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| **Table 1: Main Characteristics of Included Studies. The pre-specified outcomes of the review (desensitization: the change in the threshold of the tree nut in question required to elicit an allergic reaction while on treatment, and sustained unresponsiveness: the ability to consume foods containing the tree nut in question after discontinuing treatment) are marked in bold.** | | | | | |
| **Study Information** | **Study Design** | **Population/Condition tested/Population recruited** | **Intervention** | **Primary Outcome/ Method of outcome measurement** | **Outcomes reported** |
| **Authors; Country; Study/Cohort name; Registration** |  |  |  |  |  |
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| **SLIT** | | | | | |
| Enrique et al. 2005; Spain; NS; NS | Randomized, Double-Blind, Placebo-Control | Adults 18-60 y.o. with IgE mediated hazelnut allergy/ 12 participants, 25% males, mean age 29.2 years in active treatment, and 11 participants, 63.3% males, median age 29.6 in placebo | All participants underwent SLIT with hazelnut extract standardized in unit masses of major allergens, Cor a 1 and Cor a 8, or with placebo. (1) Build-up phase with increasing strengths up to 66.25mg for 4 days. (2) Daily maintenance with 13.25 mg. | (1) Efficacy: **DBPCFC at baseline and after 12 weeks on maintenance**. (2) Safety: Adverse reactions and treatment required during the intervention. (3) Immunological changes at baseline and after 12 weeks on maintenance. | (1a) Changes in ED in DBPCFC 12 weeks after treatment initiation. (1b) Comparison of changes in ED between SCIT and control group. (1c) Proportion of subjects reached the highest level (20gr) in DBPCFC 12 weeks year after treatment initiation in both groups. (2) Systemic and local reactions per dose administered. (3) Changes in sIgE to hazelnut, Cor a 1 and Cor a 8, sIgG4 to hazelnut, and IL-10 12 weeks after treatment in both groups. |
| Enrique et al. 2008; Spain; NS; NS | Prospective Cohort | Adults 18-60 y.o with IgE-mediated hazelnut allergy who participated in the active group of the original study/ 11 subjects, no other information provided. | All participants continued SLIT with hazelnut extract standardized in unit masses of major allergens, Cor a 1 and Cor a 8, on daily maintenance with 13.25mg. | (1) Efficacy: **DBPCFC at baseline and after 1 year on maintenance**. (2) Safety: Adverse reactions and treatment required during the intervention. (3) Immunological changes at baseline and after 1 year on maintenance. | (1) Changes in ED in DBPCFC 12 months after treatment initiation. (2) Proportion of subjects reached the highest level (20gr) in DBPCFC one year after treatment initiation. (3) Systemic and local reactions per dose administered. (4) Changes in sIgE and sIgG4 to hazelnut, and IL-10 12 months after treatment in both groups. |
| Beitia et al. 2021; Spain; NS; NS | Quasi-Experimental Prospective Cohort | Children and adults with LTP syndrome (IgE-mediated allergy to Pru p 3)/29 participants, 48.3% males, mean age 24.7 years in active treatment and 13 participants, 30.8% males, median age 13.73 years in SOC. | All participants in the active group received Pru p 3 SLIT: (1) Build-up phase: 4-day build-up cluster schedule, with several doses per day administered at a 15-min interval, until reaching a 20-drop dose (50μg Pru p 3). (2) Maintenance: 5 drops (12.5μg of Pru p 3) daily were administered at home for at least 3 years. | (1) Efficacy: Open OFC with unpeeled peach 1 year after SLIT initiation. (2) If negative OFC to peach, **patients with a history of peanut and/or nut allergy underwent, an open OFC for the responsible food**. (3) The severity of the systemic reaction (Sampson) before starting SLIT and as a result of the OFC, 1 year after the treatment initiation. (4) Number of family plant foods avoided at the beginning and the end of the study in patients and controls. | (1) Proportion of participants in the active group with adverse reactions. (2) Proportion of participants in the active group with negative OFC to unpeeled peach 1 and 2 years after starting SLIT. **(3) Proportion of participants in the active group with negative OFC to peanut and hazelnut.** (4) Changes in severity of reactions with accidental ingestion (Sampson) in both groups during the observational period. (5) The change in the number of families of plant food involved in the allergic symptoms in the control group. |
| **Single Tree Nut OIT OIT** | | | | | |
| Elizur et al.2019; Israel; Nut CRACKER; NS | Quasi-Experimental Prospective Cohort | Children and adults > 4y.o. with IgE-mediated walnut allergy +/\_ co-allergies to pecan, hazelnut, and cashew/78 children, 36 (65%) males, median age 7.9 years received OIT/18 participants, 15 (83%) males, median age 6.8 years received SOC  \* 9 underwent WOIT, and 7 were desensitized and included in the 6-months maintenance analysis. | All participants in the active group received WOIT: (1) Initial escalation: 4 days to establish the highest tolerated dose (from 0.1 to 300mg of walnut protein. (2) Build-up phase: Monthly 1-4 days escalations in clinic with up to 4-fold escalations in the first two rounds, 3-fold in the third round, and 2-fold in the 4th and fifth rounds, monthly 50% increases thereafter until 4000 mg walnut protein. (3) Maintenance: 1200mg of walnut protein. | (1) **Walnut desensitization**: The ability to tolerate 4000mg of walnut protein. | (1a) Odds ratio of desensitization between groups. (1b) Median duration of treatment. (1c) Number of subjects partially desensitized. (1d) Proportion of patients who achieved desensitization to walnut, by reaction doses before oral immunotherapy. (2) Proportion of subjects desensitized or responded to pecan, hazelnut, or cashew. Proportion of subjects desensitized to all tested tree nuts and subjects remained allergic to at least one of these nuts. (3) Changes in walnut SPT, BAT, IgE and IgG4, IgE: IgG4 ratio, and walnut components from study start to end in active and control groups. Changes in pecan, hazelnut, or cashew SPT, BAT, IgE and IgG4, and IgE: IgG4 ratio from the study start to the end in the active group. (4) Changes in QoL at the start and end of the study in subjects desensitized to all tested nuts and those who remained allergic. (5) Proportion of subjects passing an OFC to walnut after maintenance 1200mg of walnut for 6 months. (6) Adverse reactions (number, severity, organ involvement and treatment) during hospital and home dosing, per patient and per doses received. |
| Sasamoto et al. 2021; Japan; NS; NS | Case report | Children > 5 y.o. with IgE mediated walnut allergy/3 children, 1 male, aged 7, 7, and 8 y.o. | All children received WOIT and received antihistamines from the start of OIT until there was no symptom for 1 month after desensitization. (1) Initial escalation in hospital: 3 days to establish the home starting dose protein. (2) Build-up phase: Monthly escalations until maintenance. (3) Maintenance: 75mg of walnut protein daily (4) Short-term unresponsiveness (STU): After at least 1 year from initiation OIT was discontinued for 2 weeks, and an OFC to 450mg walnut protein was performed. | (1) Efficacy: (a) **Desensitization: The absence of symptoms after ingesting 75 mg walnut on consecutive days** (b) **STU: The ability to pass an OFC to 450mg walnut protein after two weeks off OIT**. (2) Safety: Adverse reactions and treatment according to The Japanese Food Allergy Treatment Guidelines. | (1a) Time (months) to achieve desensitization. (1b) Time to achieve STU. (2a) Total rate of adverse reaction per intake at home. (2b) Number and rate per intake of adverse symptoms per child in hospital and at home. (2b) Severity of adverse symptoms per child and per OIT doses in hospital and at home. (2c) Treatment needed per child and per intake in hospital and at home. (3) Changes in walnut-sIgE, Jug r 1-sIgE, and walnut-sIgG4 between baseline, 1, 3, and 12 months of OIT. |
| Moraly et al. 2019; France; NS; NS | Retrospective Cohort | Children < 18 y.o. with IgE-mediated hazelnut allergy, who have participated at least 6 months in a hazelnut OIT protocol and performed an open food challenge (OFC) after 6 months of hazelnut OIT/100 subjects, 64% males, median age, 5 years. | All participants received HOIT with ground hazelnut: (1) Initial Dose: 1/10 of the ED then, the doses were increased monthly without exceeding half the baseline ED. (2) Build-up phase: Monthly 25-50% until 50% of initial ED. For patients not desensitized at 6 months, a new dose escalation program was initiated based on the ED of the 6-month OFC. The schema was repeated every 6 months until desensitization was achieved. (3) Maintenance: 416mg of hazelnut protein. | (1) Efficacy: **Desensitization, defined as no reaction at OFC with a cumulative dose of 1635mg after 6 months on OIT.** | (1) The proportion of desensitized patients after 6 months of OIT. (2) Average changes in ED and SPT wheal diameter after 6 months of OIT in desensitized and no-desensitized subjects. (3) Associations (Odds Ratio) between successful desensitization at 6 months and baseline variables. (4) Proportion of subjects with adverse reactions and type of non-severe and severe adverse reactions (the need for use of adrenaline, hospitalization, or death) as reported retrospectively by subjects, using a standard homemade survey. (5) Number of subjects desensitized after 12, 18, or 24 months of OIT. |
| Sabouraud et al. 2022;France;NCT04841850 | Retrospective Cohort | Children < 18 y.o. with IgE-mediated hazelnut allergy/70 children, 70% males, median age 10 years. | All children received HOIT: (1) Build-up phase: Intermediate target dose was defined individually, possibly with an OFC. Next, the children ingested daily at home 10% of the target dose, which was progressively increased to reach the intermediate target dose at 6 months. (2) Maintenance: Defined individually, according to the patient's and parents' wishes, the allergic profile, and the judgment of the allergist. \*16 (22.8%)patients received peanut OIT in parallel. | Efficacy: The proportion of children in the maintenance phase at the 1-year consultation. | (1) The proportion of children in the maintenance phase at the 1-year consultation. (2) The proportion of patients in the maintenance phase during the study period. (**3) The change of the cumulative ingested dose (the final quantity of hazelnut ingested during the OFC).** (4) Changes in hazelnut sIgE, sIgG4, and SPT wheal diameter at 1-year consultation. (5) Occurrence of adverse effects by retrospective reports at consultations. (6) Satisfaction questionnaire score (in-house no validated questionnaire) evaluating children’s aged > 8y.o. acceptance (minimal 1-maximal 7) of the OIT protocol. |
| Elizur et al.2022; Israel; Nut CRACKER/NCT02786914 | Quasi-Experimental Prospective Cohort | Children and adults 4-25 y.o. with IgE-mediated cashew allergy/ 50 patients, 28 (56%) males, median age 8 years received OIT; 15 patients, 12 (80%) males, median age 8.7 years received SOC. | All participants in the active group received COIT: (1) Initial escalation: 4 days to establish the highest tolerated dose (from 0.1 to 360mg of cashew protein. (2) Build-up phase: Monthly 1-4 days escalations in clinic with up to 4-fold escalations in the first two rounds, 3-fold in the third round, and 2-fold in the 4th and fifth round, monthly 50% increases thereafter until 4000mg cashew protein. (3) Maintenance: 1200mg of cashew protein. | **Efficacy: The ability to consume 4000 mg of cashew protein at the end of the study in OIT- treated and control participants**. | (1a) Odds ratio of desensitization between groups. (1b) Number of subjects partially desensitized. (1c) Median duration of treatment. (2) Adverse reactions (number, severity, organ involvement, and treatment) during hospital and home dosing, per patient and per dose received. (3) Changes in cashew SPT, BAT, IgE and IgG4, IgE: IgG4 ratio, and cashew components from study start to end in active and control groups. (4) Number of patients co-desensitized to pistachio and walnut. (5) Changes in pistachio SPT, BAT, IgE, and IgG4, from the study start to the end in the active group. (6) Proportion of subjects passing an OFC to cashew after a maintenance dose of 1200mg of cashew for 6 months. |
| **Multi OIT** | | | | | |
| Begin et al. 2014a; USA; Single Center Food Allergy Oral Immunotherapy Study; NCT01490177 | Quasi-Experimental Prospective Cohort | Children and adults 4-55 y.o. with IgE-mediated allergy to peanut +/- other foods/25 multi-allergic patients, 14 (56%) males, median age 8 years/15 peanut-allergic patients, 8 (53%) males, median age 10 years. | All participants received POIT or mOIT with 2-5 foods simultaneously: (1) Initial Escalation Day: In hospital administration of 0.1mg to 6mg total food protein, or the highest tolerated dose (2) Build-up phase: Bi-weekly in hospital 108-25% escalations, depended on tolerance (3) Maintenance: 4000mg of protein of each food (up to 20000mg total food protein). Subjects received cetirizine 1 hour before home doses. | (1) Safety: The occurrence of allergic reactions throughout the course of the study, comparing food-allergic participants with POIT or mOIT. | (1a) Number and Rate per dose or participant of reactions in each OIT phase. (1b) Number, rate per participant, and rate per dose of use of epinephrine in each OIT phase. (1c) Symptom profiles per dose in each OIT phase. **(2) Time to reach a 10-fold increase in threshold dose of food allergen protein, and time to reach 300 mg, 1000 mg, and 4000 mg of food allergen protein**. (3) Changes between baseline and 12 months of food-specific IgE and IgG4. |
| Andorf et al. 2017a; USA; Longitudinal Follow-up Study for Food Allergies; NCT03234764 | Quasi-Experimental Prospective Cohort | Children and adults 0.5- 60 y.o. which have reached 2 gr maintenance dose per food in an initial mOIT protocol (almond, cashew, egg, hazelnut, milk, peanut, pecan, sesame, walnut)/46 patients, 24 (52%) males, median age 10.6 years. | The clinical team, together with the patient and family, made a team decision to allow the participant to either continue to ingest the “high” maintenance dose (median 2g protein of each food allergen) or decrease to the “low” (median 300mg of each food allergen) maintenance dose. Some participants also took their dose every other day instead of daily. | **(1) Efficacy: The feasibility of sustained desensitization with reduced (300 mg–2 g) long-term maintenance dosing, assessed by OFCs every 6-12 months.** | (1) Number of participants tolerated 2g protein or more in an OFC to their respective food allergens at the end of the follow-up phase. (2a) Proportion of participants with more than one food in their OIT on a low and high maintenance dose for all foods at the end of the follow-up study. (2b) High vs. low long-term maintenance dose at the end of the follow-up study per participant for each of their respective offending foods (2c) The percentage of participants per allergen continuing high long-term maintenance dose (3) Adverse events documented as per CTCAE v4.03 criteria. (a) Reaction numbers and severity % of total reactions in total and per year. (b) Reaction numbers and severity per ITT participant in total and per year. (c) Epinephrine use. (d) Difference in safety between low vs. high maintenance dose. (4) Changes in SPT and IgG4/IgE ratios per participant and food allergen in total and in the low vs. the high maintenance group. |
| **Multi OIT with Omalizumab** | | | | | |
| Begin et al. 2014b; USA; Omalizumab With Oral Food Immunotherapy With Food Allergies Open-Label Safety Study in a Single Center; NCT01510626 | Prospective Cohort | Children and adults 4-55 y.o. allergic to at least two foods of cow’s milk, egg, peanut, nuts, grains, and sesame seed/25 participants, 19 (76%) males, median age 7.4 years. | All participants received omalizumab 8 weeks pre and 8 weeks during mOIT: (1) Initial Escalation Day: In hospital administration of 5mg to 1250mg of total food protein, or the highest tolerated dose, (2) Build-up phase: Bi-weekly in hospital 14-80% escalations, depended on tolerance, (3) Maintenance: 4000mg of protein of each food (up to 20000mg total food protein). | Safety: The occurrence of allergic reactions throughout the course of the study, reported by participants in diaries. | (1a) Risk of symptom occurrence per dose during initial escalation day, dose escalations, and home dosing. (1b) Severity of reaction per dose [Bock's criteria (1989)], (1c) Epinephrine use. **(2a) Time to reach and maintain doses of 300mg, 1000mg, and 4000mg per food allergen protein, (2b) Time to reach a 10-fold increase from the baseline reactivity threshold to each food allergen protein.** (3) Changes in peanut sIgE, sIgG4, and SPTs. |
| Andorf et al. 2017b; USA; Longitudinal Follow-up Study for Food Allergies; NCT03234764, NCT01510626 | Prospective Cohort | Children and adults 0,5-70 y.o. with multiple food allergies, who have reached 2 gr maintenance dose per food in an initial mOIT +omalizumab protocol/34 participants, 23(68%) males, median age 8.7 years. | The clinical team, together with the patient and family, made a team decision to allow the participant to either continue to ingest the “high” maintenance dose (median 2g protein of each food allergen) or decrease to the “low” (median 300mg of each food allergen) maintenance dose. | (**1) Sustained desensitization while on therapy: OFCs every 6-12 months**. (2) Immunological changes: food-specific IgE, IgG4, and SPT. (3) Safety: Self-reported adverse events as per CTCAE v4.03 criteria. | **(1a) Number of participants who passed OFC,** (1b) Number of participants co-desensitized to walnut and pecan, (1c) Number of participants on "low" and "high" maintenance dose per allergen, (1d) The percentage of participants who continued the high long-term maintenance dose per food (as opposed to low long-term maintenance dose) over time. (2a) sIgG4/IgE ratios and SPTs changes per food. (3a) Number of allergic reactions over time, (3b) Total number of reactions (% of maintenance dose), (3c) Reactions severity per organ affected. |
| Andorf et al. 2018; USA; Study Using Xolair in Rush Multi Oral Immunotherapy in Multi Food Allergic Patients (MAP-X); NCT02643862 | Randomised, Double-Blind, Placebo-Control Study | Children 4-15 y.o. with IgE-mediated allergy to multiple foods/ (a) omalizumab group: 36 participants 18(50%) males, median age 8 years, (b) placebo group: 12 participants, 6 (50%) males, median age 7 years (c) control group: 12 patients, no other information. | Participants in the omalizumab and the placebo group received omalizumab or placebo 8 weeks pre and 8 weeks during mOIT: (1) Initial Escalation Day: In hospital administration of 5mg to 1250mg of total food protein, or the highest tolerated dose, (2) Build-up phase: Bi-weekly in hospital, depended on tolerance, (3) Maintenance: 2000mg of protein of each food (up to 10000mg total food protein mg food protein. Participants in the control group received SOC. | (1) Efficacy: **The proportion of participants who passed a food challenge at 36 weeks to 2g of protein for any two foods included in each participant’s mOIT**. (2) Treatment failure: (a)failure to tolerate 5mg of total food protein during the initial dose escalation day (week 8); (b) failure to reach at least 300mg of total protein by week 16; (c) as determined by the principal investigator or medical monitor. Treatment failures of the mOIT group at week 17 crossed over to open-label mOIT+oma group. (3) Desensitisation failure: (a) inability to ingest 2g or more of each offending food at week 34, (b) severe reactions at least 4 weeks before week 36; (c) clinical reactivity (grade 1 or worse) during the food challenge to 2g of all, or all but one, of the foods at week 36. | (1a) The percentage of participants per study arm who tolerated 2g (primary endpoint) or 4g (secondary endpoint) in DBPCFCs to at least 2 foods at week 36. (1b) The proportion of participants who (i) passed a food challenge to 4g each of at least two foods at week 36, (ii) passed a food challenge to 2g each of three, four, or five foods at week 36, (iii) successfully completed the build-up phase of oral immunotherapy to the highest dose with only mild (grade 1) symptoms (iv) successfully underwent the build-up and maintenance phases of oral immunotherapy with only mild symptoms. (2) Safety outcomes determined by CTCAE version 4.03 criteria: median per-participant percentage of oral immunotherapy doses with any adverse events in total, per organ, and per severity occurred at the three phases of OIT. (3) The time to achieve the maintenance dose for each food. (4) The median tolerated dose on the initial dose escalation. (5) SPTs wheal sizes and allergen-specific IgE and IgG4 levels, changes. (6) The percentage of participants cross-desensitized to pistachio and pecan. |
| Andorf et al. 2019; USA; Multi Immunotherapy to Test Tolerance and Xolair (M-TAX); NCT02626611 | Randomized, Double-blind, Placebo-Controlled | Children 4-15 y.o. with IgE-mediated allergy to multiple foods who have successfully reached maintenance dose by week 28-29 of multi-OIT/70 participants enrolled in the open-label study of whom 60, 37 (62%) males, mean age 9.8 years were randomized. | All participants received omalizumab 8 weeks pre and 8 weeks during multi -OIT: (1) Initial Escalation Day: In hospital administration of 5mg to 625 mg of total food protein, or the highest tolerated dose, (2) Build-up phase: Bi-weekly in hospital 900-15% escalations until maintenance (2000mg total food protein) (3) Maintenance: 2000mg of total food protein. After reaching maintenance participants were randomized to receive: (a) 1000mg maintenance group: 19 patients, 16(84%) males, mean age 9.1 years, (b) 300mg maintenance: 21 patients, 11(52%) males, mean age 10 years, (c) 0mg maintenance: 20 patients, 10 (50%) males, mean age 10.3 years. | Sustained desensitization: **The ability to tolerate an oral food challenge to 2000mg of at least 2 allergens at week 36**. | (1a) The percent of participants who tolerated an OFC of a cumulative dose of at least 2g of each of at least 2 allergens at week 36, (1b) The percent of participants who passed an OFC at week 36 of at least 2g of each of their 3, 4, or 5 food allergens, (1b) The percent of participants who passed an OFC at week 36 of at least 4g of each of 2 food allergens. (2) The number of participants cross-desensitized to pistachio and pecan. (3) Peanut-specific IgE, IgG4, and SPTs change (4) Number and percentage of participants that experienced Adverse Events (AEs) by week range and randomization arm in total, by system, and by severity, including those non-randomized. |
| **Other Treatments** | | | | | |
| Rial et al. 2019; Spain; NS; NS | Case Report | A 30-year-old woman with LTP-syndrome and pistachio allergy. | Dupilumab 600mg initial and 300mg/2 weeks thereafter. | Efficacy: **Ability to pass OFC to implicated foods while on treatment for 3 months.** | Results of OFCs to 50gr of pistachios and 100gr of canned corn. |
| Fiocchi et al. 2019; Italy; NS; NS | Prospective Cohort | Children and adults > 6y.o. with severe asthma treated with omalizumab and immediate reactions to at least 2 foods or to 1 food and failure of OIT/ 15 participants, 12 males, median age 12 years, 1 participant, males, 9y.o. with hazelnut allergy. | All participants received omalizumab 0,016mg/Kg/IgE every 2 to 4 weeks for 4 months. | **Change in tolerance threshold to foods (TTF),** during an OFC, performed 2 days before omalizumab injection. | (1) The change in tolerance threshold to foods (TTF), per patient and per food. (2) The number of foods fully tolerated. (3) The number of participants developing full clinical tolerance to foods (full tolerance: cow’s milk=144.4 mL/4700 mg of proteins; baked milk = 80 g/ 6960 mg of proteins; hen’s egg= 45 g eggs/ 11,160 mg of proteins; baked egg = 80 g/ 9520 mg of proteins; hazelnut= at 64 g/ 8847.5 mg of proteins; wheat = 220 g/10,060 mg of proteins. (4) The number of allergic reactions to the unintentional ingestion of foods per patient in the 4 months before the treatment, and during the 4 months of treatment. (5) The change in the PedsQL 4.0 questionnaire score for parents and patients before and after treatment. |
| Crespo et al. 2021; Spain; NS; NS | Prospective Cohort | Children < 18 y.o. with IgE-mediated multiple food allergy unable to receive OIT/5 patients, 4 (80%) males, mean age 6 years. | Omalizumab 0,016mg/Kg/IgE every 4 weeks. | The effect of omalizumab on food allergy, assessed by :(1) **OFCs at least after 6 months on omalizumab**. (2) SPTs, sIgEs and tIgE before and after 2 years on omalizumab. (3) QoL assessed by FAQLQ-PF before and after 2 years on omalizumab. | (1) Results for OFCs and immunological changes are reported per patient. (2) QoL changes are reported narratively for overall participants. |
| *BAT: Basophile activation test, COIT: Cashew-OIT, DBPCFC: Double-blind placebo-controlled food challenge, ED: Eliciting dose, mOIT: multi-food-OIT, NS: Not specified, OFC: Oral food challenge, OIT: Oral Immunotherapy, oma: omalizumab, POIT: peanut-OIT, QoL: Quality of life, SCIT: Subcutaneous Immunotherapy, SLIT: Sublingual Immunotherapy SOC: Standard of care,, SPT: Skin prick test, tTN: test tree nut WOIT: Walnut-OIT* | | | | | |