 or profilin panallergens, which are usually labile and are responsible for mild reactions, limited to mouth and oropharynx[38]. This approach is unlikely to be beneficial in patients with primary tree nut allergy to seed storage proteins, which are the cause of severe, life-threatening reactions.

Sublingual immunotherapy has been investigated only for hazelnut allergy, with moderate efficacy but a favorable safety profile[14,34]. Nevertheless, the sample size was small, and the extract used was standardized for Cor a 1 (PR-10) and Cor a 8 (LTP) allergens, and not for Cor a 9 (legumin) or Cor a 14 (2S albumin), which better predict severe hazelnut allergy[39,40]. LTP allergy has an extremely variable clinical presentation[41], which could explain the loss of protection described in one patient in the follow-up study after he had tolerated the highest dose in the original study.

The same might account for the trials using omalizumab or dupilumab without OIT in multi-allergic patients, in which tree nut allergy seems to be a manifestation of the LTP-syndrome[29,30,36].

OIT trials varied substantially regarding the escalation protocol, the maintenance dose, the definition of desensitization, and the method used to report adverse reactions. In general, the efficacy and the safety of tree nut OIT were found to be similar to that demonstrated by peanut OIT trials[42], regardless of whether the intervention is single tree nut-, multi-food-, or omalizumab-facilitated-OIT. Omalizumab appears to allow for faster desensitization with fewer adverse reactions, especially during the build-up phase. Maintenance doses, between 300[13] and 4000mg[19], seem to be effective in achieving desensitization to the full range of tree nuts (a full portion), while a maintenance dose as low as 75mg protein per day may confer protection from accidental ingestions[37].

As expected, sustained unresponsiveness depended on the length of avoidance, with fewer participants maintaining their desensitization over time[13,23,37]. The current knowledge of immune modulation during OIT[43] does not support the acquisition of a permanent tolerance phenotype. The frequency and the dose required to maintain desensitization are probably dependent on individual biomarkers, still not fully elucidated.

Cross-desensitization between cashew and pistachio, or walnut and cashew, was described in multi-OIT and single-OIT studies[12,13,22,27], attributed to the close phylogenetic affinity of respective nuts[38]. Interestingly, cross-desensitization to distant phylogenetic nuts through walnut and cashew OIT was also documented in three studies[22,23,25], although details about the implicating nuts lack in one of them[23]. Linear and structural

homologies of vicilin, legumin, and 2S albumin epitopes of tree nuts belonging to different botanical families have been demonstrated[38]. These homologies could contribute to the observed cross-desensitization, which straightly affects the management options for multi-nut allergic patients.

Managing tree nut allergy seems to have a positive effect on the quality of life of patients and families, irrespectively of the intervention used. The effect is pronounced when desensitization to more nuts is achieved.

The heterogeneity of the studies included in this review prevented pooling and meta-analysis. 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 obstacle, 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 been recycled.

Although there are recent reviews on the management and diagnosis of tree nut allergy[44-48], 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.

Even though strict avoidance remains the only approved care for patients with tree nut allergy, alternative approaches have been tested in clinical trials and real-life studies. Among them, oral immunotherapy seems to be the most effective option, although not without the risk of allergic reactions. The possibility to simultaneously achieve desensitization to multiple nuts with only one nut in OIT is of great interest for multi-nut allergic individuals and requires further investigation.

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Tables : 4

Figure 1 Legend: PRISMA diagram for study selection

Appendix 1: Search Strategy and Study Selection.

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). We followed the EAACI definition of allergen-specific immunotherapy, which is "repeated allergen exposure at regular intervals to modulate the immune response, to reduce symptoms and the need for medication for clinical allergies, and to prevent the development of new allergies".

The pre-specified inclusion criteria were randomized and non-randomized comparative studies, one group non-randomized pre-post-studies, descriptive studies which include analysis of outcomes (single-subject design, case series) and case reports, of children and adults of any age, with a diagnosis of IgE-mediated allergy to one or more tree nuts (walnut, hazelnut, pistachio, cashew, almond), confirmed by IgE sensitization (SPTs or/and sIgEs) and oral food challenge or a recent (within two years) history of reactions.

The pre-specified exclusion criteria were studies in which the diagnosis of IgE-mediated tree nut allergy was based solely on IgE sensitization and/or distant (>2 years) history of reaction and studies without an exit food challenge to the culprit nut to verify tolerance or an increase in the tolerance threshold. We did not exclude studies in which the IgE-mediated allergy diagnosis was based only on a recent history reaction rather than a food challenge, because we expected that this would result in a small number of retrieved studies.

This review's main outcome was 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 first performed on 10/02/2020 for PUBMED and SCOPUS databases and 09/12/2020 for COHRANE LIBRARY and repeated regularly; the last search was done on 13/07/2022.

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).

Appendix 2: Overall Characteristics of included studies.

The population in question was adults in five studies[16,17,28,36,38], children in eleven[14,23-25,31-35,37,39], and both in eight[15,18,21,22,26,27,29,30]. Two studies were addressed to the caregivers of children[19,20].

Two studies, including a RDBPC, investigated the effect of one-year pollen subcutaneous immunotherapy on hazelnut and walnut allergy[17,28] in a total of 26 adults. Both studies assessed tree nut allergy by food challenges at baseline. The RDBPC trial used histamine injections as the placebo, while for the prospective

cohort, the baseline assessment was used as a comparator. The primary outcome in both studies was the changes in Eliciting Dose (ED) during the exit food challenge. One study assessed immunological changes. No study assessed sustained unresponsiveness, cross-desensitization, or changes in the quality of life.

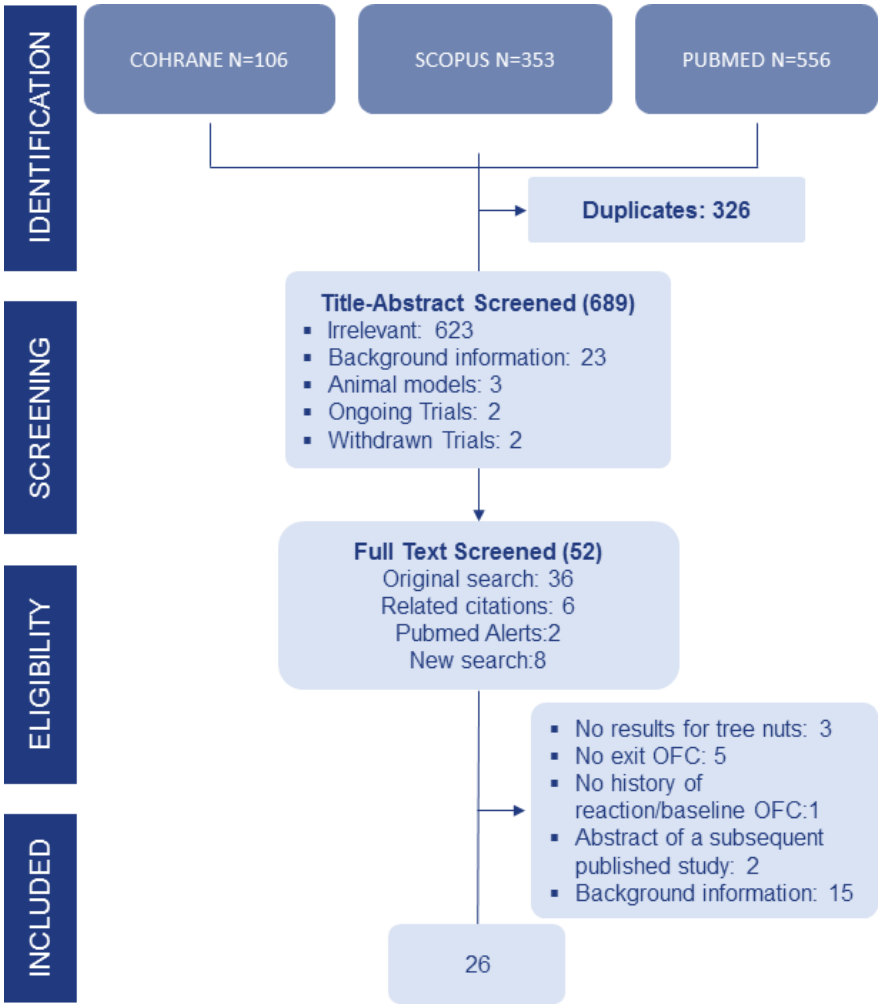
Three studies investigated sublingual immunotherapy[16,26,36]. One RDBPC and a follow-up trial were conducted by the same team and investigated sublingual immunotherapy with hazelnut extracts, standardized in unit masses of the major allergens Cor a 1 and Cor a 8[16,36], in 12 and 7 adults, after 8-12 weeks, and 11 months, respectively. All participants had a positive double-blinded, placebo-control food challenge (DBPCFC) at baseline. The primary outcome in both studies was the changes in Eliciting Dose (ED) during the exit food challenge. The third study[26] investigated the effect of Pru p 3 SLIT in 29 children and adults with a history of an allergic reaction within the previous year to several fruits with/without symptoms with vegetables, and/or peanuts or nuts compared to 13 participants who followed the standard of care/avoidance. The primary aim was to assess the effectiveness of 1-year Pru p 3 SLIT by open oral food challenges (OFCs) to unpeeled peach and nuts. Two studies[16,36] assessed immunological changes, and none assessed sustained unresponsiveness, cross-desensitization, or changes in the quality of life

Seven reports, by five published studies[24,27,34,35,39]and two conference abstracts[23,25], have investigated oral immunotherapy (OIT) to a single tree nut. The implicated tree nut was walnut in three studies[24,25,39], hazelnut in two[34,35], cashew in one[27], and one conference abstract reported peanut and/or tree nut OIT without further information[23]. All studies included children. In total, 66 children received walnut OIT, 170 children received hazelnut OIT, 50 children received cashew OIT[27], and 37 children reported in an abstract[23] received peanut/ tree OIT, with no further information provided. Inclusion required a positive oral food challenge, open or double-blinded, in three studies[23,34,39], and a positive OFC or a history of a recent reaction in three [24,27,35]. In one study, children with no history of reaction, but a strong immunological suggestion of tree nut allergy, were also included[35]. In one abstract[25], inclusion criteria were not reported. In three studies, the control group received standard of care (avoidance)[23,24,27], and four studies used baseline assessment as a comparator[25,34,35,39]. The primary outcome was desensitization in five studies[23,24,27,34,35], sustained unresponsiveness in one[39], and both in one[25]. The oral immunotherapy protocol, the maintenance dose, and the time of intervention varied between studies. One study used antihistamine premedication until the maintenance dose was reached[39]. Three studies assessed cross-desensitization to another nut[24,25,27], two studies assessed changes in quality of life[23,24], and one study assessed the acceptance of children and their caregivers of the OIT protocol[35].

Multiple oral Immunotherapy (multi-OIT), including tree nuts, was reported in nine studies[14,15,19-22,29,30,33]. Most studies were generated from the same group[14,15,19-22,29,30]. Two studies included children[14,33], five children and adults[15,21,22,29,30], and two caregivers of children[19,20]. In total, 194 participants included cashew in their OIT, pistachio, 156 walnut, 121 pecan, 58 hazelnut, and 47 almond. With one exception[33], the studies required food challenges prior to intervention. Two studies used baseline assessment as a comparator[20,21], and two used patients on standard care or on a waiting list for multi-OIT. One study compared multi OIT to single peanut OIT[22], one study compared multi OIT with and without omalizumab with the standard of care[14], and three compared different maintenance doses[15,29,30]. Safety was the main outcome in three studies[21,22,33], efficacy in two [14,15], and both in two [29,30]. In two studies, the change in the quality of life reported by caregivers was the main outcome[19,20]. No other study assessed quality of life. The oral immunotherapy protocol, the maintenance dose, and the time of intervention varied. One study used antihistamines as adjuvant[22], and five used omalizumab[14,15,19,21,29]. One study assessed sustained unresponsiveness[15], and three assessed cross-desensitization [14,15,29].

The remaining studies investigated the effectiveness of other interventions in multi-food allergic patients, including patients with a tree nut allergy. Two studies used omalizumab as the intervention in children, including two children allergic to cashew, one to pistachio, four to walnut, six to hazelnut, and three to almond[31,32]. In a case report, dupilumab was used in an adult with pistachio and corn allergy and sensitization to cashew, walnut, hazelnut, and almond[38]. Traditional Chinese Medicine[37] and Chinese Herbal Medicine (Food Allergy Herbal Formula-2)[18] were used in multi allergic subjects in the remaining studies.

Three studies performed OFCs prior to intervention[18,32,38]; one required a recent history of allergic reaction[37] and one a positive OFC and/ or convincing history[31]. One study assessed sustained unresponsiveness[18], and three assessed changes in the quality of life[31,32,37] through different questionnaires.



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