1

Cambios en calidad de vida: ¿cuánto es suficiente para ITA?

Determining the minimal important differences in the RQLQ score with grass and tree allergy immunotherapy versus placebo in adults with moderate-to- severe allergy.

Michael S. Blaiss, Ruta Gronskyte Juhl, Leonard Q.C. Siew, Eva Hammerby, Philippe Devillier

Allergy 2022 Jan 5. doi: 10.1111/all.15207. Online ahead of print.

ARTÍCULO DESTACADO

BACKGROUND

Pollen from grasses and trees can trigger allergic rhinitis (AR), where the symptoms and associated consequences can negatively affect quality of life (QoL). The Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) is frequently used in clinical trials of AR to assess QoL. To help interpret RQLQ data, the minimal important difference (MID) can be used to assess whether a mean difference in QoL between treatment groups is clinically meaningful. In seasonal allergy, an MID differs according to the allergen, pollen exposure, symptom severity, patient age and treatment; the same MID cannot be applied to all scenarios.

METHODS

Using data from four Phase III clinical trials of SQ sublingual immunotherapy-tablets in adults with moderate-to- severe allergy, betweengroup MIDs were derived for the RQLQ in grass pollen allergy (during the peak [n = 501] and entire [n = 514] pollen seasons), and in tree pollen allergy (during the birch [n = 516] and tree [n = 518] pollen seasons), using anchor-based methodology, supported by distribution based methods.

RESULTS

For grass pollen allergy, anchor-based derived between-group MIDs were 0.22 for the entire pollen season (n = 343) and 0.10 for the peak pollen season (n = 335). For tree pollen allergy, anchor-based derived between-group MIDs were 0.26 for the tree pollen season (n = 306) and 0.16 for the birch pollen season (n = 305) (representative of peak season). Distribution-based derived MIDs were supportive of the anchor-based values.

CONCLUSIONS

This analysis has derived between-group MIDs specific to the trial populations evaluated and to the conditions under which the data were obtained, and highlights the need for a range of MIDs to reflect the unique nature of seasonal allergic disease.

2

ITO con cacahuete en niños: ventana de oportunidad para los más pequeños

Efficacy and safety of oral immunotherapy in children aged 1–3 years with peanut allergy (the Immune Tolerance Network IMPACT trial): a randomised placebo-controlled study .

Stacie M Jones, Edwin H Kim, Kari C Nadeau , et al

Lancet 2022 Jan 22;399(10322):359-371. doi: 10.1016/S0140-6736(21)02390-4.

BACKGROUND

For young children with peanut allergy, dietary avoidance is the current standard of care. We aimed to assess whether peanut oral immunotherapy can induce desensitisation (an increased allergic reaction threshold while on therapy) or remission (a state of non-responsiveness after discontinuation of immunotherapy) in this population.

METHODS

We did a randomised, double-blind, placebo-controlled study in five US academic medical centres. Eligible participants were children aged 12 to younger than 48 months who were reactive to 500 mg or less of peanut protein during a double-blind, placebo-controlled food challenge (DBPCFC). Participants were randomly assigned by use of a computer, in a 2:1 allocation ratio, to receive peanut oral immunotherapy or placebo for 134 weeks (2000 mg peanut protein per day) followed by 26 weeks of avoidance, with participants and study staff and investigators masked to group treatment assignment. The primary outcome was desensitisation at the end of treatment (week 134), and remission after avoidance (week 160), as the key secondary outcome, were assessed by DBPCFC to 5000 mg in the intention-to-treat population. Safety and immunological parameters were assessed in the same population. This trial is registered on ClinicalTrials.gov, NCT03345160.

FINDINGS

Between Aug 13, 2013, and Oct 1, 2015, 146 children, with a median age of 39·3 months (IQR 30·8–44·7), were randomly assigned to receive peanut oral immunotherapy (96 participants) or placebo (50 participants). At week 134, 68 (71%, 95% CI 61–80) of 96 participants who received peanut oral immunotherapy compared with one (2%, 0·05–11) of 50 who received placebo met the primary outcome of desensitisation (risk difference [RD] 69%, 95% CI 59–79; p<0·0001). The median cumulative tolerated dose during the week 134 DBPCFC was 5005 mg (IQR 3755–5005) for peanut oral immunotherapy versus 5 mg (0–105) for placebo (p<0·0001). After avoidance, 20 (21%, 95% CI 13–30) of 96 participants receiving peanut oral immunotherapy compared with one (2%, 0·05–11) of 50 receiving placebo met remission criteria (RD 19%, 95% CI 10–28; p=0·0021). The median cumulative tolerated dose during the week 160 DBPCFC was 755 mg (IQR 0–2755) for peanut oral immunotherapy and 0 mg (0–55) for placebo (p<0·0001). A significant proportion of participants receiving peanut oral immunotherapy who passed the 5000 mg DBPCFC at week 134 could no longer tolerate 5000 mg at week 160 (p<0·001). The participant receiving placebo who was desensitised at week 134 also achieved remission at week 160. Compared with placebo, peanut oral immunotherapy decreased peanut-specific and Ara h2-specific IgE, skin prick test, and basophil activation, and increased peanut-specific and Ara h2-specific IgG4 at weeks 134 and 160. By use of multivariable regression analysis of participants receiving peanut oral immunotherapy, younger age and lower baseline peanut-specific IgE was predictive of remission. Most participants (98% with peanut oral immunotherapy vs 80% with placebo) had at least one oral immunotherapy dosing reaction, predominantly mild to moderate and occurring more frequently in participants receiving peanut oral immunotherapy. 35 oral immunotherapy dosing events with moderate symptoms were treated with epinephrine in 21 participants receiving peanut oral immunotherapy.

INTERPRETATION

In children with a peanut allergy, initiation of peanut oral immunotherapy before age 4 years was associated with an increase in both desensitisation and remission. Development of remission correlated with immunological biomarkers. The outcomes suggest a window of opportunity at a young age for intervention to induce remission of peanut allergy.

3

¿Qué ocurre después de la ITA?

Allergen immunotherapy for long-term tolerance and prevention

Martin Penagos, Stephen R. Durham

J Allergy Clin Immunol. 2022 Jan 24;S0091-6749(22)00075-6. doi: 10.1016/j.jaci.2022.01.007. Online ahead of print.

ABSTRACT

Allergen immunotherapy is effective for the treatment of allergic rhinitis, allergic asthma and Hymenoptera venom allergy. In view of potential side effects, cost, and the necessary patient commitment, an important question is whether allergen immunotherapy provides persistent clinical benefits after treatment discontinuation. Here we appraise the existing evidence for long-term effects of both subcutaneous and sublingual immunotherapy in terms of clinical efficacy, immune mechanisms, prevention of asthma development and prevention of new allergen sensitisations. Evidence from large, randomised, double-blind, placebo controlled clinical trials that include a followup phase after treatment cessation demonstrate long term efficacy. The data strongly support recommendations in international guidelines that both sublingual and subcutaneous immunotherapy should be continued for a minimum of 3 years to achieve disease modification and long-term tolerance. Grass pollen immunotherapy for seasonal rhinitis may inhibit the onset of asthma symptoms and requirements for asthma medication. Whether early intervention in infancy with mite sublingual immunotherapy may prevent asthma remains to be tested.

4

Tratamiento de la alergia alimentaria: la evidencia apoya a la ITA

Allergen immunotherapy and/or biologicals for IgE-mediated food allergy: A systematic review and meta-analysis.

Debra de Silva Pablo Rodríguez del Río Nicolette W. de Jong et al.

Allergy . 2022 Jan 9. doi: 10.1111/all.15211. Online ahead of print.

BACKGROUND

There is substantial interest in immunotherapy and biologicals in IgE-mediated food allergy.

METHODS

We searched six databases for randomized controlled trials about immunotherapy alone or with biologicals (to April 2021) or biological monotherapy (toSeptember 2021) in food allergy confirmed by oral food challenge. We pooled the data using random-effects meta-analysis.

RESULTS

We included 36 trials about immunotherapy with 2126 mainly child participants. Oral immunotherapy increased tolerance whilst on therapy for peanut (RR 9.9, 95% CI 4.5.-21.4, high certainty); cow's milk (RR 5.7, 1.9-16.7, moderate certainty) and hen's egg allergy (RR 8.9, 4.4-18, moderate certainty). The number needed to treat to increase tolerance to a single dose of 300 mg or 1000 mg peanut protein was 2. Oral immunotherapy did not increase adverse reactions (RR 1.1, 1.0-1.2, low certainty) or severe reactions in peanut allergy (RR 1,6, 0.7-3.5, low certainty), but may increase (mild) adverse reactions in cow's milk (RR 3.9, 2.1-7.5, low certainty) and hen's egg allergy (RR 7.0, 2.4-19.8, moderate certainty). Epicutaneous immunotherapy increased tolerance whilst on therapy for peanut (RR 2.6, 1.8-3.8, moderate certainty). Results were unclear for other allergies and administration routes. There were too few trials of biologicals alone (3) or with immunotherapy (1) to draw conclusions.

CONCLUSIONS

Oral immunotherapy improves tolerance whilst on therapy and is probably safe in peanut, cow's milk and hen's egg allergy. More research is needed about quality of life, cost and biologicals.

5

¿Qué pacientes asmáticos van a ser “respondedores”?

Which patients with asthma are most likely to benefit from allergen immunotherapy?

Frédéric de Blay, Alina Gherasim, Tomas B. Casale, Virginie Doyen, David Bernstein

J Allergy Clin Immunol. 2022 Jan 23;S0091-6749(22)00080-X.

ABSTRACT

If AIT is to be considered as a treatment option for allergic asthma, it must undergo the same developmental steps as other anti-asthmatic drugs. The bronchial allergen challenge model has demonstrated excellent negative predictive value for the development of new therapies for asthma. SCIT appears to have a clinical and significant effect on the early asthmatic response to mite, cat, and birch and grass pollens in children and adults. Use of AIT in asthmatic children is widely practiced but not supported by as strong a level of evidence as in adults. HDM SLIT tablets demonstrate efficacy in asthma exacerbations and other outcomes when used as add-on therapy in adult patients. Using a biologic to improve the patient’s lung functions and asthma control prior to initiating AIT can make unsuitable candidates for AIT into appropriate candidates. Since AIT is a personalized medicine, phenotyping the most suitable patient is necessary. Adults and children field studies have suggested that polysensitized patients with rhinitis and GINA 2 to 4 asthma appear most likely to be good responders. We hypothesized that AIT responders are those who demonstrate a high eosinophilic response to natural or experimental exposure.

6

¿Será la IL-4 el biomarcador que estábamos buscando?

Identification of Robust Biomarkers for Early Predicting Efficacy of Subcutaneous Immunotherapy in Children With House Dust MiteInduced Allergic Rhinitis by Multiple Cytokine Profiling

Xie, Fan, Tang et al

Front. Immunol. 2022 Jan 12;12:805404.doi: 10.3389/fimmu.2021.805404. eCollection 2021.

BACKGROUND

Subcutaneous immunotherapy (SCIT) is an effective treatment for children with allergic rhinitis (AR), but its efficacy fluctuates among patients. There are no reliable candidate biomarkers for monitoring and predicting the response to SCIT. The present study aims to identify novel biomarkers for early predicting the efficacy of SCIT in pediatric AR patients based on multiple cytokine profiling.

METHODS

We prospectively recruited 72 children with house dust mite (HDM)-induced AR who were assigned to receive SCIT. The serum samples were collected and multiple cytokine profiling was conducted by Luminex assay at baseline. All patients were followed-up for 1 year and then categorized into effective and ineffective group based on their efficacy, and levels of 48 selected cytokines were tested and compared between the two groups. The potential cytokines were further validated by enzyme-linked immunosorbent assay (ELISA) in a cohort with 54 responders and 26 non-responders.

RESULTS

Sixty-nine of 72 children completed one-year follow-up schedule with 46 included in effective group and 23 in ineffective group. The results of multiple cytokine profiling showed that 15 cytokines (eotaxin, G-CSF, GM-CSF, IFN-g, IL-12(p40), IL-13, IL- 15, IL-16, IL-4, MIF, MIP-1a, RANTES, SCF, SDF-1a and VEGF) were dysregulated between effective and ineffective group (all $P < 0.05$). Unadjusted and adjusted multivariate analysis models highlighted that serum eotaxin, IFN-g, IL-4 and MIF levels closely associated with the efficacy of SCIT in pediatric HDM-induced AR patients. In addition, receiver operating characteristic (ROC) curves revealed potential values of these four biomarkers in predicting the response to SCIT. Further ELISA validation results in the cohort of 80 pediatric patients demonstrated that serum eotaxin and IL-4 levels were elevated in responders while IFN-g levels decreased in responders (all $P < 0.05$). ROC curves demonstrated that serum IL-4 exhibited more reliable accuracy in predicting SCIT effi cacy than eotaxin and IFN-g.

CONCLUSION

Our discover- validation study suggested that cytokines including IL-4, eotaxin and IFN- g may serve as robust biomarkers for early predicting response of SCIT in children with HDM-induced AR. These results strengthen the evidence that cytokines were associated with the response of SCIT and contributed to understand its underlying therapeutic mechanisms.

7

Provocación bronquial con alérgenos: también en la práctica diaria

EAACI position paper on the clinical use of the bronchial allergen challenge: Unmet needs and research priorities

Ioana Agache, Dario Antolin-Amerigo, Frederic de Blay et al

Allergy. 2022 Jan 2.doi: 10.1111/all.15203. Online ahead of print.

ABSTRACT

Allergic asthma (AA) is a common asthma phenotype, and its diagnosis requires both the demonstration of IgE-sensitization to aeroallergens and the causative role of this sensitization as a major driver of asthma symptoms. Therefore, a bronchial allergen challenge (BAC) would be occasionally required to identify AA patients among atopic asthmatics. Nevertheless, BAC is usually considered a research tool only, with existing protocols being tailored to mild asthmatics and research needs (eg long washout period for inhaled corticosteroids). Consequently, existing BAC protocols are not designed to be performed in moderate-to- severe asthmatics or in clinical practice. The correct diagnosis of AA might help select patients for immunomodulatory therapies. Allergen sublingual immunotherapy is now registered and recommended for controlled or partially controlled patients with house dust mite-driven AA and with FEV1 $\geq$ 70%. Allergen avoidance is costly and difficult to implement for the management of AA, so the proper selection of patients is also beneficial. In this position paper, the EAACI Task Force proposes a methodology for clinical BAC that would need to be validated in future studies. The clinical implementation of BAC could ultimately translate into a better phenotyping of asthmatics in real life, and into a more accurate selection of patients for long-term and costly management pathways.

8

Alergia respiratoria e ITA: desde el origen hasta un futuro brillante

Allergen immunotherapy for allergic airway diseases: Use lessons from the past to design a brighter future

Hesse, Oude Elberink, van Oosterhout, Nawijn

Pharmacy Ther. 2022 Jan 19;237:108115. doi: 10.1016/j.pharmthera.2022.108115. Online ahead of print.

ABSTRACT

Allergic respiratory diseases, such as allergic dermatitis, food allergy, allergic rhino conjunctivitis and allergic asthma, are chronic inflammatory diseases with increasing prevalence. Symptoms include such as watery or itchy itching of the mouth, skin, or the eyes, swelling of the face or throat, sneezing, congestion or vomiting, wheezing, shortness of breath and coughing. For allergic asthma, additional symptoms include tightness of chest, cough,wheezing, and reversible airflow limitation. These symptoms can be triggered by inhalation of allergens such as food allergens or airborne allergens such as those from tree- or grass pollen and house dust mites. Pharmacological intervention in allergic disease includes the use of antihistamines, immune suppressive drugs and in case of asthma, the use of (long acting) beta-agonists for relaxation of the constricted airways. These treatment options merely suppress symptoms and do not cure the disease. Allergen immunotherapy (AIT), in contrast, has the capacity of inducing long-term tolerance, with symptom relief persisting decennia after discontinuation of treatment, despite recurrent re exposure to the allergen. However, AIT is not effective for all allergic disorders, and treatment for several years is required to obtain long-term protection. Moreover, some forms of AIT have safety concerns, with risk of mild to severe allergic reactions. To improve safety and efficacy of AIT, the underlying mechanisms have been studied extensively in the clinic as well as in experimental models of allergic airway inflammation. Despite more than a century of clinical experience and a vast body of experimental and translational studies into the immunological and cellular mechanisms underpinning its therapeutic potential, AIT is still not implemented in routine clinical care for allergic asthma. This review provides an overview of the substantial developments that contribute to our knowledge of the pathogenesis of allergic airway diseases, the mechanism of action of AIT, its treatment routes and schedules, the standardization of extracts and use of adjuvantia. Moreover, the main conclusions from experimental models of AIT with regard to the safety and effectiveness of the treatment are summarized, and future directions for further improvements are outlined. AIT urgently requires further improvements in order to increase its efficiency and shorten the treatment duration while remaining safe and costeffective.

9

¿Está justificado el miedo a las reacciones adversas de la ITA en niños?

Safety of allergen-specific immunotherapy in children

Maria De Filippo, Martina Votto, Lucia Caminiti, et al.

Pediatr Allergy Immunol. 2022 Jan;33 Suppl 27:27-30.doi: 10.1111/pai.13622.

ABSTRACT

Allergic respiratory diseases, such as asthma and allergic rhinitis, are global health issues and have had an increasing prevalence in the last decades. Allergen-specific immunotherapy (AIT) is the only curative treatment for allergic rhinitis and asthma, as it has a disease-modifying effect. AIT is generally administered by two routes: subcutaneous (SCIT) and sublingual immunotherapy (SLIT). Local side effects are common, but usually well-tolerated and self-limited. However, systemic side effects are rare, and associated with uncontrolled asthma and bronchial obstruction, or related to errors in administration. Physicians should constantly assess potential risk factors for not only reporting systemic reactions and fatalities but also implementing other therapies to improve AIT safety. This paper highlights recent evidence on local and systemic reactions related to SCIT and SLIT in children.

10

Los alérgicos al anacardo también quieren ITO

Cashew oral immunotherapy for desensitizing cashew-pistachio allergy (NUT CRACKER study)

Arnon Elizur, Michael Y, Appel,Liat Nachshon, et al

Allergy . 2022 Jan 9.doi: 10.1111/all.15212. Online ahead of print.

BACKGROUND

Oral immunotherapy (OIT) is a treatment option for patients with milk, egg, and peanut allergy, but data on the efficacy and safety of cashew OIT are limited.

METHODS

A cohort of 50 cashew-allergic patients aged ≥4 years, who were consecutively enrolled into cashew OIT (target dose 4000 mg protein) between 4/2016 and 12/2019. Fifteen cashew-allergic patients who continued cashew elimination served as observational controls. Co-allergy to pistachio and walnut was determined. Full desensitization rate and associated immunological changes in both groups were compared. Patients fully desensitized to cashew were instructed to consume a dose of 1200 mg cashew protein for 6 months and were then challenged to a full dose. Patients with co-allergy to pistachio or walnut were challenged to the respective nut.

RESULTS

Forty-four of 50 OIT-treated patients (88%) compared to 0% in controls tolerated a dose of 4000 mg cashew protein at the end of the study (odds ratio 8.3, 95% CI 3.9–17.7, $p < 0.001$). An additional three patients were desensitized to 1200 mg cashew protein, and three patients stopped treatment. Three patients (6%) were treated with injectable epinephrine for home reactions. Desensitized patients had decreased SPT, sIgE, basophil reactivity, and increased sIgG4, following treatment. Following cashew desensitization, all pistachio (n = 35) and four of eight walnut co-allergic patients were cross desensitized to the respective nut. All (n = 44) patients consuming a low cashew dose for ≥6 months following desensitization passed a full-dose cashew OFC.

CONCLUSIONS

Cashew OIT desensitizes most cashew-allergic patients and cross desensitizes to pistachio. Safety is similar to OIT for other foods.

1

ITA: estudios en vida real y efecto a largo plazo

Long-term real-world effectiveness of allergy immunotherapy in patients with allergic rhinitis and asthma: Results from the REACT study, a retrospective cohort study.

Benedikt Fritzsching, Marco Contoli, Celeste Porsbjerg, Sarah Buchs, Julie Rask Larsen, Lisa Elliott, Mercedes Romano Rodriguez, Nick Freemantle

The Lancet Regional Health – Europe 2022;13: 100275 https://doi.org/10.1016/j. lanepe.2021.100275

ARTÍCULO DESTACADO

BACKGROUND

Allergen immunotherapy (AIT) is the only causal treatment for respiratory allergy. Long-term real-life effectiveness of AIT remains to be demonstrated beyond the evidence from randomised controlled trials (RCTs).

METHODS

REACT (Real world effectiveness in allergy immunotherapy) is a retrospective cohort study using claims data between 2007 and 2017. Study eligibility was a confirmed diagnosis of allergic rhinitis (AR), with or without asthma, and AIT. To ensure comparable groups, AIT-treated subjects were propensity score matched 1:1 with control subjects, using characteristic and potential confounding variables. Outcomes were analysed as within (pre vs post AIT) and between (AIT vs control) group differences across 9 years of follow-up (ClinicalTrial.gov: NCT04125888).

FINDINGS

46,024 AIT-treated subjects were matched with control subjects and 14,614 were included in the pre-existing asthma cohort. AIT-treated subjects were 29¢5 (16¢3) years and 53% were male. Compared to pre index year, AIT was consistently associated with greater reductions compared to control subjects in AR and asthma prescriptions, including both asthma controller and reliever prescriptions. Additionally, the AIT group had significantly greater likelihood of stepping down asthma treatment (P <0¢0001). In addition to the reduction in asthma treatment in the AIT group, a greater reduction in severe asthma exacerbations was demonstrated (P<0¢05). Reductions in pneumonia with antibiotic prescriptions, hospitalisations, and duration of inpatients stays were all in favour of AIT.

INTERPRETATION

The study extends the existing RCT evidence for AIT by demonstrating longer-term and sustained effectiveness of AIT in the real world. Additionally, in patients with concurrent asthma, AIT was associated with reduced likelihood of asthma exacerbations and pneumonia.

2

ITO con cacahuete: ¿y si le añadimos un probiótico?

Probiotic peanut oral immunotherapy versus oral immunotherapy and placebo in children with peanut allergy in Australia (PPOIT-003): a multicentre, randomised, phase 2b trial.

Paxton Loke, Francesca Orsini, Adriana C Lozinsky

Lancet Child Adolesc Health 2022 Published Online February 3, 2022 https://doi.org/10.1016/ S2352-4642(22)00006-2.

BACKGROUND

Oral immunotherapy is effective at inducing desensitisation to allergens and induces sustained unresponsiveness (ie, clinical remission) in a subset of patients, but causes frequent reactions. We aimed to investigate whether addition of a probiotic adjuvant improved the efficacy or safety of peanut oral immunotherapy.

METHODS

PPOIT-003, a multicentre, randomised, phase 2b trial, was conducted in three tertiary hospitals in Australia (Adelaide [SA], Melbourne [VIC], and Perth [WA]) in children aged 1–10 years, weighing more than 7 kg, with peanut allergy confirmed by a double blind placebo-controlled food challenge (cumulative 4950 mg dose of peanut protein) and positive peanut skin prick test (≥3 mm) or peanut-specific IgE (≥0·35 kU/L). Children were randomly assigned (2:2:1) to receive probiotic and peanut oral immunotherapy (PPOIT), placebo probiotic and peanut oral immunotherapy (OIT), or placebo probiotic and placebo OIT (placebo) for 18 months, and were followed up until 12 months after completion of treatment. Oral immunotherapy consisted of increasing doses of peanut protein (commercially available food-grade 12% defatted peanut flour [50% peanut protein]) until a 2000 mg daily maintenance dose was reached. The probiotic adjuvant was a daily dose of 2×10^{10} colony-forming units of the probiotic Lactobacillus rhamnosus ATCC 53103. Placebo immunotherapy comprised maltodextrin, brown food colouring, and peanut essence, and placebo probiotic was maltodextrin. Dual primary outcomes were 8-week sustained unresponsiveness, defined as no reaction to a cumulative dose of 4950 mg peanut protein at treatment completion and 8 weeks after treatment completion, in the PPOIT versus placebo groups and the PPOIT versus OIT groups, analysed by intention to treat. Safety endpoints were adverse events during the treatment phase, and peanut ingestion and reactions in the 12-month post-treatment period. This study is registered with the Australian New Zealand Clinical Trials Registry, 12616000322437.

FINDINGS

Between July 4, 2016, and Sept 21, 2020, 201 participants were enrolled and included in the intention-to-treat analysis. 36 (46%) of 79 children in the PPOIT group and 42 (51%) of 83 children in the OIT group achieved sustained unresponsiveness compared with two (5%) of 39 children in the placebo group (risk difference 40·44% [95% CI27·46 to 53·42] for PPOIT vs placebo, p<0·0001), with no difference between PPOIT and OIT (-5·03% [-20·40 to 10·34],p=0·52). Treatment-related adverse events were reported in 72 (91%) of 79 children in the PPOIT group, 73 (88%) of83 children in the OIT group, and 28 (72%) of 39 children in the placebo group. Exposure-adjusted incidence of adverse events was 10·58 in the PPOIT group, 11·36 in the OIT, and 2·09 in the placebo group (ratio 0·92 [95% CI 0·85 to 0·99]for PPOIT vs OIT, p=0·042; 4·98 [4·11–6·03] for PPOIT vs placebo, p<0·0001; 5·42 [4·48 6·56] for OIT vs placebo,p<0·0001), with differences seen primarily in gastrointestinal symptoms and in children aged 1–5 years. During the12-month post-treatment period, 60 (85%) of 71 participants in the PPOIT group, 60 (86%) of 70 participants in the OITgroup, and six (18%) of 34 participants in the placebo group were eating peanut; rescue epinephrine use was infrequent(two [3%] of 71 in the PPOIT group, four [6%] of 70 in the OIT group, and none in the placebo group).

INTERPRETATION

Both PPOIT and OIT were effective at inducing sustained unresponsiveness. Addition of a probiotic did not improve efficacy of OIT, but might offer a safety benefit compared with OIT alone, particularly in preschool children.

3

ITAs con Vespula y Polistes en doble sensibilización: ¿las combinamos?

Management of Double Sensitization to Vespids in Europe.

Berta Ruiz-Leon, Pilar Serrano, Carmen Vidal, Carmen Moreno-Aguilar

Toxins 2022, 14, 126. https://doi.org/10.3390/toxins14020126

ABSTRACT

Wasp allergy with a diagnostic profile of double sensitizations to vespid venom is a frequent clinical problem in areas where different genera of wasps are present. Identification of the insect responsible for serious reactions poses a diagnostic challenge as the only effective treatment to date is immunotherapy based on the specific venom. In southern Europe, the double sensitization to Vespula and Polistes venoms is highly frequent. It has been shown that the major allergenic proteins (Phospholipase A1 and Antigen 5) share sequences across the different genera and species, which would be the cause of cross-reactivity. Additionally, the minor allergens (Dipeptidyl-peptidases, Vitellogenins) have been found to share partial sequence identity. Furthermore, venom contains other homologous proteins whose allergenic nature still remains to be clarified. The traditional diagnostic tools available are insufficient to discriminate between allergy to Vespula and Polistes in a high number of cases. IgE inhibition is the technique that best identifies the cross-reactivity. When a double sensitization has indeed been shown to exist or great uncertainty surrounds the primary sensitization, therapy with two venoms is advisable to guarantee the safety of the patient. In this case, a strategy involving alternate administration that combines effectiveness with efficiency is possible.

4

“Señales de peligro”: promoción o prevención de la activación inmune en alergo-oncología.

AllergoOncology: Danger signals in Allergology and Oncology. A European Academy of Allergy and Clinical Immunology (EAACI) Position Paper.

Aurelie Poli, Ioana Agache, Rodolfo Bianchini et al

OTO Open. 2021 Oct 25;5(4):2473974X211052955. doi: 10.1177/2473974X211052955.

The immune system interacts with many nominal ‘danger’ signals, endogenous danger associated (DAMP), exogenous pathogen (PAMP) and allergen (AAMP)- associated molecular pattern molecules. The immune context under which these are received can promote or prevent immune activating or inflammatory mechanisms and may orchestrate diverse immune responses in allergy and cancer. Each can act either by favouring a respective pathology or by supporting the immune response to confer protective effects, depending on acuity or chronicity. In this Position Paper under the collective term danger signals or DAMPs, PAMPs, and AAMPs, we consider their diverse roles in allergy and cancer and the connection between these in AllergoOncology. We focus on their interactions with different immune cells of the innate and adaptive immune system and how these promote immune responses with juxtaposing clinical outcomes in allergy and cancer. While danger signals present potential targets to overcome inflammatory responses in allergy, these may be reconsidered in relation to a history of allergy, chronic inflammation and autoimmunity linked to the risk of developing cancer, and with regards to clinical responses to anti-cancer immune and targeted therapies. Cross-disciplinary insights in AllergoOncology derived from dissecting clinical phenotypes of common danger signal pathways may improve allergy and cancer clinical outcomes.

METHODS

This Position Paper is a product of the EAACI Working Group for AllergoOncology, an expert panel of clinical immunologists, allergists, biochemists and epidemiologists. The topic of the manuscript was identified at the WG workshop in May 2020 and a streamline of relevant subtopics was extensively revised and designated to individual WG members. After following workshops and using a circulation process, the final manuscript was recirculated for review to the WG authors, compiled and again recirculated for complete consensus on text, tables and figures. The final manuscript was read and approved by all authors and represents an expert consensus position, with recommendations summarized in the “Highlights box”.

5

¿Es el diagnóstico por componentes la clave para la medicina de precisión?

Precision medicine in the allergy clinic: the application of component resolved diagnosi.

Carmen Panaitescu, Laura Haidar, Maria Roxana Buzan, et al

Expert Review of Clinical Immunology, 18:2, 145-162, DOI: 10.1080/1744666X.2022.2034501

INTRODUCTION

A precise diagnosis is key for the optimal management of allergic diseases and asthma. In vivo or in vitro diagnostic methods that use allergen extracts often fail to identify the molecules eliciting the allergic reactions.

AREAS COVERED

Component-resolved diagnosis (CRD) has solved most of the limitations of extract based diagnostic procedures and is currently valuable tool for the precision diagnosis in the allergy clinic, for venom and food allergy, asthma, allergic rhinitis, and atopic dermatitis. Its implementation in daily practice facilitates: a) the distinction between genuine multiple sensitizations and cross-reactive sensitization in polysensitized patients; b) the prediction of a severe, systemic reaction in food or insect venom allergy; c) the optimal selection of allergen immunotherapy based on the patient sensitization profile. This paper describes its main advantages and disadvantages, cost-effectiveness and future perspectives.

EXPERT OPINION

The diagnostic strategy based on CRD is part of the new concept of precision immunology, which aims to improve the management of allergic diseases.

6

El dilema de qué hacer (y qué no hacer) antes de prescribir una ITA.

Workup and Clinical Assessment for Allergen Immunotherapy Candidates.

Constantinos Pitsios, Konstantinos Petalas, Anastasia Dimitriou et al

Cells 2022, 11, 653. https://doi.org/10.3390/cells11040653

ABSTRACT

Allergen Immunotherapy (AIT) is a well-established, efficient, and safe way to treat respiratory and insect-venom allergies. After determining the diagnosis of the clinically relevant culprit allergen, AIT can be prescribed. However, not all patients are eligible for AIT, since some diseases/conditions represent contraindications to AIT use, as described in several guidelines. Allergists are often preoccupied on whether an extensive workup should be ordered in apparently healthy AIT candidates in order to detect contra-indicated diseases and conditions. These preoccupations often arise from clinical, ethical and legal issues. The aim of this article is to suggest an approach to the workup and assessment of the presence of any underlying diseases/conditions in patients with no case history before the start of AIT. Notably, there is a lack of published studies on the appropriate evaluation of AIT candidates, with no globally accepted guidelines. It appears that Allergists are mostly deciding based on their AIT training, as well as their clinical experience. Guidance is based mainly on experts’ opinions; the suggested preliminary workup can be divided into mandatory and optional testing. The evaluation for possible underlying neoplastic, autoimmune, and cardiovascular diseases, primary and acquired immunodeficiencies and pregnancy, might be helpful but only in subjects for whom the history and clinical examination raise suspicion of these conditions. A workup without any reasonable correlation with potential contraindications is useless. In conclusion, the evaluation of each individual candidate for possible medical conditions should be determined on a case-by-case basis.

7

La evaluación del riesgo para prevenir reacciones en la ITA.

Systemic Allergic Reactions and Anaphylaxis Associated with Allergen Immunotherapy.

Yashu Dhamija, Tolly E.G. Epstein, David I. Bernstein

Immunol Allergy Clin N Am 42 (2022) 105–119 https://doi.org/10.1016/j.iac.2021.09.012

ABSTRACT

Although the rates of SRs have declined to an estimated rate of 1 per 1000 injections, FRs still occur. A risk stratification before the initiation of AIT may be of value to better select patients for such treatment. Risk versus benefit is a consideration for any treatment program, including SCIT. Risk factors for FRs include the following: uncontrolled asthma, a history of SR, and injections administered during a peak pollen season.Unmet needs include the safety of SLIT versus SCIT in highrisk populations and safety of modified recombinant allergens. In addition, the impact of COVID-19 on the use of SCIT and SLIT, as well as SRs, is still unclear.

8

Tabletas de ácaros y asma: ¿quién se puede beneficiar más de esta ITA?

Efficacy and safety of house dust mite sublingual immunotherapy tablet in allergic asthma: A systematic review of randomized controlled trials

Chamard Wongsa, Phichayut Phinyo, Mongkhon Sompornrattanaphan, et al

Clin Exp Pharmacol Physiol. 2021 Oct 30. doi: 10.1111/1440-1681.13607. Epub ahead of print.

BACKGROUND

House dust mite sublingual immunotherapy (HDM SLIT) effectively treats allergic rhinitis (AR). However, the evidence of HDM SLIT for allergic asthma remained limited.

OBJECTIVE

To systematically review the efficacy and safety of HDM SLIT tablets in patients with allergic asthma.

METHODS

We performed a systematic search through PubMed, Scopus, EMBASE, Web of Science, the Cochrane Center of Controlled Trials, and Google Scholar for randomized controlled trials (RCTs) that addressed the efficacy and safety of HDM SLIT tablets compared with placebo or no intervention in allergic asthma from their inception date until September 2021. The primary outcome was the reduction in inhaled corticosteroid (ICS) dose. Additional outcomeswere asthma control, exacerbation, lung function, quality-of-life, and adverse events (AEs).

RESULTS

There were seven RCTs, 5 studies in allergic asthma (4 in adults and one in children), and 2 in AR with or without asthma. The 6 SQ-HDM effectively reduced ICS dose in well- to partly-controlled mild-to-moderate asthma in 1 RCT. Two RCTs evaluated the efficacy of 6 SQ- and 12 SQ-HDM in reducing asthma exacerbation in partly-controlled moderate-to severe asthma, and their results were inconsistent. One study in children with mild-to moderate asthma found no benefit of HDM SLIT. Two RCTs in AR with or without mild-to moderate asthma showed improvement of asthma symptoms. AEs were primarily local, and anaphylaxis treated with epinephrine was reported in 3 patients.

CONCLUSION

HDM SLIT tablets tend to effectively reduce ICS use in adults and adolescents with well- to partly-controlled mild-to-moderate allergic asthma with a favorable safety profile.

9

Encuesta: ITA sublingual en tabletas versus ITA subcutánea.

Preference for sublingual immunotherapy with tablets in a Spanish population with allergic rhinitis.

Mette Bøgelund, Ana Rosado Ingelmo, Jose María Ausín Ruiz et al.

Clin Transl Allergy. 2022;e12118. https://doi.org/10.1002/clt2.12118.

BACKGROUND

This study investigated patients' preference for allergy immunotherapy (AIT) administered as either sublingual immunotherapy-tablets versus monthly or weekly subcutaneous immunotherapy (SCIT) from a Spanish patient perspective.

METHODS

A discrete choice experiment (DCE) consisting of two blocks with eight choice sets in each was constructed to elicit the preferences for AIT. Three attributes were included in the DCE for the mode of administration, including the frequency of administration, the risk of systemic reactions and the co-payment. Adults and caregivers of children with moderate to severe allergic rhinitis (AR) were included if they were not currently receiving or had not previously received AIT.

RESULTS

In total, 587 adults and 613 caregivers started the survey. Of those, 579 adults and 611 caregivers completed the survey and were included in the study. Both adults and caregivers had a significant preference for tablets compared with both monthly and weekly injections ($p \leq 0.0001$). Furthermore, the respondents showed a significant preference for reducing the risk of systemic reactions. Subgroup analyses showed that caregivers of polyallergic children and female caregivers were significantly less price sensitive when choosing their preferred treatment.

CONCLUSION

Our study demonstrated that both adults with AR and caregivers of children with AR prefer daily SLIT-tablets to SCIT with either a weekly or monthly dose schedule.

10

“Estado del arte” en la alergia a veneno de himenópteros.

Anaphylaxis to Stinging Insect Venom

Karla E. Adams, James M. Tracy, David B.K. Golden

Immunol Allergy Clin N Am 42 (2022) 161–173 https://doi.org/10.1016/j.iac.2021.09.003.

ABSTRACT

-The clinical history of an insect reaction is key to determining the diagnostic evaluation and therapeutic options that are needed. -Patients with Hymenoptera venom allergy should be assessed for factors that may place them at risk during the diagnostic evaluation and treatment of venom allergy. -Venom immunotherapy is the treatment of choice to decrease future risk in Hymenoptera venom allergy and should be considered for all patients with insect-triggered anaphylaxis. Patients deemed to be at high risk for relapse should be candidates for lifelong immunotherapy.

1

ITA y prevención del asma: los grupos con mayor beneficio.

Allergen Immunotherapy for asthma prevention: a systematic review and meta-analysis of randomised and non-randomised controlled studies.

Mariana Farraia, Inês Paciência, Francisca Castro Mendes, João Cavaleiro Rufo, Mohamed Shamji, Ioana Agache, André Moreira

Allergy. 2022 Mar 28. doi: 10.1111/all.15295. Online ahead of print.

ARTÍCULO DESTACADO

BACKGROUND

Allergen immunotherapy (AIT) is a disease-modifying treatment for IgE-mediated diseases. Randomized controlled trials (RCTs) support AIT's potential role in asthma prevention but evidence from non-randomized studies of interventions (NRSI) and longitudinal observational studies has been poorly addressed. Therefore, we aimed to conduct a systematic review and meta-analysis to assess clinical data from all study types to evaluate quantitatively the preventive role of AIT in asthma onset.

METHODS

We search three databases. Studies were screened, selected and evaluated for quality using risk-of-bias (ROB) tools. Data were descriptively summarized and meta-analysed using random effects. We performed a sensitivity, influence and subgroup analyses. Publication bias and heterogeneity were assessed.

RESULTS

From the 4549 identified studies, 24 (12 RCTs and 12 NRSI) were included in the qualitative synthesis and 18 underwent metaanalysis. One study was at low ROB, seven had moderate ROB, and 15 were proven of high ROB. Random-effects analysis showed a significant decrease in the risk of developing asthma following AIT by 25% (RR, 95% CI: 0.75, 0.64-0.88). This effect was not significant in the sensitivity analysis. Publication bias raised concerns, together with the moderate heterogeneity between studies (I2 = 58%). Subgroup analysis showed a remarkable preventive effect of AIT in children (RR, 95% CI: 0.71, 0.53-0.96), when completing 3 years of therapy (RR, 95% CI: 0.64, 0.47-0.88), and in mono-sensitized patients (RR, 95% CI: 0.49, 0.39-0.61).

CONCLUSIONS

Our findings support a possible preventive effect of AIT in asthma onset and suggest an enhanced effect when administered in children, mono-sensitized, and for at least 3 years, independently of allergen type.

2

Paralelismo clínico-inmunológico tras ITO con cacahuete.

Oral desensitization therapy for peanut allergy induces dynamic changes in peanut-specific immune responses.

Veronique Bajzik, Hannah A DeBerg, Nahir Garabatos, Blake J Rust, Kimberly K Obrien et al.

Allergy. 2022 Mar 10. doi: 10.1111/all.15276. Online ahead of print

BACKGROUND

The PALISADE study, an international, phase 3 trial of peanut oral immunotherapy (POIT) with AR101, resulted in desensitization in children and adolescents who were highly allergic to peanut. An improved understanding of the immune mechanism induced in response to food allergen immunotherapy would enable more informed and effective therapeutic strategies. Our main purpose was to examine the immunological changes in blood samples from a subset of peanut allergic individuals undergoing oral desensitization immunotherapy with AR101.

METHODS

Blood samples obtained as part of enrollment screening and at multiple time points during PALISADE study were used to assess basophil and CD4+ T-cell reactivity to peanut.

RESULTS

The absence of clinical reactivity to the entry double-blinded placebo controlled peanut challenge (DBPCFC) was accompanied by a significantly lower basophil sensitivity and T-cell reactivity to peanut compared with DBPCFC reactors. At baseline, peanut-reactive TH2A cells were observed in many but not all peanut-allergic patients and their level in peripheral blood correlates with T-cell reactivity to peanut and with serum peanut-specific IgE and IgG4 levels. POIT reshaped circulating peanut-reactive T-cell responses in a subset-dependent manner. Changes in basophil and T-cell responses to peanut closely paralleled clinical benefits to AR101 therapy and resemble responses in those with lower clinical sensitivity to peanut. However, no difference in peanut reactive Treg cell frequency was observed between groups.

CONCLUSION

Oral desensitization therapy with AR101 leads to decreased basophil sensitivity to peanut and reshapes peanut-reactive T effector cell responses supporting its potential as an immunomodulatory therapy.

3

ITA intralinfática: ¿más accesible con menos costes y riesgos?

Intralymphatic immunotherapy with one or two allergens renders similar clinical response in patients with allergic rhinitis due to birch and grass pollen.

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Clin Exp Allergy. 2022 Mar 25 doi: 10.1111/cea.14138. Online ahead of print.

INTRODUCTION

There is a need for a fast, efficient and safe way to induce tolerance in patients with severe allergic rhinitis. Intralymphatic immune therapy has been shown to be effective.

METHODS

Patients with severe birch and timothy allergy were randomized and received three doses of 0.1 ml of birch and 5-grass allergen extracts (10,000 SQ units/ml, ALK-Abelló), or birch and placebo or 5 grass and placebo by ultrasound-guided injections into inguinal lymph nodes at monthly intervals. Rhinoconjunctivitis total symptom score, medication score and rhinoconjunctivitis quality of life questionnaire were evaluated before treatment and after each birch and grass pollen season during three subsequent years. Circulating proportions of T helper subsets and allergeninduced cytokine and chemokine production were analysed by flow cytometry and Luminex.

RESULTS

The three groups reported fewer symptoms, lower use of medication and improved quality of life during the birch and grass pollen seasons each year after treatment at an almost similar rate independently of treatment with one or two allergens. Mild local pain was the most common adverse event. IgE levels to birch decreased, whereas birch-induced IL-10 secretion increased in all three groups. IgG4 levels to birch and timothy and skin prick test reactivity remained mainly unchanged. Conjunctival challenge tests with timothy extract showed a higher threshold for allergen. In all three groups, regulatory T cell frequencies were increased 3 years after treatment.

CONCLUSIONS

Intralymphatic immunotherapy with one or two allergens in patients with grass and birch pollen allergy was safe, effective and may be associated with bystander immune modulatory responses.

4

¿Qué sabemos de la efectividad y seguridad de la ITA sublingual con ambrosía?

Ragweed sublingual immunotherapy (SLIT) tablets in allergic rhinoconjunctivitis: a systematic review and meta-analysis.

Sharmila Dhulipalla

Eur Arch Otorhinolaryngol. 2022 Mar 16. doi: 10.1007/s00405-022-07270-5. Online ahead of print.

PURPOSE

Ragweed allergen causes Allergic rhinoconjunctivitis and sublingual immunotherapy is one of the treatment modalities to desensitize allergic individuals. This systematic review assesses the effectiveness and safety of sublingual immunotherapy for allergic rhinoconjunctivitis caused due to Ragweed.

METHODS

The databases search was done through December 2020. English language randomized controlled trials were included if they compared sublingual immunotherapy with placebo, pharmacotherapy, or other sublingual immunotherapy regimens, and reported clinical outcomes. The strength of the evidence for each comparison and outcome was graded based on the risk of bias, consistency, magnitude of effect, and the directness of the evidence.

RESULTS

The searches performed according to the protocol identified 134 abstracts of which 67 were duplicates. A total of 37 full papers were therefore reviewed of which 5 were included for the final study. Participants' ages ranged from 4 to 58 years. The risk of bias was low in most studies. The review suggests that sublingual immunotherapy improves rhinoconjunctivitis symptoms, with 4 of 4 studies reporting efficacy showed improvement in the symptom score of SLIT groups compared to placebo. Local reactions were frequent, but anaphylaxis was not reported in any of the studies. Serious adverse events were very few in all the studies.

CONCLUSIONS

The overall evidence showed the effectiveness of sublingual immunotherapy for the treatment of allergic rhinoconjunctivitis with or without asthma, but high-quality studies are still needed to answer questions regarding optimal dosing strategies.

5

El papel predictivo de las reacciones locales extensas

Are large local reactions a marker for systemic reactions to subcutaneous immunotherapy in children?

Isil Eser Simsek, Metin Aydogan

Asian Pac J Allergy Immunol. 2022 Mar;40(1):75-80. doi: 10.12932/AP-020221-1054.

BACKGROUND

Previous studies involving predominantly adults concluded that the patients developing frequent large local reactions (LLRs) might be at greater risk for systemic reactions (SRs) during subcutaneous allergen immunotherapy (SCIT).

OBJECTIVE

To determine the rate of side effects to SCIT and evaluate frequency of LLR among pediatric patients with SRs.

METHODS

The retrospective study included pediatric patients receiving SCIT. Data on the demographic features, season at onset of SCIT, the indication for treatment, additional allergic diseases, laboratory results, the allergens applied, side effects after injection, grade of SRs, and the total number of injections for each patient were collected retrospectively from the medical records and injection charts.

RESULTS

A total of 19,562 injections were administered to 261 patients with conventional SCIT. The incidence LLRs was 0.2% per injection; 1.15% of all patients (n = 3) experienced LLRs on at least two consecutive visits. Systemic side effects were seen in 1% of all SCIT injections. No grade 3 or grade 4 SRs were observed. Logistic regression analysis showed that having an LLR was 3.32 times (95% CI, 1.313-8. 440; P = 0.011) and initiation of SCIT in summer and spring was 4.309 and 3.056 times than autumn (95% CI, 1.527-12.157, P = 0.006; 95% CI, 1.358-6.849, P = 0.007), respectively, increased risk for an SR.

CONCLUSIONS

Having LLRs might predict the risk of SRs at any time during immunotherapy in also pediatric patients. Knowing the risk factors is important for developing a personalized protocol in these patients.

6

¿La atopia en el compartimento central naosinusal?

A Prospective Analysis of Systemic and Local Aeroallergen Sensitivity in Central Compartment Atopic Disease.

Thomas S Edwards, John M DelGaudio, Joshua M Levy, Sarah K Wise.

Otolaryngol Head Neck Surg. 2022 Mar 1;1945998221082554. doi: 10.1177/01945998221082554. Online ahead of print.

OBJECTIVE

To compare systemic allergen sensitivity and local allergen sensitivity in the sinonasal tissue of patients with a recently identified subtype of chronic rhinosinusitis strongly associated with allergy: central compartment atopic disease (CCAD).

STUDY DESING

Prospective cohort study.

SETTING

Academic tertiary care rhinology clinic.

METHODS

Fifteen participants with endoscopic and radiographic evidence of CCAD underwent systemic allergy testing with skin testing and measurement of serum specific immunoglobulin E (sIgE) to 15 regionally common aeroallergens. Local allergen sensitivity was determined by measuring sIgE to these same 15 allergens in their sinonasal tissue. sIgE testing was performed by ImmunoCAP assay.

RESULTS

Of the 15 participants, 14 were sensitive to at least 1 allergen locally in the central compartment and systemically on skin or serum testing. Among all participants, 4 were sensitive to allergens on central compartment sIgE testing that they were not sensitive to on skin and serum sIgE testing (range, 1-8 discordant allergens). Comparisons between local and systemic aeroallergen sensitivity results showed statistically significant correlations ($P < .05$) ranging from weak to strong.

CONCLUSION

Systemic allergy testing is recommended in the initial workup for CCAD. Local allergen sensitivities may be present in a subset of patients with CCAD. Further study of the clinical significance of these sensitivities should be undertaken in CCAD, with evaluation of the role of medical therapies and allergen immunotherapy in the treatment of CCAD.

7

Descubriendo los alérgenos de la avispa invasora.

Dipeptidyl peptidase IV of the Vespa velutina nigrithorax venom is recognized as a relevant allergen.

Gabriela Pretre, Juan Andrés Asturias, María Teresa Lizaso, Ana Isabel Tabar

Ann Allergy Asthma Immunol . 2022 Mar 2;S1081-1206(22)00129-6. doi: 10.1016/j.anai.2022.02.018. Online ahead of print.

BACKGROUND

Vespa velutina nigrithorax (VVN), typically known as the Asian yellow-legged wasp, has been one of the most significant invasive species in western Europe since 2010. Currently, VVN has become the most prevalent cause of Hymenoptera anaphylaxis in the north and northwestern Spain. For this reason, it is crucial to diagnose anaphylaxis cases in the acute moment for carrying out the best available treatment as soon as possible.

OBJECTIVE

To achieve a complete understanding of the venom allergen composition that will help to develop efficient diagnostics and immunotherapy treatments on the basis of this venom.

METHODS

In this study, autochthonous VVN venom was obtained and characterized by sodium dodecyl sulfate-polyacrylamide gel electrophoresis, isoelectric focusing, followed by a mass spectrometry analysis. In addition, the allergenic sensitization profile of patients diagnosed with allergy to VVN in the Allergology Service of Navarra University Hospital between the years 2017 and 2020 was studied by immunoblotting and specific IgE (ImmunoCAP, Thermo Fisher Scientific, Uppsala, Sweden).

RESULTS

Two new allergens (dipeptidyl peptidase IV and serin protease) were identified in the autochthonous VVN venom, and their identity was confirmed by liquid chromatography-mass spectrometry analysis. The study by ImmunoCAP using sera from 12 patients who had a systemic reaction after a VVN sting revealed groups 5 and 1 as predominant allergens (92% and 34%, respectively). Furthermore, the immunoblotting assay recognized dipeptidyl peptidase IV (50%) in the sera of these patients.

CONCLUSION

Serine protease and the dipeptidyl peptidase IV are components of the VVN venom, and the latter is an allergen recognized in the studied population.

8

El perfil de sensibilización como biomarcador en la alergia a abeja.

Component-Resolved Evaluation of the Risk and Success of Immunotherapy in Bee Venom Allergic Patients.

Marta Rosiek-Biegus, Robert Pawłowicz, Agnieszka Kopeć, Magdalena Kosińska, Marta Wrześniak, Marita Nittner-Marszalska

J Clin Med. 2022 Mar 17;11(6):1677. doi: 10.3390/jcm11061677.

ABSTRACT

Venom immunotherapy (VIT) is the only efficient therapy for the Hymenoptera insect venom allergy. Immunotherapy with bee venom is encumbered with a higher risk of systemic side effects and/or therapeutic failures. The objective of the study was to assess if specific profiles of molecular IgE (Immunoglobulin E) responses are associated with an increased risk of systemic side effects and/or the treatment's inefficacy. The study group numbered 64 bee venom allergic patients (BVA) who received venom immunotherapy modo ultra-rush (VIT-UR (f/m: 32/32, mean age 43.4 ± 17.2). In total, 54.84% of them manifested allergic reactions of grades I-III (acc. to Mueller's scale), while 48.66% manifested reactions of grade IV. In all the patients, IgE against bee venom extract, rApi m 1 and tryptase (sBT) were assessed. In 46 patients, assessments of IgE against rApi m 2, 3, 5, 10 were also performed. BVA patients manifesting cardiovascular symptoms (SYS IV0) showed higher levels of both sIgE-rApi m 5 ($p = 0.03$) and tryptase ($p = 0.07$) than patients with SYS I-III. Systemic adverse events during VIT with bee venom were more frequent in the induction phase than in the maintenance phase: 15.22% vs. 8.7%. In BVA patients who experienced systemic adverse events during VIT, higher concentrations of sIgE-rApi m 5 ($p < 0.05$), rApi m 1 ($p = 0.009$), and sBT ($p = 0.019$) were demonstrated. We conclude that higher levels of sIgE against rApi m 1, rApi m 5, and tryptase many constitute a potential marker of the severity of allergic reactions and therapeutic complications that can occur during VIT with bee venom.

9

Cedró del Japón y síndrome polen-frutas.

Investigation of the sensitization rate for gibberellin-regulated protein in patients with Japanese cedar pollinosis.

Yuji Mori, Fumiko Okazaki, Keiko Momma, Hiroshi Narita, Yasuto Kondo

Allergol Immunopathol (Madr). 2022 Mar 1;50(2):89-92. doi: 10.15586/aei.v50i2.440. eCollection 2022.

BACKGROUND

Pollen-food allergy syndrome (PFAS) usually manifests as an itching sensation in the mouth and throat immediately after eating fresh fruits and vegetables. However, some patients with PFAS experience systemic symptoms including anaphylaxis. In Europe, cypress gibberellin-regulated protein (GRP) has been noted to cause allergenicity and exhibit cross-reactivity with peach GRP. Japanese cedar (Cryptomeria japonica), classified in the cypress family, is the primary causative substance among all environmental allergens in Japan. However, studies on the prevalence of GRP sensitization in patients with cedar pollinosis are lacking.

OBJECTIVE

This study examined the prevalence of GRP sensitization in patients with Japanese cedar pollinosis.

METHODS

We enrolled 52 patients who had requested sublingual immunotherapy treatment with mild-to-severe rhinitis during spring, and had a JCP specific immunoglobulin E (IgE) levels of >0.7 UA/mL. Peach GRP was purified using affinity chromatography with a monoclonal antibody column. Specific IgE levels to peach GRP were measured using an enzyme-linked immunosorbent assay. Samples exhibiting absorbance at 450 nm of over mean plus three standard deviations of the negative control value were defined as positive. Sera from three patients with severe peach allergy were used as positive controls.

RESULTS

Eleven sera from 52 patients with JCP-induced allergic rhinitis were positive for peach GRP.

CONCLUSION

Twenty percent of patients with cedar pollinosis were sensitized to peach GRP. Well-powered studies are needed to clarify whether these patients are at an increased risk for systemic symptoms or whether they primarily demonstrate only localized symptoms.

10

Alt a 1, protagonista.

Fungal Allergen and Mold Allergy Diagnosis: Role and Relevance of Alternaria alternata Alt a 1 Protein Family.

Patricia Sánchez 1, Ainara Vélez-Del-Burgo 1, Ester Suñén 1, Jorge Martínez 1, Idoia Postigo 1

J Fungi (Basel). 2022 Mar 9;8(3):277. doi: 10.3390/jof8030277.

ABSTRACT

Alternaria is a genus of worldwide fungi found in different habitats such as soil, the atmosphere, plants or indoor environments. Alternaria species are saprobic-largely involved in the decomposition of organic material-but they can also act as animal pathogens, causing disease in humans and animals, developing infections, toxicosis and allergic diseases. A. alternata is considered one of the most important sources of fungal allergens worldwide and it is associated with severe asthma and respiratory status. Among the A. alternata allergens, Alt a 1 is the main sensitizing allergen and its usefulness in diagnosis and immunotherapy has been demonstrated. Alt a 1 seems to define a protein family that can be used to identify related pathogenic fungi in plants and fruits, and to establish taxonomic relationships between the different fungal divisions.

1

El impacto (relativo) de los perfiles de sensibilización a ácaros sobre el efecto de la ITA

Molecular reactivity profiling upon immunotherapy with a 300 IR sublingual house dust mite tablet reveals marked humoral changes towards major allergens. : Molecular reactivity profiling upon immunotherapy with a 300 IR sublingual house dust mite tablet reveals marked humoral changes towards major allergens..

Potapova E, Bordas-Le Floch V, Schlederer T, Vrtala S, Huang HJ, Canonica GW, Valenta R, Matricardi PM, Mascarell L
Allergy. 2022 Apr 26. doi: 10.1111/all.15327. Epub ahead of print. PMID: 35474582.

ARTÍCULO DESTACADO

BACKGROUND
Molecular antibody reactivity profiles have not yet been studied in depth in patients treated by sublingual house dust mite (HDM) tablet immunotherapy. Humoral immune responses to a large panel of HDM mite allergens were studied using allergen microarray technology in a subset of clinically defined high and low responder patients from a double-blind placebo-controlled allergen-specific immunotherapy (AIT) trial using sublingual 300 IR HDM tablets.

METHODS
Serum levels of IgE, IgG and IgG4 to 13 Dermatophagoides pteronyssinus molecules were measured at baseline and after 1-year AIT, using allergen microarrays in 100 subjects exhibiting high or low clinical benefit.

RESULTS
Der p 1, Der p 2 and Der p 23 were the most frequently recognized allergens in the study population. Patients with HDM-related asthma had significantly higher allergen-specific IgE levels to Der p and Der p 23. No significant difference in the distribution of allergensensitization pattern was observed between high and low responders. An increase in serum allergen-specific IgG and IgG4 occurred upon AIT, in particular to allergens Der p 1, Der p 2 and Der p 23 ($p < 0.0001$).

CONCLUSIONS
We confirm for our study population that Der p 1-and Der p 23-specific IgE levels are associated with asthma. IgE reactivity profiles were not predicitive of sublingual AIT outcomes, with 300 IR tablets as efficacious in pauci- and multi-sensitized subjects. Our study is the first to demonstrate the induction of IgG and IgG4 specific for the HDM allergens Der p 1, Der p 2 and Der p 23 by sublingual AIT.

2

Nuevas estrategias para incrementar la tolerancia a la leche

Single low-dose exposure to cow's milk at diagnosis accelerates cow's milk allergic infants' progress on a milk ladder programme

d'Art YM, Forristal L, Byrne AM, Fitzsimons J, van Ree R, DunnGalvin A, Hourihane JO
Allergy. 2022 Apr 11. doi: 10.1111/all.15312. Epub ahead of print. PMID: 35403213

BACKGROUND
Cow's milk protein allergy (CMPA) is one of the most common food allergies in infancy. Most infants with CMPA tolerate baked milk from diagnosis and gradually acquire increased tolerance. Nevertheless, parents often display significant anxiety about this condition and a corresponding reluctance to progress with home introduction of dairy due to concerns about possible allergic reactions.

OBJECTIVE
To evaluate the impact on gradual home introduction of foods containing cows' milk after a supervised, single low-dose exposure to whole milk at time of diagnosis.

METHODS
Infants less than 12 months old referred with suspected IgE mediated cow's milk allergy were recruited to an open-label randomized, controlled trial of intervention-a single dose of fresh cow's milk, using the validated dose of milk that would elicit reactions in 5% of CMPA subjects-the ED05 - vs routine care. Both groups implemented graded exposure to CM (using the 12 step MAP Milk Tolerance Induction Ladder), at home. Parents completed food allergy quality of life questionnaires and State and Trait Anxiety Inventories (STAI). Main outcome measures were milk ladder position at 6 months and 12 months post-randomization.

RESULTS
Sixty patients were recruited, 57 (95%) were followed to 6 months. By 6 months, 27/37 (73%) intervention subjects had reached step 6 or above on the milk ladder compared to 10/20 (50%) control subjects ($p = .048$). By 6 months, 11/37 (30%) intervention subjects had reached step 12 (i.e. drinking unheated cow's milk) compared to 2/20 (10%) of the controls ($p = .049$). Twelve months postrandomization, 31/36(86%) of the intervention group and 15/19(79%) of the control group were on step 6 or above. However, 24/37 (65%) of the intervention group were at step 12 compared to 7/20 (35%) of the control group ($p = .03$). Maternal STAIs were significantly associated with their infants' progress on the milk ladder and with changes in skin prick test and spIgE levels at 6 and 12 months.

CONCLUSION
This study demonstrates the safety and effectiveness of introduction of baked milk implemented immediately after diagnosis of cows' milk allergy in a very young cohort. A supervised single dose of milk at the ED05 significantly accelerates this further, probably by giving parents the confidence to proceed. Maternal anxiety generally reflects infants' progress towards completion of the milk ladder, but pre-existing high levels of maternal anxiety are associated with poorer progress.

3

Se confirma la seguridad de la ITA en el embarazo

Exposure to Allergen-Specific Immunotherapy in Pregnancy and Risk of Congenital Malformations and Other Adverse Pregnancy Outcomes

Mitselou N, Stephansson O, Melén E, Ludvigsson JF

J Allergy Clin Immunol Pract. 2022 Apr 16:S2213-2198(22)00246-X. doi: 10.1016/j.jaip.2022.03.005. Epub ahead of print

BACKGROUND

Owing to insufficient data, current guidelines recommend against initiating allergen-specific immunotherapy (AIT) during pregnancy but suggest that well-tolerated ongoing immunotherapy may be continued.

OBJECTIVE

To evaluate the safety of AIT in pregnancy, especially the risk for congenital malformations.

METHODS

This nationwide Swedish cohort study identified pregnancies exposed to AIT, both subcutaneous and sublingual, through the Swedish Medical Birth register and the Prescribed Drug Register between 2005 and 2014. Information on congenital malformations in offspring was retrieved from the National Patient Register. Using the personal identity number, we linked data between registers. Using logistic regression, we calculated odds ratios (ORs) with 95% CIs for congenital malformations and other adverse pregnancy outcomes after adjusting for potential confounders.

RESULTS

From 2005 to 2014, we identified 924,790 singleton pregnancies. Among these, 743 pregnancies had been exposed to AIT 3 months before conception up until gestational week 22. Allergen-specific immunotherapy in pregnancy was not linked to congenital malformations (OR = 0.90; 95% CI, 0.63-1.27) or other adverse pregnancy outcomes (preterm birth: OR = 0.98; 95% CI, 0.71-1.35; stillbirth: OR = 0.79; 95% CI, 0.26-2.47; or cesarean delivery: OR = 0.91; 95% CI, 0.76-1.09). Stratification by route of immunotherapy, subcutaneous or sublingual, resulted in similar ORs. Restricting the pregnancy cohort to women with asthma or pulmonary disease, nulliparous women, births in 2012 to 2014, or Swedish-born women yielded similar results.

CONCLUSIONS

This nationwide study found no evidence of congenital malformations or other adverse pregnancy outcomes in women treated with AIT in pregnancy.

4

Inmunogenicidad de la combinación ITO con cacahuete + probiótico

Longitudinal antibody responses to peanut following probiotic and peanut oral immunotherapy (PPOIT) in children with peanut allergy.

Hsiao KC, Ponsonby AL, Ashley S, Lee CYY, Jindal L, PPOIT Study Team, Masters of advanced practice nursing, Tang MLK

Clin Exp Allergy. 2022 Apr 11. doi: 10.1111/cea.14146. Epub ahead of print. PMID: 35403286.

INTRODUCTION

Probiotic and Peanut Oral Immunotherapy (PPOIT) is effective at inducing sustained unresponsiveness (SU) at end-of-treatment and this effect persists up to four years post-treatment, referred to as persistent SU. We sought to evaluate (i) how PPOIT altered peanutspecific humoral immune indices, and (ii) how such longitudinal indices relate to persistent SU.

METHODS

Longitudinal serum/plasma levels of whole peanut- and peanut component- (Ara-h1, -h2, -h3, -h8, -h9) specific-IgE (sIgE) and specific-IgG4 (sIgG4) antibodies were measured by ImmunoCAP and salivary peanut-specific-IgA (sIgA) by ELISA in children (n=62) enrolled in the PPOIT-001 randomised trial from baseline (T0) to 4-years post treatment (T5). Multivariate regression analyses of log-transformed values were used for point-in-time between group comparisons. Generalised estimating equations (GEE) were used for longitudinal comparisons between groups.

RESULTS

PPOIT was associated with changes in sIgE and sIgG4 over time. sIgE levels were significantly reduced post-treatment [T5, PPOIT v.s. Placebo ratio of geometric mean (GM): Ara-h1 0.07, p=0.008; Ara-h2 0.08, p=0.007; Ara-h3 0.15, p=0.021]. sIgG4 levels were significantly increased by end-of-treatment (T1, PPOIT v.s. Placebo ratio of GM: Ara h1 3.77, p=0.011; Ara-h2 17.97, p<0.001; Ara-h3 10.42, p<0.001) but levels in PPOIT group decreased once treatment was stopped and returned to levels comparable with Placebo group by T5. Similarly, salivary peanut sIgA increased during treatment, as early as 4 months of treatment (PPOIT v.s. Placebo, ratio of GM: 2.04, p=0.014), then reduced post-treatment.

CONCLUSION

PPOIT was associated with broad reduction in peanut specific humoral responses which may mediate the clinical effects of SU that persists to 4-years post-treatment.

5

¿Es coste-efectiva la ITA en niños asmáticos alérgicos a los ácaros?

Cost-effectiveness analysis of house dust mite allergen immunotherapy in children with allergic asthma.

Farraia M, Paciência I, Mendes FC, Cavaleiro Rufo J, Shamji MH, Agache I, Moreira A

Allergy. 2022 Apr 22. doi: 10.1111/all.15321. Epub ahead of print. PMID: 35451128.

BACKGROUND

Cost-effectiveness studies evaluating allergen immunotherapy (AIT) in children are limited but needed to drive clinical and policy-making decisions such as reimbursement of new interventions. In this study, we compared the cost-effectiveness of subcutaneous (SCIT) and sublingual immunotherapy (SLIT) tablets to the standard of care (SOC) treatment in children with house dust mite-driven (HDM) allergic asthma.

METHODS

We developed a hypothetical Markov model based on the Global Initiative for Asthma (GINA) severity steps to compare the three strategies over a 10-year horizon divided by cycles of six months. SOC was used as a reference to calculate the incremental cost-effectiveness ratio (ICER). Deterministic and probabilistic sensitivity analyses were used to assess models' uncertainty. Other scenarios were evaluated to strengthen the presentation of results.

RESULTS

The ICER for SCIT and SLIT tablets was 1281€ and 7717€, respectively. The cost-effectiveness threshold for Portugal was 18482,80€; both treatment approaches were below this limit. The major contributors to these results were the AIT effects on reducing moderate and severe exacerbations and asthma controller medication. In the sensitivity analysis, SCIT revealed a higher probability of cost-effectiveness than SLIT. When including allergic rhinitis as comorbidity, ICER values reduced markedly, especially for SCIT intervention.

CONCLUSIONS

AIT was cost-effective in children with HDM-driven allergic asthma, especially when given by the subcutaneous route. The high probability of cost-effectiveness, especially for SCIT, may drive future policy decisions and AIT prescribing habits. AIT adherence greatly influenced the results highlighting the value of implementing strategies to promote adherence rates.

6

Factores determinantes de (in)tolerancia a alérgenos alimentarios

Oropharyngeal symptoms without systemic reactions as a risk factor for food allergen intolerance: a longitudinal pediatric study.

Hamada M, Saeki K, Sakurai Y

Allergy Asthma Clin Immunol. 2022 Apr 18;18(1):34. doi: 10.1186/s13223-022-00675-1

BACKGROUND

The determinants of tolerance to food allergens are not fully understood. We aimed to elucidate the longitudinal association between oropharyngeal symptoms without systemic reactions (OSw/oS) and tolerance to food allergens.

METHODS

We included all patients diagnosed with single food allergy to egg (n = 121), milk (n = 55), and wheat (n = 41) using the oral food challenge test (OFC) from 2014 to 2017. These patients received oral immunotherapy at home and/or in the hospital after diagnosis by OFC. We compared the incidence proportion of tolerance within 2 years by OSw/oS and other variables for 217 patients with food allergy. We defined OSw/oS as isolated symptoms of oropharyngeal discomfort that occurred after ingestion of a safe dose of the allergenic food determined by the OFC in the first 6 months.

RESULTS

Of the 217 patients (median age 37.5 months, male 64.5%), 53 developed OSw/oS (24.4%), and 151 (egg, 85 milk, 36 and wheat, 30) attained tolerance in 2 years. Patients without OSw/oS showed a significantly higher incidence of tolerance than those with the symptoms (crude hazard ratio [HR] 5.62, 95% confidence interval [CI] 3.58-8.82, $p < 0.001$). The association was consistently significant in the multivariable model (adjusted HR 9.50, 95% CI 5.25-17.20, $p < 0.001$) independent of other risk factors for intolerance, such as concomitant bronchial asthma (adjusted HR 3.33), history of anaphylaxis (adjusted HR 2.16), milk allergy (adjusted HR 2.02), and allergic symptoms with low dose OFC (adjusted HR 1.52).

CONCLUSION

Our results suggest that OSw/oS may be a risk factor for intolerance to food allergens. To reveal a high risk of food allergen intolerance may help patients and their families as well as healthcare professionals prepare for the challenge of continuing oral immunotherapy.

7

Niños alérgicos a la leche y riesgo de reacciones potencialmente fatales

Life-threatening anaphylaxis in children with cow's milk allergy during oral immunotherapy and after treatment failure.

Badina L, Burlo F, Belluzzi B, Babich S, Berti I, Barbi E
Immun Inflamm Dis. 2022 Apr;10(4):e607. doi: 10.1002/iid3.607.

BACKGROUND
Oral immunotherapy (OIT) is a promising therapeutic approach for children with persistent IgE-mediated cow's milk allergy (CMA) but data are still limited.
OBJECTIVE
To analyze the prevalence of life-threatening anaphylaxis in children with persistent CMA undergoing OIT and to evaluate potential risk factors.
METHODS
This is a retrospective cohort study among children with persistent CMA undergoing OIT over a 20-year period, following a specific Oral Tolerance Induction protocol. Adverse reactions during the whole period and data on long-term outcome were registered. Descriptive and nondescriptive statistics were used to describe data.
RESULTS
Three hundred forty-two children were evaluated. During OIT, 12 children (3.5%) presented severe anaphylactic reactions that needed an adrenaline injection. None required intubation, intensive care unit (ICU) admission, or showed a fatal outcome. Five of them abandoned OIT, five reached unrestricted diet and the others are still undergoing OIT. As far as outcome is concerned, 51.2% reached an unrestricted diet; 13.5% are at the build-up stage; and 28.0% (97 patients) stopped the OIT. Among these 96 children, 6.3% experienced a severe reaction induced by accidental ingestion of milk with two fatal outcomes.
CONCLUSIONS
The risk of life-threatening reactions was nearly two times lower (3.5% vs. 6.3%) among patients assuming milk during OIT than in those who stopped the protocol. A trend in favor of more severe reactions, requiring ICU admission, or fatal, was shown in patients who stopped OIT.

8

Las claves de la tolerancia inducida por la ITA

Mechanisms of allergen immunotherapy supporting its disease-modifying effect

Bumbacea RS, Boustani R, Panaitescu C, Haidar L, Buzan MR, Bumbacea D, Laculiceanu A, Cojanu C, Spanu D, Agache I
Immunotherapy. 2022 Apr 13. doi: 10.2217/imt-2021-0325. Epub ahead of print. PMID: 35416072.

ABSTRACT
Allergen immunotherapy (AIT) is considered the only disease modifying treatment available at present for allergic disorders. Its main benefits include improvement of symptoms, decreased need for pharmacotherapy, prevention of new sensitizations and sustained effect after AIT completion. The key pillars of AIT-induced tolerance include a shift from Th2 to Th1 response, an increase of regulatory T and B cells, pro-inflammatory effector cell downregulation and IgE suppression, in addition to IgG4, IgA and IgD induction. AIT may also induce trained immunity, characterized by a durable decrease in group 2 of innate lymphoid cells (ILCs) and increased ILC1 and ILC3s. Understanding the immune mechanisms of AIT is essential for validating biomarkers for the prediction of AIT response and for achieving AIT success.

9

Nueva evidencia sobre el beneficio de la ITA subcutánea en alérgicos a ácaros

Efficacy of subcutaneous house dust mite immunotherapy in patients with moderate to severe allergic rhinitis.

Valero A, Ibáñez-Echevarría E, Vidal C, Raducan I, Castelló Carrascosa JV, Sánchez-López J
Immunotherapy. 2022 Apr 25. doi: 10.2217/imt-2021-0353. Epub ahead of print. PMID: 35465692.

AIM
To evaluate the efficacy of subcutaneous immunotherapy (SCIT) for the treatment of allergy to house dust mites (HDM) in adults with moderate/severe allergic rhinitis (AR). Methods: Patients sensitized to HDM were randomized to SCIT plus rescue medication (Group A, n = 38) or rescue medication alone (Group B, n = 18), and assessed at baseline and 2, 6 and 12 months.
RESULTS
At month 12, Group A presented significant improvement with respect to baseline as evaluated by a visual analogue scale at three concentrations of antigen (0.1, 1 and 10 IR/ml; $p < 0.0001$). Group A presented significant decreases in symptom scores after 2 months of treatment, which were maintained after 1 year. After 12 months of treatment, Group A showed rescue medication consumption reductions ($p< 0.001$) and quality of life improvements ($p < 0.0001$). SCIT elicited a strong immunological response and was well tolerated.
CONCLUSION
SCIT is efficacious for HDM allergy in patients with AR, generating a strong immunological response. Trial Registration Number: EUCTR2009-018155-16-ES (Cochrane Central Register of Controlled Trials).

10

Valor diagnóstico y clínico del TAB tras una ITA de ácaros

Exploring the role of basophil activation test in diagnosis of Dermatophagoides farinae sensitization and evaluation of therapeutic efficacy of subcutaneous immunotherapy in children.

Li Y, Liu C, Li H, Wang X

Scand J Immunol. 2022 Apr 2:e13168. doi: 10.1111/sji.13168. Epub ahead of print. PMID: 35366340.

ABSTRACT

It aims to detect basophil activation ratio (%CD63+) in peripheral blood of children with allergic asthma and rhinitis by using flow cytometry (FCM), so as to analyse the application values and clinical relevance of the basophil activation test (BAT) in diagnosis of Dermatophagoides farinae (Derf) sensitization and monitoring therapeutic efficacy of subcutaneous immunotherapy (SCIT). It was a prospective study. From the newly diagnosed children with asthma and rhinitis in our paediatric clinic, 39 patients diagnosed Derf sensitization and 15 patients not allergic to Derf were enrolled; another 4 healthy children were taken as control group. Using Derf extracts in concentration of 1, 10 μg/mL and 100μg/mL as the stimulus, BAT results were expressed as %CD63+ in diagnosis of Derf sensitization and its correlation with skin prick tests (SPT), serum total IgE (tIgE), specific IgE (sIgE), sIgE/tIgE, specific IgG4 (sIgG4), FEV1%pred in pulmonary ventilation function, exhaled nitric oxide (FeNO), children asthma control test (C-ACT) and visual analogue scale (VAS) were observed. In sensitization group, %CD63+ , sIgG4 and clinical indicators were detected again from patients who had received SCIT to analyse their internal connections. The average levels of %CD63+ in 3 concentrations showed an increasing concentration-dependent trend overall. %CD63+ in sensitization group was significantly higher than that in the other 2 groups. The analysis of ROC for Derf sensitization showed the area under the curve (AUC) for BAT in 3 concentrations was higher than that for sIgE whose AUC is 0.893. %CD63+ was positively correlated with SPT grade, sIgE, sIgE/tIgE and VAS, and negatively correlated with C-ACT. In patients receiving SCIT, %CD63+ became lower and sIgG4 level became higher than pretreatment. There was no obvious change in sIgG4 in those who had not received SCIT. BAT is a reliable and non invasive tool for diagnosis of Derf sensitization in children with asthma and rhinitis. CD63-based BAT has clinical value to monitor outcome of SCIT, and the change in basophil activation is inherently related to induction of sIgG4.

1

En la ITA, más no siempre es mejor

Major Allergen Content In Allergen Immunotherapy Products: The Limited Value of Numbers.

Becker S, Fassio F, Muñoz-Cano R, Klimek L, Vidal C, et al.

J Investig Allergol Clin Immunol. 2022 May 6:0. doi: 10.18176/jiaci.0822. Epub ahead of print. PMID: 35522054.

ARTÍCULO DESTACADO

ABSTRACT

The prevalence of allergic disorders drastically increased over the last 50 years that today they can be considered epidemic. At present, allergen-specific immunotherapy (AIT) is the only therapy targeting the underlying cause of allergic disorders, and its superior evidence is based on accumulated data from clinical trials and observational studies demonstrating efficacy and safety. However, several aspects remain unsolved, such as harmonization and standardization of manufacturing and quantification procedures across manufacturers, homogeneous reporting of strength, and also the establishment of international reference standards for many allergens. This article discusses the issues related to the measurement of major allergen content in AIT extracts, raising the question of whether comparison of products by different manufacturers are appropriate as basis to choose among the different AIT products. Allergen standardization in immunotherapy products is critical to ensure quality and thereby safety and efficacy. However, lack of harmonization in manufacturing process, allergen quantification (methodologies and references), national regulatory differences, clinical practice, and labeling shows that the comparison of AIT products solely based on major allergen amounts is not rationale and, in fact, impossible. Moreover, further inherent characteristics of products and their clinical use such as their state of extract modification, addition of adjuvant or adjuvant-system, route of administration (sublingual/subcutaneous) and cumulative dose as per posology (including the volume per administration) need to be taken into account, when rating the information given for a specific product. Finally, only convincing clinical data can serve as the product-specific evaluation, or the basis for cross-product comparability, for individual products.

2

Novedosa ITA de ácaros con manano

First-in-human phase 2 trial with mite allergoids coupled to mannan in subcutaneous and sublingual immunotherapy.

Nieto A, Mazón Á, Nieto M, Ibáñez E, Jang DT, Calaforra S, Alba P, Pérez-Francés C, Llusar R, Montoro J, De Mateo A, Alamar R, El-Qutob D, Fernández J, Moral L, Toral T, Antón M, Andreu C, Ferrer Á, Flores IM, Cerdá N, Del Pozo S, Caballero R, Subiza JL, Casanovas M

Allergy. 2022 May 16. doi: 10.1111/all.15374. Epub ahead of print. PMID: 35570712.

BACKGROUND

Polymerized allergens conjugated to non-oxidized mannan (PM-allergoids) are novel vaccines targeting dendritic cells (DCs). Previous experimental data indicate that PM-allergoids are readily taken up by DCs and induce Treg cells. This first-in-human study was aimed to evaluate safety and to find the optimal dose of house dust mite PM-allergoid (PM-HDM) administered subcutaneously (SC) or sublingually (SL).

METHODS

In a randomized, double-blind, double-dummy, placebo-controlled trial, 196 subjects received placebo or PM-HDM at 500, 1000, 3000, or 5000 mannan-conjugated therapeutic units (mTU)/mL in 9-arm groups for 4 months. All subjects received 5 SC doses (0.5 ml each) every 30 days plus 0.2 ml SL daily. The primary efficacy outcome was the improvement of titrated nasal provocation tests (NPT) with D. pteronyssinus at baseline and at the end of the study. All adverse events and reactions were recorded and assessed. Secondary outcomes were the combination of symptom and medication scores (CSMS) and serological markers.

RESULTS

No moderate or severe adverse reactions were reported. Subjects improving the NPT after treatment ranged from 45% to 62% in active SC, 44% to 61% in active SL and 16% in placebo groups. Statistical differences between placebo and active groups were all significant above 500 mTU, being the highest with 3000 mTU SL ($p = 0.004$) and 5000 mTU SC ($p = 0.011$). CSMS improvement over placebo reached 70% ($p < 0.001$) in active 3000 mTU SC and 40% ($p = 0.015$) in 5000 mTU SL groups.

CONCLUSIONS

PM-HDM immunotherapy was safe and successful in achieving primary and secondary clinical outcomes in SC and SL at either 3000 or 5000 mTU/ml.

3

Reprogramación de redes genéticas en la ITO con cacahuete

Remission of peanut allergy is associated with rewiring of allergen-driven T helper 2-related gene networks.

Ashley SE, Jones AC, Anderson D, Holt PG, Bosco A, Tang MLK

Allergy. 2022 May 25. doi: 10.1111/all.15324. Epub ahead of print. PMID: 35615783

BACKGROUND

The immunological changes underpinning acquisition of remission (also called sustained unresponsiveness) following food immunotherapy remain poorly defined. Limited access to effective therapies and biosamples from treatment responders has prevented progress. Probiotic peanut oral immunotherapy is highly effective at inducing remission, providing an opportunity to investigate immune changes.

METHODS

Using a systems biology approach, we examined gene co-expression network patterns in peanut-specific CD4+ T cell responses before and after probiotic and peanut oral immunotherapy in subjects enrolled in the PPOIT-001 randomized trial: Responders who attained remission (n = 16), placebo-treated who remained allergic (n = 16).

RESULTS

Acquisition of remission was associated with rewiring of gene network patterns, which was characterized by integration of T helper 2 and interferon signalling modules, markedly reduced T helper 2 gene connectivity, and shutdown in co-expression activity between T helper 2 effectors and cell cycle regulators.

CONCLUSION

The immunological changes underlying remission following peanut oral immunotherapy are mediated by reprogramming of T helper 2-associated gene networks in the CD4+ T cell compartment. Findings provide insight into immune mechanisms driving the acquisition of remission following oral immunotherapy, paving the way for the development of improved approaches to induce remission/sustained unresponsiveness in patients with food allergy.

4

Un metaanálisis que habla de la ITA intranasal: ¿a favor o en contra?

Local nasal immunotherapy for allergic rhinitis: A systematic review and meta-analysis.

Kasemsuk N, Ngaotepprutaram P, Kanjanawasee D, Suwanwech T, Durham SR, Canonica GW, Tantilipikorn P

Int Forum Allergy Rhinol. 2022 May 11. doi: 10.1002/alr.23011. Epub ahead of print. PMID: 35543418.

INTRODUCTION

Local nasal immunotherapy (LNIT), an alternative noninjection immunotherapy method, is theoretically an efficient method for inducing immunotolerance directly in the affected organ. LNIT is more convenient and less invasive than injection immunotherapy, with fewer systemic reactions. The development of adjuvants to overcome LNIT's limitations raises the possibility of it being an alternative allergen immunotherapy.

OBJECTIVES

To evaluate the clinical and immunological efficacy and safety of LNIT for patients with allergic rhinitis.

METHODS

A systematic search for randomized controlled trials comparing LNIT and placebo was performed using OVID Medline and Embase. Outcomes were total nasal symptom score (TNSS), symptom-medication score (SMS), medication score, immunological assessment, and nasal provocation threshold. Data were pooled for meta-analysis.

RESULTS

A total of 20 studies with 698 participants were included. The LNIT group had greater posttreatment improvement in TNSS, SMS, and medication score than control (TNSS: standardized mean difference [SMD], -1.37 [95% confidence interval [CI], -2.04 to -0.69]; SMS: SMD, -1.55 [95% CI, -2.83 to -0.28]; and medication score: SMD, -1.09 [95% CI, -1.35 to -0.83]). Immunological assessments showed no significant differences in serum-specific IgE (mean difference [MD], 6.35; 95% CI, -4.62 to 17.31), nasal IgE (MD, -0.59; 95% CI, -1.99 to 0.81), or nasal eosinophil cationic protein (MD, 7.63; 95% CI, -18.65 to 33.91). Only serum IgG significantly increased with LNIT (MD, 0.45; 95% CI, 0.20, 0.70). Posttreatment, nasal provocation threshold was higher with LNIT (MD, 27.30; 95% CI, 10.13-44.46). No significant adverse events were reported.

CONCLUSIONS

LNIT is a safe alternative allergen immunotherapy route without significant adverse events. It improves clinical symptoms, reduces medication usage, and increases the nasal provocation threshold.

5

Respondedores y no respondedores a la ITO con cacahuete: ¿qué marca la diferencia?

Reduced pro-inflammatory dendritic cell phenotypes are a potential indicator of successful peanut oral immunotherapy.

Anvari S, Watkin LB, Minard CG, Schuster K, Hassan O, Anagnostou A, Orange JS, Corry DB, Davis CM

PLoS One. 2022 May 26;17(5):e0264674. doi: 10.1371/journal.pone.0264674.

ABSTRACT

Dendritic cells are important mediators in the early presentation of antigen and regulation of the differentiation of T cells. Peanut oral immunotherapy (POIT) results in desensitization in most peanut allergic individuals (responders), but not in others due to allergic reactions (non-responders). Delineation of early immunologic changes contributing to desensitization would help clarify the POIT mechanism of action. We analyzed dendritic cells in 15 pediatric subjects (5-12 years) undergoing a phase 1 single-center POIT study. We examined dendritic cells at baseline, 6-, 12-, 18- and 24-weeks after initiation of POIT and responders of therapy were compared to non-responders and healthy controls. The distribution frequency of myeloid DCs (mDCs) and plasmacytoid DCs (pDCs) from peripheral blood samples were measured in vitro. A general linear mixed model was used, and included fixed effects for cohort (responder, non-responder, or healthy control), time (0-, 6-, 12-, 18-, and 24-weeks), and the cohort-time interaction term. P-values were adjusted for multiple hypothesis testing using Tukey's method. We observed that POIT responders had reduced TNFa producing myeloid dendritic cells (mDCs) compared to non-responders. Additionally, non-responders had increased OX40L expressing mDCs at 18-weeks compared to responders. In conclusion, our findings suggest that a reduced pro-inflammatory phenotype in DCs could potentially serve as a predictor of early outcome and success of POIT desensitization.

6

Quimiocinas como potenciales biomarcadores

Circulating C-X-C Motif Ligand 13 as a Biomarker for Early Predicting Efficacy of Subcutaneous Immunotherapy in Children With Chronic Allergic Rhinitis.

Cheng S, Wen S, Xie S, Zhang C, Zhang H, Gao K, Fan R, Xie Z, Jiang W

Front Pediatr. 2022 May 4;10:872152. doi: 10.3389/fped.2022.872152. PMID: 35601415.

BACKGROUND

C-X-C motif ligand 13 (CXCL13) and B cell-activating factor (BAFF) are proven to be involved in inflammatory diseases, but their role in allergic rhinitis (AR) remains unclear. The aim of this study was to investigate the role of serum CXCL13 and BAFF in AR and their clinical values as objective biomarkers to predict the efficacy of subcutaneous immunotherapy (SCIT).

METHODS

We prospectively recruited 90 children with AR treated with SCIT and collected their serum specimens before SCIT. One-year follow-up was conducted for all patients, and they were categorized into effective and ineffective groups based on efficacy. The serum concentrations of CXCL13 and BAFF were detected and compared between the two groups. A validation cohort of 52 responders and 26 non-responders were further assessed for both cytokines and serum CXCL13 and BAFF levels were assayed by enzyme-linked immunosorbent assay (ELISA).

RESULTS

Eighty children completed the follow-up schedule, and 56 children were categorized into the effective group and 24 children into the ineffective group. The serum levels of CXCL13 in the effective group were clearly higher than those in the ineffective group ($P < 0.05$). Receiver operating characteristic (ROC) curves revealed the potential values of CXCL13 as a biomarker in predicting the response of SCIT. Further, in the validation cohort, ELISA results demonstrated that serum CXCL13 levels were increased in responders than non-responders ($P < 0.05$). ROC curves showed good accuracy of serum CXCL13 in predicting the efficacy of SCIT.

CONCLUSION

Our discovery-validation study demonstrated that circulating CXCL13 might serve as a novel biomarker to predict the outcome of SCIT in childhood AR. The findings indicated that CXCL13 was involved in the pathological mechanisms of AR and made help to the fundamental therapeutic mechanism of SCIT.

7

El efecto de la ITA en el asma (estacional y perenne)

Allergen immunotherapy effectively reduces the risk of exacerbations and lower respiratory tract infections in both seasonal and perennial allergic asthma: a nationwide epidemiological study.

Woehlk C, Von Bülow A, Ghanizada M, Baastrup Søndergaard M, Hansen S, Porsbjerg C

Eur Respir J. 2022 May 26:2200446. doi: 10.1183/13993003.00446-2022. Epub ahead of print. PMID: 35618279.

BACKGROUND

Allergic asthma is associated with increased risk of respiratory tract infections and exacerbations. It remains unclear whether this susceptibility is conditioned by seasonal or by perennial allergy. Aim: To investigate perennial allergy compared with seasonal allergy as a risk factor for lower respiratory tract infections and exacerbations in asthma and whether this risk can be reduced by allergen immunotherapy (AIT).

Methodology

This is a prospective register-based nationwide study of 18-44-year-olds treated with AIT during1995-2014. Based on the type of AIT and use of anti-asthmatic drugs, patients were subdivided into two groups: perennial allergic asthma (PAA) versus seasonal allergic asthma (SAA). Data on antibiotics against lower respiratory tract infections (LRTI) and oral corticosteroids for exacerbations were analyzed before starting AIT (baseline) and three years after completing AIT (follow-up).

RESULTS

We identified 2688 patients with asthma treated with AIT, among whom, 1249 had PAA and 1439 had SAA. At baseline, patients with SAA had more exacerbations, 23.8%, respectively, 16.5% p=<0.001 but there were no differences in LRTI. During the three-year follow-up, we observed a highly significant reduction of exacerbations with an average decrease of 57% in PAA and 74% in SAA. We also observed a significant reduction of LRTI in both PAA and SAA: 17% and 20% decrease, respectively.

CONCLUSION

AIT effectively reduced the risk of exacerbations and lower respiratory tract infections in both seasonal- and perennial allergic asthma. Perennial allergy is seemingly not a stronger risk factor for respiratory infections and exacerbations than is seasonal allergy.

8

Puntuación Predictiva de Respuesta a la ITA

Predictive Response to Immunotherapy Score: A Useful Tool for Identifying Eligible Patients for Allergen Immunotherapy.

Mormile I, Granata F, Detoraki A, Pacella D, Della Casa F, De Rosa F, Romano A, De Paulis A, Rossi FW

Biomedicines. 2022 Apr 22;10(5):971. doi: 10.3390/biomedicines10050971. PMID: 35625708.

ABSTRACT

A specific predictive tool of allergen immunotherapy (AIT) outcome has not been identified yet. This study aims to evaluate the efficacy of a disease score referred to as Predictive Response to Immunotherapy Score (PRIS) to predict the response to AIT and identify eligible patients. A total of 110 patients diagnosed with allergic rhinitis with or without concomitant asthma were enrolled in this study. Before beginning sublingual immunotherapy (SLIT), patients were evaluated by analyzing clinical and laboratory parameters. A specific rating was assigned to each parameter to be combined in a total score named PRIS. At baseline (T0) and follow-up [after 12 (T12) and 24 months (T24) of SLIT], a Visual Analogue Scale (VAS) was used to calculate a mean symptom score (MSS). Finally, the percentage variation between the MSS at T0 and at T12 [ΔMSS-12(%)] and T24 [ΔMSS-24 (%)] was measured. We observed a significant improvement of symptoms at T12 and T24 compared to T0 in all groups undergoing SLIT. PRIS was effective in predicting ΔMSS-24 (%) in patients treated with single-allergen SLIT. In addition, PRIS was effective in predicting ΔMSS-24 (%) in both patients with only rhinitis and with concomitant asthma. PRIS assessment can represent a useful tool to individuate potential responders before SLIT prescription.

9

Con la ayuda del Omalizumab

Long-term outcome of omalizumab-assisted desensitisation to cow's milk and eggs in patients refractory to conventional oral immunotherapy: real-life study.

Ayats-Vidal R, Riera-Rubió S, Valdesoiro-Navarrete L, García-González M, Larramona-Carrera H, Cruz OA, Bosque-García M

Allergol Immunopathol (Madr). 2022 May 1;50(3):1-7. doi: 10.15586/aei.v50i3.537. PMID: 35527650.

BACKGROUND

Oral immunotherapy (OIT) is a promising approach to cow's milk and egg allergies, but reactions are frequent and some patients cannot be desensitized.

OBJECTIVE

To evaluate long-term OIT outcomes with omalizumab (OMZ) in paediatric patients with severe egg and/or milk allergies. Methods: This retrospective real-life study analysed findings in children with Immunoglobulin E-mediated allergy to cow's milk and/or hen eggs refractory to conventional OIT, who underwent OIT with OMZ in our department between 1 January 2010 and 31 December 2015.

RESULTS

In all, 41 patients were included (median age: 7 years; interquartile range [IQR]: 5.5-9.5); 26/41 (63.4%) underwent OIT for milk, 8/41 (19.5%) for egg and 7/41 (17.1%) for both. The median time between initiation of OMZ and OIT was 27 weeks (IQR: 22-33). Forty (97.56%) patients reached the maintenance phase (200 mL of cow's milk and 30 mL of raw egg or 1 cooked egg) in a median time of 27 weeks (IQR: 18-37). The median total time with OMZ was 117 weeks (IQR: 88-144). During the OMZ period, 2.44% (1/41) of patients presented anaphylaxis. After discontinuation of OMZ, 29.3% (12/41) presented anaphylaxis, 50% of them had a poor adherence to daily ingestion. One patient (2.44%) was diagnosed with eosinophilic esophagitis after 2 years of discontinuation of OMZ. Currently, after a median time of 9 years (IQR: 7-10) since the initiation of OMZ, 75.6% (31/41) are desensitized (27/31 without OMZ).

CONCLUSIONS

Omalizumab allows desensitisation of children with severe allergies to cow's milk and/or egg without developing severe reactions while receiving this treatment. However, discontinuation of OMZ leads to severe allergic reactions, and hence must be monitored carefully.

10

Niños alérgicos a ácaros en Indonesia: ¿es segura la ITA?

Safety Profile and Issues of Subcutaneous Immunotherapy in the Treatment of Children with Allergic Rhinitis.

Endaryanto A, Nugraha RA

Cells. 2022 May 9;11(9):1584. doi: 10.3390/cells11091584. PMID: 35563890.

ABSTRACT

This study aims to evaluate safety issues of house dust mite subcutaneous immunotherapy (SCIT) among allergic rhinitis (AR) children. A retrospective cohort study was done between 2015 and 2020 to investigate the side effects of SCIT among AR children caused by a house dust mite allergy. Among 1098 patients who received house dust mite subcutaneous immunotherapy injections, 284 patients (25.87%) had side effects (SE). SE were found to be 699 times higher or in 2.27% of the 30,744 subcutaneous immunotherapy injections. A total of 17.9% of the patients had local SE during SCIT administration. Systemic side effects occurred in 8.38% of children receiving SCIT and in 0.53% of the total population who received SCIT injections. Only 2/92 (2.18%) of patients suffered an allergic reaction within 30 minutes of injection and these patients responded well to antiallergic medication. Severe anaphylaxis occurred in 0.091% of the 1098 patients in the SCIT group and in 0.0033% of the 30,774 SCIT injections. Systemic SE after SCIT occurred in 8.38% of patients receiving SCIT or 0.53% of the total number of SCIT injections. Anaphylactic episodes occurred in 16 patients (1.46%) and 15 patients (1.37%) who had first and second episodes. One severe attack was found and it was resolved with adrenaline. This study demonstrates that in pediatric patients with AR who received HDM SCIT for 18 months with high adherence, some experienced significant local SE and systemic SE caused by SCIT, but this did not interfere with the course of AR treatment or the effectiveness of SCIT.

1

Ventana de oportunidad tras introducción temprana fallida para los alérgicos al cacahuete

The Case for Prompt Salvage Infant Peanut Oral Immunotherapy Following Failed Primary Prevention.

Chua GT, Greenhawt M, Shaker M, Soller L, Abrams EM, Cameron SB, Cook VE, Erdle SC, Fleischer DM, Mak R, Vander Leek TK, Chan ES

J Allergy Clin Immunol Pract. 2022 Jun 22:S2213-2198(22)00596-7. doi: 10.1016/j.jaip.2022.05.040. Epub ahead of print. PMID: 35752433.

ARTÍCULO DESTACADO

ABSTRACT

Recent guideline recommendations have shifted from recommending prolonged avoidance of allergenic foods in the first three years of life to a primary prevention approach involving the deliberate early introduction to infants at risk of developing food allergy. Despite this, some infants, especially those with severe eczema who are at highest risk for developing peanut allergy, fail to receive the preventative benefits of early peanut introduction due to hesitancy and other factors. Difficulty adhering to regular ingestion following introduction further reduces the effectiveness of primary prevention. As emerging real-world evidence has demonstrated that performing peanut oral immunotherapy (OIT) among infants is effective and safe, peanut OIT could be a treatment option for infants with peanut allergy. This review discusses the benefits, risks, and barriers to offering peanut OIT to infants who fail primary prevention strategies. We propose the novel concept that infants with peanut allergy be offered peanut OIT as soon as possible after failed peanut introduction through a shared decision-making process with the family, where there is a preference for active management rather than avoidance.

2

Combo dupilumab + ITA sublingual para asmáticos por ácaros

Efficacy of a house dust mite sublingual immunotherapy tablet as add-on dupilumab in asthma with rhinitis.

Hoshino M, Akitsu K, Kubota K, Ohtawa J

Allergol Int. 2022 Jun 16:S1323-8930(22)00051-X. doi: 10.1016/j.alit.2022.05.010. Epub ahead of print. PMID: 35718711.

BACKGROUND

HDM SLIT is one of the disease-modifying treatment for allergic asthma, and has demonstrated efficacy in clinical trials. Dupilumab, blocks IL-4 and IL-13 signaling, key drivers of type 2 inflammation, and is approved for patients with uncontrolled, moderate-to-severe asthma. The aim of this study was to evaluate outcomes after HDM SLIT initiation in asthma with rhinitis not optimally controlled with dupilumab in a real-world setting.

METHODS

At baseline and 48 weeks after treatment, asthma control questionnaire (ACQ)-5, asthma quality of life questionnaire (AQLQ) and rhinoconjunctivitis quality of life questionnaire (RQLQ) were assessed. Spirometry, type 2 inflammatory biomarkers and quantitative computed tomographic parameters of airway remodeling were also collected.

RESULTS

Of 47 patients received HDM SLIT and 41 completed the study. Combined HDM SLIT and dupilumab improved ACQ-5 ($p < 0.05$), AQLQ ($p < 0.05$), RQLQ ($p < 0.05$), and increased lung function and reduced FeNO ($p < 0.05$) and airway percentage wall area, and wall thickness (each, $p < 0.05$). The change in ACQ-5 and AQLQ score correlated with both changes in FeNO and FEV1 percent predicted. Multiple regression analysis showed that the change in FEV1 percent predicted was independent factor for improvement of AQLQ ($r2 = 0.510$, $p = 0.012$). Based on ROC analysis for predicting SLIT responders, the baseline area under the curves in serum HDM specific-IgE, total IgE and FEV1 percent predicted were high (>0.8).

CONCLUSIONS

These results support the benefits of adding HDM SLIT to pharmacotherapy plus dupilumab in uncontrolled asthma with rhinitis.

3

Los rápidos efectos de la ITO con cacahuete

Kinetics of basophil hyporesponsiveness during short-course peanut OIT.

Kulis MD, Smeekens JM, Burk C, Yue X, Guo R, Orgel KA, Ye P, Herlihy L, Hamilton D, Li Q, Keet C, Shreffler W, Vickery BP, Burks AW, Kim EH

J Allergy Clin Immunol. 2022 Jun 15:S0091-6749(22)00792-8. doi: 10.1016/j.jaci.2022.05.020. Epub ahead of print. PMID: 35716952.

BACKGROUND

Oral immunotherapy (OIT) leads to suppression of mast cell and basophil degranulation along with changes in the adaptive immune response.

OBJECTIVE

We aimed to determine how rapidly these effects occur during OIT and more broadly, the kinetics of basophil and mast cell suppression throughout the course of therapy.

METHODS

Twenty participants, aged 4-12, were enrolled in a peanut OIT trial and assessed for desensitization and sustained unresponsiveness (SU) after nine months of therapy. Blood was collected five times in the first month and then intermittently throughout to quantify immunoglobulins and assess basophil activation by CD63, CD203c, and phosphorylated SYK (pSYK). Results: Twelve of sixteen participants that completed the trial were desensitized after OIT, with nine achieving SU after discontinuing OIT for four weeks. Basophil hyporesponsiveness, defined by lower CD63 expression, was detected as early as day 90. pSYK was correlated with CD63 expression and there was a significant decrease in pSYK by day 250. CD203c expression remained unchanged throughout therapy. Interestingly, although basophil activation was decreased across the cohort during OIT, basophil activation did not correlate with individual clinical outcomes. Serum peanut-specific IgG4 and IgA increased throughout therapy, whereas IgE remained unchanged.

CONCLUSION

Suppression of basophil activation occurs within the first 90 days of peanut OIT, ultimately leading to suppression of signaling through pSYK.

4

La batalla contra la alergia alimentaria

Food allergy, mechanisms, diagnosis and treatment: Innovation through a multi-targeted approach

Sayantani B Sindher, Andrew Long, Andrew R Chin, Angela Hy, Vanitha Sampath, Kari C Nadeau, R Sharon Chinthrajah

Allergy. 2022 Jun 22. doi: 10.1111/all.15418. Online ahead of print. PMID: 35730331 DOI: 10.1111/all.15418.

OBJECTIVE

The incidence of food allergy (FA) has continued to rise over the last several decades, posing significant burdens on health and quality of life. Significant strides into the advancement of FA diagnosis, prevention, and treatment have been made in recent years. In an effort to lower reliance on resource-intensive food challenges, the field has continued work toward the development of highly sensitive and specific assays capable of high-throughput analysis to assist in the diagnosis FA. In looking toward early infancy as a critical period in the development of allergy or acquisition of tolerance, evidence has increasingly suggested that early intervention via the early introduction of food allergens and maintenance of skin barrier function may decrease the risk of FA. As such, large scale investigations are underway evaluating infant feeding and the impact of emollient and steroid use in infants with dry skin for the prevention of allergy. On the other end of the spectrum, the past few years have been witness to an explosive increase in clinical trials of novel and innovative therapeutic strategies aimed at the treatment of FA in those whom the disease has already manifested. A milestone in the field, 2020 marked the approval of the first drug, oral peanut allergen, for the indication of peanut allergy. With a foundation of promising data supporting the safety and efficacy of single- and multi-allergen oral immunotherapy, current efforts have turned toward the use of probiotics, biologic agents, and modified allergens to optimize and improve upon existing paradigms. Through these advancements, the field hopes to gain footing in the ongoing battle against FA.

5

ITA sublingual: ¿la hora de administración importa?

Morning Versus Evening Dosing of Sublingual Immunotherapy in Allergic Asthma: A Prospective Study.

Liao F, Chen S, Wang L, Quan YY, Chen LL, Lin GH

Front Pediatr. 2022 Jun 9;10:892572. doi: 10.3389/fped.2022.892572. PMID: 35757136

BACKGROUND

Sublingual immunotherapy (SLIT) has been proved to be an effective and safe treatment for allergic asthma (AS) in children. Nonetheless, several issues regarding SLIT remain to be resolved, including the information about optimal administration timing.

METHODS

A total of 163 AS children aged 4-13 years were enrolled and randomized into the morning dosing (MD) group and the evening dosing (ED) group. Participants received SLIT with Dermatophagoides farinae drops between 7:00 a. m. and 9:00 a.m. (for the MD group) or between 8:00 p. m. and 10:00 p.m. (for the ED group). The total asthma symptom score (TASS), total asthma medicine score (TAMS), Asthma Control Questionnaire (ACQ), forced expiratory volume in one second (FEV1), FEV1/forced volume vital capacity (FVC), fractional exhaled nitric oxide (FeNO) and adverse events (AEs) were assessed at baseline, 0.5 and 1 year during the 1-year SLIT.

RESULTS

After 1 year, 62 patients in the MD group and 63 patients in the ED group completed the entire study. The clinical efficacy, pulmonary function and FeNO in both groups improved significantly at 0.5 and 1 year ($p < 0.001$). Compared to the MD group, the ED group showed significant lower ACQ score at 0.5 year ($p < 0.001$) and lower FeNO at 1 year ($p < 0.05$). No significant difference between two groups was observed in AE rate ($p > 0.05$). All AEs occurred in the first month, with no systemic AEs reported.

CONCLUSION

1-year house dust mite (HDM) SLIT is effective and well-tolerated in AS children regardless of administration time. SLIT dosing in the evening might enhance the asthma control level and reduce FeNO level compared with SLIT dosing in the morning.

6

Se añaden nuevos biomarcadores a la (creciente) lista

Circulating MMP-12 as Potential Biomarker in Evaluating Disease Severity and Efficacy of Sublingual Immunotherapy in Allergic Rhinitis.

Zhou Y, Xu M, Gong W, Kang X, Guo R, Wen J, Zhou D, Wang M, Shi D, Jing Q

Mediators Inflamm. 2022 Jun 12;2022:3378035. doi: 10.1155/2022/3378035. PMID: 35733520.

BACKGROUND

Allergic rhinitis (AR) is a highly heterogeneous disease, and allergen-specific immunotherapy (AIT) is an effective treatment. This study aims to evaluate the circulating mas-related G protein-coupled receptor-X2 (MRGPRX2) and matrix metalloproteinase-12 (MMP-12) levels in evaluating disease severity and predicting efficacy of SLIT in AR patients.

METHODS

We enrolled 110 moderate-severe persist AR patients (AR group) and 40 healthy controls (HC group). Circulating levels of MRGPRX2 and MMP-12 were measured, and their associations with disease severity were evaluated. All AR patients were assigned to receive sublingual immunotherapy (SLIT), and the efficacy was evaluated, and serum samples were collected at 1 year and 3 years after treatment. The correlations between serum MRGPRX2 and MMP-12 and clinical efficacy were assessed.

RESULTS

The serum concentrations of MRGPRX2 and MMP-12 were significantly higher in the AR group than the HC group, and the elevated MMP-12 levels were correlated with VAS and TNSS, and serum MRGPRX2 levels were correlated with VAS. Finally, 100 and 80 patients completed 1-year and 3-year follow-up and were classified into effective and ineffective groups. Serum MRGPRX2 and MMP-12 levels were lower in the effective group than the ineffective group. Although serum MRGPRX2 and MMP-12 levels did not significantly change after 1 year SLIT, serum MMP-12 levels were decreased 3 years post-SLIT than baseline and 1 year post-SLIT levels. Receiver operating characteristic (ROC) showed that serum MMP-12 was a potential biomarker for predicting the efficacy of SLIT.

CONCLUSION

Serum MRGPRX2 and MMP-12 appeared to be promising biological indicators in reflecting disease severity in AR patients. Moreover, circulating MMP-12 might serve as a reliable predictor for clinical responsiveness of SLIT.

7

¿Qué papel tiene la ITA en el mundo de la ORL?

The Role of Allergen-Specific Immunotherapy in ENT Diseases: A Systematic Review.

Cantone E, Gallo S, Torretta S, Detoraki A, Cavaliere C, Di Nola C, Spirito L, Di Cesare T, Settimi S, Furno D, Pignataro L, De Corso E

J Pers Med. 2022 Jun 9;12(6):946. doi: 10.3390/jpm12060946. PMID: 35743730; PMCID: PMC9224998.

ABSTRACT

Previous studies have demonstrated that both subcutaneous (SCIT) and sublingual specific immunotherapy (SLIT) are effective in treating allergic rhinitis (AR). Further studies have evaluated the efficacy of allergen-specific immunotherapy (AIT) on different ear, nose, and throat (ENT) manifestations, in which allergy might have an etiopathogenetic role, such as local allergic rhinitis (LAR), rhinosinusitis (RS), otitis media (OM), and adenotonsillar (AT) disease. Nevertheless, the management of allergy in ENT diseases is still debated. To the best of our knowledge, this is the first systematic review assessing the efficacy of AIT in ENT diseases aside from AR. Literature data confirmed that AIT might be an effective therapeutic option in LAR, although its effect is restricted to studies with short-term follow-up. Furthermore, previous research demonstrated that AIT may improve symptoms and surgical outcomes of chronic rhinosinusitis when used as an adjunctive treatment. Few studies supported the hypothesis that AIT may exert positive therapeutic effects on recurrent upper airway infections as adenotonsillar disease. Finally, some clinical observations suggested that AIT may add some benefits in the management of otitis media with effusion (OME). The results of this systematic review allow us to conclude that the efficacy of AIT in ENT disorders has been only slightly investigated and additional studies are needed.

8

Efecto a largo plazo de la ITA intralinfática: ¿qué podemos esperar?

A five-year open follow up of a randomized, double-blind placebo-controlled trial of intralymphatic immunotherapy for birch and grass reveals remaining beneficial effects.

Hjalmarsson E, Hellkvist L, Karlsson A, Winquist O, Kumlien Georén S, Westin U, Olaf Cardell L

J Investig Allergol Clin Immunol. 2022 Jun 2:0. doi: 10.18176/jiaci.0832. Epub ahead of print. PMID: 35671100.

BACKGROUND AND OBJECTIVES

Intralymphatic immunotherapy (ILIT) has been proposed as a novel, less time-consuming alternative to conventional allergy immunotherapy (AIT). Few previous studies have evaluated its long-term effects. The objective of the study was to complete a 5-year follow-up of a previously performed randomized, double-blind placebo-controlled trial of ILIT for a combination of birch and grass allergens.

METHODS

Fifty-eight patients with allergic rhinitis were treated with either placebo or a combination of ALK Alutard Birch and Grass 1000 SQ-U, three intralymphatic injections with one-month intervals. A year after the vaccination, symptoms induced by nasal provocation were significantly reduced. 5-6 years later, 20 out of 26 actively treated patients were followed up with a nasal provocation test (NPT), seasonal registration of the combined symptoms and medications score (CSMS), IgE and IgG4 levels in the blood and immunological markers in blood and lymph nodes and compared with 13 unvaccinated controls.

RESULTS

The ILIT induced reduction in the NPT response seen in year one could not be convincingly reproduced in year five. The new CSMS scores were markedly lower among the previously treated patients than for the control group. Further, grass-specific IgG4 was increased, grass-specific IgE decreased, FcεR1 on basophils reduced, and the amount of memory T-cells in the lymph nodes increased.

CONCLUSION

The combination of seasonal derived clinical data and immunological parameters supports the notion of a long-lasting effect of ILIT. These data support the concept of ILIT as a good alternative to traditional AIT in pollen-induced allergic rhinitis.

9

Modelo experimental de alergia alimentaria: ¿se trasladará a la clínica?

Semaphorin-3 Promotes Specific Immunotherapy Effects on Experimental Food Allergy

Huang Huang, Yu Liu, Yanan Wang, Huazhen Liu, Bailing Xie, Michael B W Zheng, Liteng Yang, Qinmiao Huang, Yongjin Wu, Gaohui Wu, Pengyuan Zheng, Pingchang Yang

J Immunol Res. 2022 Jun 19;2022:5414993. doi: 10.1155/2022/5414993. PMID: 35769512

ABSTRACT

Sustaining higher frequency of mast cells in the allergic lesion site has been recognized. Factors causing high numbers of mast cells in the local tissues are not fully understood yet. RAS signaling plays a role in sustaining certain cell activities. This study is aimed at elucidating the role of RAS activation in the apoptosis resistance induction in mast cells and at employing semaphorin 3A to regulate RAS activities in sensitized mast cells and alleviating the allergic response in the intestine. A food allergy (FA) mouse model was developed. Mast cells were isolated from FA mouse intestinal tissues by flow cytometry. Mast cell apoptosis was assessed by staining with annexin V and propidium iodide. We found that aberrantly higher p21-activated kinase-1 (Pak1) expression in FA mast cells was associated with mast cell aggregation in the intestine. Sensitization increased Pak1 expression and apoptosis resistance in intestinal mast cells. RAS and Pak1 mutually potentiated each other in sensitized mast cells. Semaphorin 3A (sema3A) suppressed the Pak1 expression and RAS activation in mast cells. sema3A restored the apoptosis sensitivity in sensitized mast cells. Administration of sema3A potentiated allergen-specific immunotherapy in experimental FA. In conclusion, mast cells of FA mice showed higher Pak1 expression and high RAS activation status that contributed to apoptosis resistance in mast cells. Administration of sema3A restored the sensitivity to apoptosis inducers and promoted the therapeutic effects of specific immunotherapy on experimental FA.

10

Estado del arte de una ITA sublingual

Update about Oralair® as a treatment for grass pollen allergic rhinitis.

Klimek L, Brehler R, Mösges R, Demoly P, Mullol J, Wang DY, O'Hehir RE, Didier A, Kopp M, Bos C, Karagiannis E
Hum Vaccin Immunother. 2022 Jun 15:1-10. doi: 10.1080/21645515.2022.2066424. Epub ahead of print. PMID: 35704772.

ABSTRACT

Sublingual immunotherapy (SLIT) is a well-tolerated, safe, and effective approach to treating allergic rhinitis (AR). Oralair® is a five-grass pollen SLIT tablet containing natural pollen allergens from five of the major grass species responsible for seasonal AR due to grass pollen allergy. Recommended use is in a pre-coseasonal regimen, starting daily treatment approximately 4 months before the start of the pollen season, with treatment then continued daily throughout the season; treatment should continue for 3-5 y. Clinical efficacy and safety of Oralair® in patients with grass pollen-induced AR has been demonstrated in a comprehensive clinical development program of randomized controlled trials. Effectiveness has been substantiated in subsequent observational studies with sustained efficacy following treatment cessation and a favorable level of adherence, quality of life, benefit, and satisfaction for the patients. Supportive evidence for a benefit in reducing the risk or delaying the development of allergic asthma is emerging.

1

Conocer la heterogeneidad de los mecanismos inmunológicos va de la mano con las nuevas terapias para RA

Update on pathomechanisms and treatments in allergic rhinitis

Zhang Y, Lan F, Zhang L

Allergy. 2022 Jul 27. doi: 10.1111/all.15454. Epub ahead of print. PMID: 35892225

ARTÍCULO DESTACADO

ABSTRACT

Allergic rhinitis (AR) is a global health problem with increasing prevalence, and association with an enormous medical and socioeconomic burden. New recognition of immune cells such as type 2 innate lymphocytes (ILC2s), T helper (Th2) 2 cells, follicular helper T cells, follicular regulatory T cells, regulatory T cells, B cells, dendritic cells and epithelial cells in AR pathogenesis has been updated in this review paper. An in-depth understanding of the mechanisms underlying AR will aid the identification of biomarkers associated with disease and ultimately provide valuable parameters critical to guide personalized targeted therapy. As the only etiological treatment option for AR, allergen-specific immunotherapy (AIT) has attracted increasing attention; with evidence for effectiveness of AIT recently demonstrated in several randomized controlled trials and long-term real-life studies. The exploration of biologics as therapeutic options has only involved anti-IgE and anti-type 2 inflammatory agents; however, the cost-effectiveness of these agents remains to be elucidated precisely. In the midst of the currently on-going COVID-19 pandemic, a global life-threatening disease, although some studies have indicated that AR is not a risk factor for severity and mortality of COVID-19, this needs to be confirmed in multi-centre real-life studies of AR patients from different parts of the world.

2

Se confirma un mínimo de 3 años para conseguir una ITA efectiva a largo plazo (SCIT y SLIT)

Long-term efficacy of the sublingual and subcutaneous routes in allergen immunotherapy

Penagos M, Durham SR

Allergy Asthma Proc. 2022 Jul 1;43(4):292-298. doi: 10.2500/aap.2022.43.220026. PMID: 35818157

ABSTRACT

Allergen immunotherapy is highly effective in selected patients with allergic rhinitis, allergic asthma, and Hymenoptera venom allergy. Unlike anti-allergic drugs, both subcutaneous and sublingual immunotherapies have been shown to modify the underlying cause of the disease, with proved long-term clinical benefits after treatment cessation. In this review, we analyzed 10 randomized, double-blind, placebo controlled clinical trials of allergen immunotherapy that included blinded follow-up for at least 1 year after treatment withdrawal. Three studies of pollen subcutaneous immunotherapy provided evidence that a sustained, tolerogenic effect of subcutaneous immunotherapy can be achieved after 3 years of treatment. Six trials of sublingual immunotherapy provided robust evidence for long-term clinical benefit and persistent immunologic changes after grass pollen, house-dust mite, or Japanese cedar immunotherapy, whereas a clinical trial of both sublingual and subcutaneous grass pollen immunotherapies showed that 2 years of immunotherapy were efficacious but insufficient to induce long-term tolerance. These studies strongly supported international guidelines that recommend at least 3 years of allergen immunotherapy of proven value to achieve disease modification and sustained clinical and immunologic tolerance.

3

7 tipos de biomarcadores para predecir la eficacia en la ITA

Mechanisms and biomarkers of subcutaneous immunotherapy and sublingual immunotherapy in allergen immunotherapy

Tan TJ, Layhadi JA, Shamji MH

Allergy Asthma Proc. 2022 Jul 1;43(4):254-259. doi: 10.2500/aap.2022.43.220030. PMID: 35818151

ABSTRACT

There are currently no biomarkers that can accurately predict clinical outcomes and segregate responders from nonresponders in allergen immunotherapy (AIT). Therefore, identifying a reliable predictive biomarker is essential to enable clinicians to tailor personalized therapy. New developments in AIT biomarkers are currently being explored, and it would be important to identify key areas of development and their feasibility for use in the clinic. Biomarkers can be categorized broadly into seven domains: (i) Immunoglobulin E (IgE), (ii) IgG and IgA responses, (iii) IgE - facilitated allergen binding/blocking factor, (iv) basophil activation, (v) cytokines and chemokines, (vi) cellular markers, and (vii) in vivo biomarkers. Despite their potential, most biomarkers remain infeasible to be translated to the clinical setting due to requirements of complex instruments such as flow cytometry. The identification of suitable biomarkers remains key in predicting outcomes of AIT and requires more research. Additional exploration into integrative biomarkers may be required.

4

Por qué es importante medir la calidad de vida en los estudios de alergia alimentaria

Measuring the Impact of Food Immunotherapy on Health-Related Quality of Life in Clinical Trials

Lloyd M, Dunn Galvin A, Tang MLK

Front Allergy. 2022 Jul 12;3:941020. doi: 10.3389/falgy.2022.941020. PMID: 35910858; PMCID: PMC9326481

ABSTRACT

Food allergy is a common, and often lifelong, disorder with considerable negative impact on the quality of life of those affected and their families. While several promising immunotherapies for food allergy have either been approved or are in late-phase clinical trials based on demonstrated effectiveness at inducing desensitization, evidence of benefit in terms of improving patient-centered outcomes is inconsistent. Historically, health-related quality of life has not been prioritized as an endpoint in food immunotherapy trials and, even when included, findings have been undermined by methodological limitations of the measurement instruments used and issues with data interpretation. This review highlights the importance of measuring health-related quality of life as an endpoint in food immunotherapy trials and discusses the strengths and limitations of available evidence in this regard, with a focus on the appropriate use of assessment instruments and interpretation of findings. There remains much to learn regarding the impact of food immunotherapies on patient wellbeing, both during treatment and over the longer term. Our aim is to assist clinicians, researchers, policy makers and consumers in their interpretation of the existing literature, and to promote greater scientific rigor in the design and selection of outcome measurement frameworks for future studies evaluating the efficacy of immunotherapy treatments for food allergy.

5

OIT con leche: cuándo mantenerla y cuándo no

Risk factors for discontinuing oral immunotherapy in children with persistent cow milk allergy

Benelli E, Trombetta A, Badina L, Andrade S, Zamagni G, Prisco A, Traini E, Barbi E, Berti I

Immun Inflamm Dis. 2022 Jul;10(7):e668. doi: 10.1002/iid3.668. PMID: 35759227; PMCID: PMC9208286

BACKGROUND

There are no universally accepted criteria for discontinuing milk oral immunotherapy (MOIT) in patients with persistent cow milk allergy (CMA) and little data are available on predictive risk factors for dropping out from oral immunotherapy (OIT), due to allergic reactions or other reasons.

METHODS

We retrospectively reviewed clinical records of patients with persistent severe CMA undergoing MOIT in a tertiary care center hospital to investigate risk factors associated with discontinuation of OIT. Persistent and severe allergy was defined as the history of systemic reactions and any milk protein-specific IgE level >85 kU/ml. All patients were first admitted for an in-hospital rush phase eventually followed by an at-home dose increase. We evaluated the effect of various factors on two primary outcomes: the highest dose of milk ingested during the in-hospital rush phase and during the home OIT phase.

RESULTS

We identified 391 patients, of whom 131 met the inclusion criteria for the retrospective study, 54 females and 77 males. Data of the home OIT phase were available for 104 patients (27%). Regarding the home OIT outcome, an association for having a cow milk avoiding diet was found with reaching a dose below 10 ml during the in-hospital rush phase (relative risks [RR]: 2.33, confidence interval [CI]: 0.85; 6.42), an age above than 10 years from the time of admission (RR: 3.29, CI: 0.85; 12.73), and a higher total number of reactions occurred during the hospitalization (RR: 1.54, CI: 1.02; 2.32), whereas the presence of respiratory reactions with wheezing (RR: 1.93, CI: 0.49; 7.61) and an IM adrenaline use was related to a higher risk of having an OIT still in progress (RR: 5.47, CI: 0.33; 7.73).

CONCLUSIONS

In this cohort of children with persistent CMA undergoing OIT who presented with respiratory reactions with wheezing, the development of anaphylaxis with the need for IM adrenaline, and age above 10 years were predictors of poor long-term outcome.

6

El papel de la evidencia del “mundo real” con ITA en la práctica clínica

Integrating the evidence in allergen immunotherapy: Why real-world data should be important for the practicing clinician?

Calderon MA, Demoly P

Allergy Asthma Proc. 2022 Jul 1;43(4):305-309. doi: 10.2500/aap.2022.43.220006. PMID: 35818147

ABSTRACT

Data obtained from controlled clinical trials are the gold standard for evaluation of allergen immunotherapy (AIT) efficacy and safety. Less prone to biases (with a strong internal validity), they allow their use and external validation in the real world. The quantity and diversity of real-world data has increased exponentially, and access to large cohorts and electronic medical records have made this information increasingly accessible and useful for research and regulatory purposes. New retrospective database studies have confirmed the sustained benefits of grass, birch pollen, and house dust mite AIT for both allergic rhinitis and asthma symptom and medication scores, the prevention of asthma (when used in nonasthmatic rhinitics), and the real rate of adverse systemic reactions. They also have addressed clinical practice issues not elsewhere analyzed, including the management of polysensitized patients with respiratory allergies and adherence to AIT. Real-world evidence has its own biases and limits that need to be taken into account. In this article we present a concise summary of the literature about the role of real-world evidence in AIT.

7

Nueva generación de vacunas: diseño computacional para impedir la unión de IgE

Designing Next-Generation Vaccines Against Common Pan-Allergens Using In Silico Approaches

Sircar G, Ghosh N, Saha S

Monoclon Antib Immunodiagn Immunother. 2022 Jul 18. doi: 10.1089/mab.2021.0033. Epub ahead of print. PMID: 35852870

ABSTRACT

Next-generation allergy vaccines refer to allergen-derived attenuated molecules that can boost allergen-blocking IgG response. These IgG antibodies are specifically directed toward the IgE epitope of allergens and interfere in allergen-IgE interaction. Our study is a computational approach to design such vaccines against four widespread pan-allergens families. Pan-allergens display extensive immunological cross-reactivity due to the presence of conserved IgE epitope and T cell epitope. In this study, the vaccine design is based on hapten-carrier concept in which the carrier protein is an immunogenic component providing T cell help. Either PreS protein of hepatitis B or cholera enterotoxin B (CTB) fused with three tetanus toxoid fragments (TTFrC) was used here as the carrier. The hapten components are nonanaphylactic peptides (NAPs) derived from experimentally determined antigenic regions of the allergens. The charged residues of NAPs are selectively modified to obliterate IgE, as well as T cell reaction, and hence, are safe to apply in allergy patients. Various combinations of vaccine constructs (PreS/CTB+TTFrC and NAPs) were designed with intermediate linker motifs. Screening of constructs was performed through a three-step method such as physicochemical parameters, secondary structures, and tertiary structures using various bioinformatic tools. The final construct with best quality and stability was selected for each allergen family. Suitability of these constructs for being expressed in recombinant form was checked at DNA, RNA, and protein level. Presence of putative epitopes inducing tolerogenic interleukin-10 was also predicted for these constructs. The present work led to the design of putative vaccines with immunotherapeutic potential and broad applicability for allergic diseases caused by a wide array of cross-reactive allergens.

8

Compartir la toma de decisiones con los pacientes (herramienta SDM), en ITA

Allergen immunotherapy and shared decision-making

Settipane RA, Bukstein DA

Allergy Asthma Proc. 2022 Jul 1;43(4):350-355. doi: 10.2500/aap.2022.43.220017. PMID: 35818138

ABSTRACT

Clinical decision-making in allergic rhinoconjunctivitis management involves a significant degree of complexity given the number of pharmaceutical agents; the option for allergen immunotherapy (AIT); and the risk for disease advancement, including the development of asthma as well as new environmental allergic sensitivities. Given the complex array of treatment options that are currently available, there is an opportunity to use a shared decision-making (SDM) approach with associated aids and tools that facilitate the interactive participation of practitioners and patients in the SDM process. This article reviews the general constructs of SDM, the unmet need for SDM aids, the collection of patient preference data for allergic rhinoconjunctivitis, the utility of SDM aids which have been specifically created for AIT, and outlines actionable steps to implement AIT SDM in clinical practice.

9

AIT: ¿Cómo conseguir una buena adherencia?

Long-term adherence strategies for allergen immunotherapy

Larenas-Linnemann D

Allergy Asthma Proc. 2022 Jul 1;43(4):299-304. doi: 10.2500/aap.2022.43.210120. PMID: 35818153

ABSTRACT

Adherence is crucial for allergen immunotherapy (AIT) efficacy, and a long-term 3-year adherence is indispensable for the long-term benefits beyond AIT administration. Nonadherence causes should be analyzed not only at the patient level but from a broader perspective, including socioeconomic factors, health-care system factors, and disorder- and therapy-related factors. Subcutaneous immunotherapy (SCIT) adherence is ~50% at best and, for sublingual immunotherapy, the numbers are even much worse in some regions. In this review, causes for AIT loss of adherence and strategies, published and from personal experience, to reduce nonadherence are presented. Although the broader picture of causes of nonadherence has to be taken into account, in all this, the patient-physician and patient-health care professional (AIT nurse, assistant) are still in the center, and, in SCIT, each clinic visit for a shot is an opportunity to exploit this interaction in a positive way and stimulate adherence. Patient factors of nonadherence are not so much forgetfulness but more perception of ineffectiveness and adverse effects. An explanation of what can be expected before starting AIT is crucial because most of those who drop out are seen during the first year. Adherence is especially under risk when administration is temporarily interrupted (lockdown, illness, disease flare, vacation, preseasonal AIT administration schedules). The pandemic has caused higher rates of nonadherence specifically due to a fear of getting infected with severe acute respiratory syndrome coronavirus 2, which can be mitigated with good hygiene techniques and strict sanitization protocols, which ensure the patients. Also, patient mobile discussion networks related to AIT can help encourage adherence and reduce fear of infection, even in these difficult times.

10

Pautas rápidas: más beneficios que riesgos (en los pacientes adecuados)

Accelerated/rush allergen immunotherapy

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Allergy Asthma Proc. 2022 Jul 1;43(4):344-349. doi: 10.2500/aap.2022.43.210108. PMID: 35818154

ABSTRACT

Accelerated allergy shot schedules for inhalant and venom allergens provide individuals with allergy symptom relief but in a shorter time frame than conventional therapy. Accelerated immunotherapy (IT) protocols allow patients to reach therapeutic doses in a shorter time frame while improving adherence and reducing direct costs (e.g., fewer office visits and medications) and indirect costs (e.g., less travel time, missed work or school). Rush IT and cluster IT are believed to work through mechanisms similar to conventional subcutaneous IT (SCIT). The risk for severe systemic reactions during accelerated IT is low when appropriately administered; however, life-threatening and fatal reactions do occur. To reduce the incidence of systemic allergic reactions during cluster and rush IT protocols, premedication is recommended. It is important to exclude individuals at high risk such as those with poorly controlled asthma or those who are on b -blockers to mitigate the risk for developing systemic allergic reactions. However, accelerated SCIT regimens offer increased convenience, faster improvement in allergy symptoms, and the potential to reduce health-care costs while providing equivalent safety outcomes compared with conventional IT protocols.

1

Un futuro prometedor para los alérgicos al gato

REGN1908/1909 prevented cat allergen-induced early asthmatic responses in an environmental exposure unit

de Blay FJ, Gherasim A, Domis N, Meier P, Shawki F, Wang CQ, Orengo JM, DeVeaux M, Ramesh D, Jalbert JJ, Kamal MA, Abdallah H, Dingman R, Perlee L, Weinreich DM, Herman G, Yancopoulos GD, O'Brien MP

J Allergy Clin Immunol. 2022 Aug 4:S0091-6749(22)00984-8. PMID: 35934082

ARTÍCULO DESTACADO

BACKGROUND

The dominant allergen in cat dander, Felis domesticus allergen 1 (Fel d 1), is a persistent trigger for allergic rhinitis and asthma symptoms.

OBJECTIVE

Evaluate the efficacy of Fel d 1 monoclonal antibodies (REGN1908/1909) in preventing cat allergen-induced early asthmatic responses (EAR) in cat-allergic patients with mild asthma.

METHODS

Patients were randomized to single-dose REGN1908/1909 600 mg (n = 29) or placebo (n = 27). Forced expiratory volume in 1 second (FEV1) was measured for up to 4 hours in a cat allergen environmental exposure unit (EEU) up to 85 days after dosing. Assessments included between-group differences in change from baseline in FEV1 area under the curve (AUC; 0-2 hours) and incidence of EAR (FEV1 reduction ≥20%).

RESULTS

Single-dose REGN1908/1909 significantly prevented reductions in FEV1 on days 8, 29, 57, and 85. Most REGN1908/1909 patients did not have an EAR by 4 hours (last timepoint tested). In contrast, placebo-treated patients experienced ≥20% mean FEV1 reduction on days 8, 29, 57, and 85 post-dosing, with most experiencing an EAR within 1 hour. REGN1908/1909-treated patients tolerated 3-fold higher allergen quantities ($P < .05$ at all timepoints) versus placebo. REGN1908/1909 substantially reduced skin test reactivity to cat allergen versus placebo at all timepoints tested (nominal $P < .001$). REGN1908/1909 was generally well tolerated; no serious adverse events or deaths were reported.

CONCLUSION

Single-dose REGN1908/1909 significantly prevented reductions in FEV1 in cat-allergic patients with mild asthma upon cat-allergen EEU exposure at 8 days and up to 85 days post-dose.

2

Asma grave y reacciones sistémicas con la ITA: ¿se relacionan?

Safety of Subcutaneous Immunotherapy in Patients with Severe Asthma

Chow TG, Palka JM, Stone B, Trojan T, Epstein TG, Khan DA

Ann Allergy Asthma Immunol. 2022 Aug 20:S1081-1206(22)00693-7. mPMID: 35998846

BACKGROUND

Severe asthma (SA) has been identified as a risk factor for severe systemic reactions (SR) to allergen subcutaneous immunotherapy (SCIT). However, the incidence and characterization of SRs in SA in comparison to less severe or no asthma is not known. Objective: The objective of this study was to characterize the incidence of SRs in SA patients receiving SCIT in comparison to patients with no asthma or less severe asthma.

METHODS

A retrospective cohort study was performed of patients receiving SCIT from a multicenter national network of private allergy practices between January 2015 to December 2019. Demographics, asthma severity (ICD-10 codes), concomitant medications, aeroallergen skin testing, measures of asthma control with the asthma control test (ACT) and FEV1 values, SCIT prescription, and a SR standardized form were assessed.

RESULTS

65,855 patients, with 1072 SA patients, receiving SCIT were included with a total of 4415 SRs (19.9 SR per 10,000 injection visits). SA had 23.9 SRs per 10,000 injection visits (incidence rate 0.239; 95% CI [0.189, 0.298). There were 155 grade III/IV SRs; 5 (3.2%) occurred in SA group. There was no difference in rates of grade III/IV SRs between SA and no asthma as well as in rates of total SRs between SA and less severe asthma.

CONCLUSION

In a large cohort of patients with SA undergoing multi-allergen SCIT drawn from a diverse outpatient allergy population, the diagnosis of SA was not associated with increased moderate-severe SRs compared to patients without asthma and any severity of asthma.

3

¿Qué respuesta induce en la mucosa oral la ITO con cacahuete?

Peanut-Specific IgG4 and IgA in Saliva Are Modulated by Peanut Oral Immunotherapy

Smeekens JM, Baloh C, Lim N, Larson D, Qin T, Wheatley L, Kim EH, Jones SM, Burks AW, Kulis MD

J Allergy Clin Immunol Pract. 2022 Aug 6:S2213-2198(22)00800-5. PMID: 35944894

BACKGROUND

Antigen-specific immunoglobulin responses have yet to be studied at the oral mucosal surface during peanut oral immunotherapy (PnOIT).

OBJECTIVE

We aimed to quantify salivary peanut-specific IgG4 (PNsIgG4) and IgA (PNsIgA) and total IgG4 and IgA in participants from the Immune Tolerance Network's IMPACT study, a phase 2 PnOIT trial.

METHODS

Peanut-allergic children, aged 12 months to younger than 48 months at screening, were enrolled and randomized to PnOIT or placebo oral immunotherapy (OIT) for 134 weeks. Per-protocol analysis included 69 PnOIT and 23 placebo participants. Double-blind, placebo-controlled food challenges were conducted at weeks 134 and 160 to assess desensitization and remission, respectively. Saliva samples were collected at baseline and 30, 82, 134, and 160 weeks to quantify PNsIgG4, PNsIgA, and total IgG4 and IgA.

RESULTS

Participants who received PnOIT experienced significant increases in PNsIgG4 in saliva, whereas participants on placebo did not ($P < .01$ at all time points). The PNsIgA/total IgA ratio was also significantly increased in participants treated with PnOIT when compared with those receiving placebo at 30 and 82 weeks ($P < .05$). During PnOIT, desensitized participants had increased PNsIgA that plateaued, whereas the not desensitized/no remission group did not change over time. Interestingly, when the PnOIT group was evaluated by clinical outcome, PNsIgA was higher at baseline in the not desensitized/no remission group than in the desensitized/remission group ($P < .05$).

CONCLUSIONS

PnOIT induces substantial increases in allergen-specific IgG4 and IgA in saliva. These data provide insight into OIT-induced mucosal responses and suggest the utility of these easily obtained samples for biomarker development.

4

Provocación oral como criterio de inclusión en los estudios con cacahuete: ¿si, no o no importa?

Participant Characteristics and Safety Outcomes of Peanut Oral Immunotherapy in the RAMSES and ARC011 Trials

Ciaccio C, Goldsobel AB, Anagnostou A, Beyer K, Casale TB, Deschildre A, Fernández-Rivas M, Hourihane JO, Krawiec M, Lieberman J, Scurlock AM, Vickery BP, Smith A, Tilles SA, Adelman DC, Brown KR, RAMSES (ARC007) and ARC011 Study Groups

Ann Allergy Asthma Immunol. 2022 Aug 13:S1081-1206(22)00657-3. PMID: 35973655

BACKGROUND

Clinical trials (PALISADE [ARC003], ARTEMIS [ARC010]) proving efficacy and safety of peanut (Arachis hypogaea) allergen powder-dnfp (PTAH) used double-blind, placebo-controlled food challenges (DBPCFCs) to screen for eligibility and to evaluate efficacy. In routine clinical practice, individuals with peanut allergy do not always undergo food challenges to confirm diagnosis or determine candidacy for treatment.

OBJECTIVE

To describe PTAH safety/tolerability in participants selected by clinical history and peanut sensitization parameters not undergoing DBPCFC during trails and to compare findings with previously published data.

METHODS

RAMSES (ARC007) was a 6-month, phase 3, randomized, double-blind, placebo-controlled trial in children aged 4 to 17 years with physician-confirmed peanut allergy. ARC011 was the subsequent 6-month follow-on maintenance PTAH study. The primary endpoint for RAMSES and ARC011 was frequency of treatment-emergent adverse events (AEs). We descriptively compared baseline characteristics and safety outcomes from RAMSES/ARC011 to participants undergoing DBPCFCs in phase 3 PALISADE/ARTEMIS trials.

RESULTS

In 506 patients randomized to study treatment, baseline characteristics appeared balanced between groups. Proportion of participants with ≥1 AE was 55% for PTAH versus 33.9% for placebo during initial dose escalation and 98.8% versus 94.0%, respectively, during updosing. Most participants with AEs had mild/moderate events. The most common AEs were gastrointestinal. Comparisons to pooled PALISADE and ARTEMIS data showed higher baseline median peanut-specific immunoglobulin E and skin prick test values for RAMSES participants. Safety outcomes during trial periods were comparable.

CONCLUSION

Safety data from clinically selected children with peanut allergy receiving PTAH do not appear different from those in phase 3 trials requiring DBPCFC to enter trials.

5

Los alergólogos: un ejemplo de asistencia sanitaria de calidad

Value-Based, Cost-Effective Care: The Role of the Allergist-Immunologist

Shaker M, Mauger D, Fuhlbrigge AL

J Allergy Clin Immunol Pract. 2022 Aug 6:S2213-2198(22)00747-4. PMID: 35944893

ABSTRACT

Asthma and allergic disease impact millions of patients and are associated with high costs. Up to 30% of all medical care involves wasted spending. Across the spectrum of care provided by the allergist-immunologist, there are opportunities to improve value and reduce medical waste. Several examples highlight this reality. Evidence suggests that most patients may receive cost-effective care in the management of chronic spontaneous urticaria without the need for laboratory testing. For patients with asthma, although a single maintenance and reliever therapy approach may be cost-effective, insurance-mandated therapy changes are not, and may harm patients. Biologics may be very effective in improving asthma control but are too expensive for this indication-as demonstrated by cost-effectiveness analyses and highlighted by the Institute of Clinical and Economic Review, which concluded that the value-based price for asthma biologics ranges between $6500 and 14,3000 per year. Early introduction may prevent food allergy, but screening before first introduction is neither necessary nor cost-effective, although early salvage food oral immunotherapy may result in improved quality of life and cost savings. Evidence does not support the presence of allergic disease as a risk factor for anaphylaxis to coronavirus disease 2019 vaccination, and risk-stratified vaccination approaches do not appear cost-effective. Allergen immunotherapy is a very cost-effective treatment option. The practice of allergy-immunology has continued to evolve in recent years and can provide a leading example of high-value practice.

6

El impacto del óxido nítrico nasal en la eficacia de la ITA

Predictive Value of Nasal Nitric Oxide and Serum NOS2 Levels in the Efficacy of Subcutaneous Immunotherapy in Pediatric Patients with Allergic Rhinitis

Wen S, Cheng S, Xie S, Zhang H, Zhang J, Wang F, Xie S, Xie Z, Jiang W

Mediators Inflamm. 2022 Aug 16;2022:1679536. PMID: 36016661

BACKGROUND

Subcutaneous immunotherapy (SCIT) is an effective therapy for allergic rhinitis (AR), but some AR patients still do not benefit from it. Nasal nitric oxide (nNO) and inducible nitric oxide synthase (iNOS/NOS2) act important roles in AR. This study aims to explore the abilities of serum NOS2 and nNO in predicting the clinical efficacy of SCIT in AR patients.

METHODS

We recruited 40 healthy controls (HCs) and 120 AR patients in this study. Serum NOS2 and nNO levels were compared between the two groups. In the AR group, patients underwent and finished 1-year of SCIT, and divided into the effective and ineffective groups, and the relationships between serum NOS2 and nNO levels and efficacy of SCIT were evaluated.

RESULTS

The serum NOS2 and nNO levels were higher in AR patients than HCs. In the effective group, the serum NOS2 and nNO levels were increased than the ineffective group. ROC curves presented that a combination of serum NOS2 and nNO exhibited promising predictive ability in predicting the clinical efficacy of SCIT.

CONCLUSIONS

Serum NOS2 and nNO levels were enhanced in AR patients and might affect the efficacy of SCIT. The combined use of serum NOS2 and nNO levels could be a reliable and useful method for predicting the clinical efficacy of SCIT.

7

Ajuste de dosis como optimización del riesgo-beneficio en la ITA sublingual

The MaDo real-life study of dose adjustment of allergen immunotherapy liquid formulations in an indication of respiratory allergic disease: Reasons, practices, and outcomes

Thétis-Soulié M, Hosotte M, Grozelier I, Baillez C, Scurati S, Mercier V

Front Allergy. 2022 Aug 9;3:971155. PMID: 36017469

ABSTRACT

Sublingual allergen immunotherapy (SLIT) is a safe, effective, disease-modifying treatment for moderate-to-severe respiratory allergies. The function and responsiveness of the immune system components underlying the effects of allergen immunotherapy may vary from one patient to another. Furthermore, the severity of the symptoms of allergic disease can fluctuate over time, due to changes in environmental allergen exposure, effector cell responsiveness, and cell signaling. Hence, the allergen dose provided through SLIT can be fine-tuned to establish an optimal balance between effectiveness and tolerability. The objective of the MaDo study was to describe and understand dose adjustments of SLIT liquid formulations in France. We performed a retrospective, observational, cross-sectional, real-life study of allergists and other specialist physicians. Physicians described their patients via an anonymous case report form (CRF). The main patient inclusion criteria were age 5 years or over, at least one physician-confirmed IgE-driven respiratory allergy, and treatment for at least 2 years with one or more SLIT liquid preparations. A nationally representative sample of 33 specialist physicians participated in the study. The physicians' main stated reasons for dose adjustment were adverse events (according to 90.9% of the physicians), treatment effectiveness (60.6%), sensitivity to the allergen (42.4%) and other characteristics (30.3%: mainly symptom severity, type of allergen, and asthma). 392 CRFs (mean ± standard deviation patient age: 27.8 ± 17.5; under-18s: 42.1%; polyallergy: 30.9%) were analyzed. Respectively 53.6%, 25.8%, 15.3%, and 8.7% of the patients received house dust mite, grass pollen, birch pollen and cypress pollen SLIT. Dose adjustments were noted in 258 (65.8%) patients (at the start of the maintenance phase for 101 patients (39.2%) and later for 247 (95.7%)). Dose adjustment was not linked to sex, age, or the number of allergens administered. All measures of disease severity (including symptom severity noted on a 0-to-10 visual analogue scale by the physician) decreased significantly during SLIT. Notably, the mean AR symptom severity score decreased to a clinically relevant extent from 7.6 at SLIT initiation to 2.4 at last follow-up, and the mean asthma symptom severity score decreased from 5.0 to 1.3. The few differences in effectiveness between patients with vs. without dose adjustment were not major. For about one patient in five, a specialist physician decided to reduce or increase the SLIT liquid dose at the start of maintenance treatment and/or during maintenance treatment. This decision was influenced by a broad range of patient and treatment factors, mainly to improve tolerability to treatment and/or enhance effectiveness. In France, dose adjustment of SLIT liquid preparations as a function of the patient profile and/or treatment response is anchored in clinical practice. Precision dosing might optimize the overall benefit-risk profile of AIT for individual patients throughout their entire treatment course, enabling them to achieve both short- and long-term treatment goals, whilst maximizing the safety and tolerability.

8

Anafilaxia por ITA: la magnitud (real) del problema

Is allergy immunotherapy-induced anaphylaxis still a real problem?

Bernstein DI, Berendts K

Curr Opin Allergy Clin Immunol. 2022 Aug 17. PMID: 35980016

PURPOSE OF REVIEW

The current review describes the incidence and risk for anaphylaxis due to allergy injections.

RECENT FINDINGS

The incidence of fatal anaphylaxis occurs with approximately one in 7.2 million injection visits. Severe anaphylaxis may occur once in every 160 000 visits. The major risk for fatal anaphylaxis is severe and uncontrolled asthma.

SUMMARY

Understanding risk factors for anaphylaxis to allergy injections has led to clinic protocols aimed at preventing such events. The efficacy of these preventive measures remains to be determined in future studies.

9

Factores que repercuten en la seguridad de la ITA subcutánea en niños

Effectiveness and adverse reactions to subcutaneous immunotherapy in children with allergic rhinitis/asthma

Duman Senol H, Topyildiz E, Ekici B, Gulen F, Demir E

Int J Pediatr Otorhinolaryngol. 2022 Aug 19;162:111292. PMID: 36007303.

OBJECTIVE

Adverse reactions, which are mostly local and rarely systemic, can be seen during subcutaneous immunotherapy (SCIT). It was not possible to continue SCIT at times due to systemic reactions. The purpose of the present study was to identify the incidence and risk factors associated with adverse reactions during subcutaneous allergen-specific immunotherapy (AIT).

METHODS

A total number of 344 patients under 18 years old with allergic rhinitis and/or asthma who underwent SCIT between 2005 and 2021 were included in the study. Demographic characteristics of the patients, laboratory findings [Total Immunglobulin E(IgE), aeroallergen prick test, inhaler, and allergen specific IgE(sIgE) and eosinophil counts], and adverse events observed during AIT were recorded retrospectively. Descriptive and univariate/multivariate logistic regression analyses were used to identify risk factors for adverse events

RESULTS

Among 344 patients, 33.4% (n = 115) were female, mean age was 133.1 ± 41.0 months, and 42.2% (n = 145) were >12 years old. One hundred-thirty eight (40.1%) of the patients were mono-sensitized, 47 (13.7%) had asthma, 207 (60.2%) allergic rhinitis, and 90 (26.2%) asthma and allergic rhinitis. Single allergen content was administered to 187 (54.4%) patients (62 mite, 114 grass mix, 11 olea), and multiple allergens to 157 (45.6%) patients (121 pollen mix, 36 other (mite/alternaria)]. A total number of 33.008 injections were administered. 840 adverse reactions (262 (31.1%) at up-dosing phase, 578 (68.8%) at maintenance phase) in 195 (56.7%) patients were observed. Among the adverse reactions, 632 (75.2%) were local, 160 (19%) large local, and 48 (5.7%) (39 at maintenance, 9 at up-dosing) (in 31 patients) were systemic (28 Grade 1, 12 Grade 2, 8 Grade 3). Adrenalin was administered to 8 patients with Grade 3 systemic reaction (8/33008; %0.024). Adverse reactions, especially local ones, were seen more frequently in children under 12 years old ($p < 0.001$). Patients sensitized with grass pollen (p:0.01) and mite (p:0.004), and those who had received SCIT with pollen mixture had more adverse reactions than the others. More adverse reactions were observed in SCIT containing calcium-phosphate as adjuvant (p: 0.01). Local reactions were risk factors for large local (OR = 3.591, %95 CI:2.064-6.247, $p < 0.001$) and systemic (OR = 2.190, %95 CI:1.005-4.722 $p = 0.046$) reactions at univariate analyses. Total nasal symptom scores, Visual Analog Scale and asthma symptom control test decreased after one year of treatment ($p < 0.01$).

CONCLUSION

SCIT is a safe and effective treatment method in childhood that leads to improvements in all nasal symptoms and asthma after one year of treatment.

10

¿Tiene margen de mejora el tratamiento de la rinitis estacional?

Current treatment strategies for seasonal allergic rhinitis: where are we heading?

Ridolo E., Incorvaia C., Pucciarini F., Makri E., Paoletti G., Canonica GW.

Clin Mol Allergy. 2022 Aug 10;20(1):9. PMID: 35948975

INTRODUCTION

Allergic rhinitis (AR) is very commonly caused by pollens. The symptoms of AR consist of sneezing, nasal congestion, rhinorrhea, nasal itching and airflow obstruction. The diagnosis has long been based on clinical history, skin prick tests and in vitro measurement of specific IgE, but the innovative approach of precision medicine has made diagnostic tools of much greater accuracy available.

AREAS COVERED

This review covers the advances in the treatment of seasonal AR concerning the drugs to be used according to the grade of disease and the characteristics of the patients, and the role of allergen immunotherapy (AIT), which is the only treatment capable of acting, in addition to the symptoms, on the cause of AR and therefore to modify its natural history.

EXPERT OPINION

Drug treatment of AR include a large number of agents, the choice of which depends on the severity of the disease. AIT has high evidence of efficacy demonstrated by meta-analyses, and further improvement is currently apparent, as for diagnosis, applying the means of precision medicine. However, when AIT is performed in current practice, without the strict rules of controlled trials, long-term low adherence is a major problem to be solved.

1

Efecto a largo plazo de la ITA: del ensayo clínico a la vida real

Real-world evidence for the long-term effect of allergen immunotherapy: Current status on database-derived European studies

Vogelberg C, Klimek L, Brüggenjürgen B, Jutel M

Allergy. 2022 Sep 8. Epub ahead of print. PMID: 36074052

ARTÍCULO DESTACADO

ABSTRACT

Randomized controlled trials (RCTs) are the gold-standard for benefit-risk assessments during drug approval processes. Real-word data (RWD) and the resulting real-world evidence (RWE) are becoming increasingly important for assessing the effectiveness of drug products after marketing authorization showing how RCT results are transferred into real life care. The effectiveness of allergen immunotherapy (AIT) has been assessed in several RWE studies based on large prescription databases. We performed a literature search for retrospective cohort assessments of prescription databases in Europe to provide an overview on the methodology, long-term effectiveness outcomes, and adherence to AIT. Thirteen respective publications were selected. AIT was more effective in reducing the progression of allergic rhinitis (AR) compared to a non-AIT control group receiving only symptomatic treatment for AR for up to 6 years. The development and progression of asthma were hampered for most endpoints in patients treated with most preparations compared to the non-AIT group, receiving only anti-asthmatic medication. The results for "time to onset" of asthma were inconsistent. Adherence to AIT decreased during the recommended 3-year treatment period, however, in most studies higher adherence to subcutaneous than to sublingual AIT was shown. The analysis of long-term effectiveness outcomes of the RWE studies based on prescription databases confirms the long-term efficacy of AIT demonstrated in RCTs. Progression of rhinitis and asthma symptoms as well as delayed onset of asthma triggered by different allergens, real life adherence to the treatment shows differences in particular application routes.

2

Lo último sobre el manejo de la alergia alimentaria

Managing food allergy: GA2LEN guideline 2022

Muraro A, de Silva D, Halken S, Worm M, Khaleva E, GA2LEN Food Allergy Guideline Group

World Allergy Organ J. 2022 Sep 7;15(9):100687. PMID: 36119657

ABSTRACT

Food allergy affects approximately 2-4% of children and adults. This guideline provides recommendations for managing food allergy from the Global Allergy and Asthma European Network (GA2LEN). A multidisciplinary international Task Force developed the guideline using the Appraisal of Guidelines for Research and Evaluation (AGREE) II framework and the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach. We reviewed the latest available evidence as of April 2021 (161 studies) and created recommendations by balancing benefits, harms, feasibility, and patient and clinician experiences. We suggest that people diagnosed with food allergy avoid triggering allergens (low certainty evidence). We suggest that infants with cow's milk allergy who need a breastmilk alternative use either hypoallergenic extensively hydrolyzed cow's milk formula or an amino acid-based formula (moderate certainty). For selected children with peanut allergy, we recommend oral immunotherapy (high certainty), though epicutaneous immunotherapy might be considered depending on individual preferences and availability (moderate certainty). We suggest considering oral immunotherapy for children with persistent severe hen's egg or cow's milk allergy (moderate certainty). There are significant gaps in evidence about safety and effectiveness of the various strategies. Research is needed to determine the best approaches to education, how to predict the risk of severe reactions, whether immunotherapy is cost-effective and whether biological therapies are effective alone or combined with allergen immunotherapy.

3

La eficacia de las tabletas para la rinitis por ácaros

Efficacy and safety of house dust mite sublingual immunotherapy tablets in allergic rhinitis: A systematic review and meta-analysis

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World Allergy Organ J. 2022 Sep 7;15(9):100691. PMID: 36119654

BACKGROUND

House dust mite (HDM) sublingual immunotherapy (SLIT) tablets have been approved for the treatment of patients with allergic rhinitis (AR). However, the meta-analysis on the efficacy of HDM-SLIT tablets for HDM-induced AR patients remained limited.

METHODS

Five databases were searched including: PubMed/MEDLINE, EMBASE, Web of Science, the Cochrane Central Register of Controlled Trials, and CINAHL for randomized controlled trials (RCTs) that addressed the efficacy and safety of HDM-SLIT tablets compared with placebo until January 2022. The primary outcome was a combined symptom and medication score (CSMS) after treatment.

RESULTS

Eight eligible RCTs were identified with a total of 3601 patients treated with HDM-SLIT tablets and 2783 patients who received a placebo. The CSMS was significantly lower in the HDM-SLIT tablet group compared with the placebo (standardized mean difference (SMD) -0.28 [95% CI: -0.32 to -0.23]). There was a significant reduction in rhinitis symptom scores, rhinitis medication scores, total combined conjunctivitis scores, and rhinoconjunctivitis quality of life questionnaire scores. The consistent efficacy compared to the placebo has been exhibited over the different kinds and doses of HDM tablets (6 SQ, 12 SQ, 300 IR, and 500 IR) and age groups (>5 years old, adolescents and adults) with low degrees of variability across the studies. There was no significant difference in proportions of participants who were injected with epinephrine between the treatment- and placebo groups.

CONCLUSIONS

HDM-SLIT tablet is an effective treatment in reducing rhinitis symptoms and medication use in AR patients with favorable safety. They also improve quality of life and conjunctivitis symptoms.

4

Rinitis alérgica local e ITA: ¿buenos resultados?

Allergen immunotherapy against house dust mites in patients with local allergic rhinitis and asthma

Bozek A, Galuszka B, Gawlik R, Misiolek M, Scierski W, Grzanka A, Canonica GW

J Asthma. 2022 Sep;59(9):1850-1858. doi: 10.1080/02770903.2021.1971701. Epub 2021 Sep 6. PMID: 34429002

ABSTRACT

Local allergic rhinitis (LAR) is a clinical rhinitis phenotype characterized by the presence of nasal symptoms of AR in nonatopic patients with a negative skin prick test and undetectable specific IgE (sIgE) in serum against inhalant allergens but with a positive nasal allergen provocation test. This study evaluated the effectiveness of a 12-month course of sublingual immunotherapy (SLIT) for house dust mite (HDM) allergies in adult patients with confirmed LAR and concomitant asthma.

METHODS

The study was a prospective, double-blind, placebo-controlled trial with patients diagnosed with LAR to HDMs and with concomitant asthma who underwent a 12-month treatment course of SLIT for HDM allergies. Seventeen patients were randomized to SLIT with the use of allergen extracts of D. pteronyssinus and D. farinae (50/50%) in SQ-HDM SLIT tablets and 15 patients were randomized to the placebo group. The total rhinitis score (TRSS), total asthma symptom score (TASS), combined total symptom score (TSS), total medication score (TMS), and FEV1 were analyzed.

RESULTS

In the final analysis, 16 patients who received SLIT and 14 who received placebo who completed the study protocol were included. Significant reductions in TRSS, TASS, TSS, and TMS after 12 months of treatment were observed in patients after SLIT ($p < 0.05$). A significant increase in the mean FEV1 between baseline and after 12 months of therapy was observed in the study, with $p = 0.03$ in the study group.

CONCLUSION

SLIT can improve nasal and bronchial symptoms and reduce symptomatic treatment in patients with LAR and asthma and with hyperresponsiveness to HDMs.

5

Epítopos alergénicos como biomarcador diagnóstico y/o pronóstico en la alergia a la soja

Peptide epitopes as biomarkers of soya sensitization in rBet v 1 immunotherapy of birch-related soya allergy

Caballero LR, Treudler R, Delaroque N, Simon JC, Kern K, Szardenings M

Clin Exp Allergy. 2022 Sep 14. Epub ahead of print. PMID: 36102274

BACKGROUND

There are no diagnostic and/or prognostic markers of the treatment outcome in patients receiving allergen immunotherapy (AIT). Although numerous allergen epitopes are known, their value in this context has not been investigated. This paper deals with re-evaluation of sera from patients who underwent AIT against rBet v 1 for treatment of their soya allergy (BASALIT trial).

OBJECTIVE

To evaluate the diagnostic and/or prognostic potential of allergen epitopes recognition by antibodies from patients with birch-related soya allergy before and after rBet v 1-immunotherapy.

METHODS

PR-10 epitope-binding profiles from 34 patients were identified in silico using a statistical peptide phage display at start and at end of AIT. IgE- and IgG-binding to these peptide epitopes was measured in peptide microarrays. Clinical relevance of epitopes was evaluated by comparing these measurements to a number of treatment outcome measures recorded during double-blind placebo-controlled food challenge at start and end of AIT.

RESULTS

We showed that IgG- and IgE-recognition of peptide epitopes after AIT were surrogate markers of 5 out of 12 analysed treatment outcome measures using this patient cohort. Seven epitopes were identified from multiple PR-10 allergen sequences. Twenty-six peptide epitopes were used for IgG and IgE measurements. IgE-binding to one of the epitopes was associated with stronger intensity of oral tingling/itching after ingesting soya at start of AIT. IgG recognizing two other epitopes at start of AIT could predict decreased Cor a 1-specific IgE concentration (p = .043) and decreased lip swelling intensity (p = .016) after AIT. Tolerance to increasing amounts of soy at food challenge correlated with IgG-binding to another epitope at start of AIT (p = .046).

CONCLUSION

IgG- and IgE-binding to peptide epitopes in PR-10 is a potential indicator of the outcome and clinical course of AIT of soya-sensitized patients with rBet v 1.

6

El papel de los familiares en la ITO: abordaje educativo

Information needs of patients considering oral immunotherapy for food allergy

Mack DP, Greenhawt M, Turner PJ, Wasserman RL, Hanna MA, Shaker M, Hughes SW, Del Río PR

Clin Exp Allergy. 2022 Sep 9. doi: 10.1111/cea.14225. Epub ahead of print. PMID: 36083693

ABSTRACT

While the historic management of food allergy includes avoidance strategies and allergic reaction treatment, oral immunotherapy (OIT) approaches have become more commonly integrated into therapeutic approaches. International guidelines, phase 3 trials and real-world experience have supported the implementation of this procedure. However, OIT is an elective, rarely curative procedure with inherent risks that necessitates an increased degree of health literacy for the patients and families. Families assume the responsibility of amateur healthcare providers to ensure the daily safe administration of the allergenic food. As such, it is incumbent upon physicians to ensure that families are prepared for this role. A thorough educational and shared decision-making approach is necessary during the counselling and consent process to adequately inform the families. Educated discussion about the efficacy and patient-centred effectiveness, therapeutic alternatives and family goals is required to align physician and patient expectations. A frank discussion about the struggles, practical challenges, risks and contraindications can help to develop an understanding of the risk mitigation strategies employed to maintain safety. Physicians should develop a proactive approach to educate families about this, at times, burdensome procedure. This educational approach should encourage ongoing support starting prior to consent through the maintenance visits. By preparing families for their unique management role, physicians can help ensure the safe and successful integration of OIT into the therapeutic offering for the management of food allergies.

7

Impacto clínico de una ITA con un alergoide de Alt a 1: estudio preliminar

Clinical evaluation of subcutaneous immunotherapy with a polymerized molecular allergoid of Alt a 1 in patients with allergic rhinoconjunctivitis and/or allergic asthma caused by the mould Alternaria alternata

Ferrer Á

Eur Ann Allergy Clin Immunol. 2022 Sep 1. Epub ahead of print. PMID: 36047760

ABSTRACT

This is a retrospective analysis of the clinical evolution of 14 patients diagnosed with allergic rhinoconjunctivitis (AR) and/or allergic asthma (AA) caused by Alternaria alternata, who were attended by the allergology service of Vega Baja Hospital of Orihuela (Alicante, Spain). The purpose was to assess the clinical impact and safety of 1-year of subcutaneous immunotherapy with a polymerized molecular allergoid of Alt a 1. Impact of the treatment on allergic diseases (mean number AR/AA episodes and ARIA/GINA classifications), changes in symptoms and prescribed medication, change in the global subjective clinical status of patients and satisfaction with the treatment were also evaluated. Adverse reactions were also recorded and analysed. After 1-year of treatment, fewer AR and AA episodes (p less than 0.05) and improvements in ARIA/GINA classifications were observed. Significant improvements of symptoms (p less than 0.05) and a resulting general reduction of the medication prescribed was also detected. Improvements in the global subjective clinical status and good satisfaction rates were observed. Only 1 patient presented a local and not clinically relevant adverse reaction. The treatment showed promising effects with a significant improvement in the clinical status of all patients with a good safety profile.

8

Nuevas estrategias moleculares para predecir la respuesta a la ITA

Exosomes Derived hsa-miR-4669 as a Novel Biomarker for Early Predicting the Response of Subcutaneous Immunotherapy in Pediatric Allergic Rhinitis

Jiang S, Xie S, Fan R, Tang Q, Zhang H

J Inflamm Res. 2022 Sep 3;15:5063-5074. PMID: 36091336

PURPOSE

Subcutaneous immunotherapy (SCIT) is an effective treatment for pediatric allergic rhinitis (AR), but its efficacy fluctuates among individuals. This study aims to identify the profile of serum exosomes derived microRNAs (miRNAs) and evaluate their capacities to early predict SCIT efficacy in pediatric AR.

PATIENTS AND METHODS

High-throughput sequencing was applied to identify the miRNA of serum exosomes in AR children. GO enrichment and KEGG pathway analysis were performed to enrich the biological annotations of target mRNAs of miRNAs. Then we validated differentially expressed miRNAs in two independent cohorts by RT-qPCR. Logistic regression and receiver operating characteristic curve (ROC) were applied to evaluate the abilities of identified miRNAs in predicting the efficacy of SCIT in AR children.

RESULTS

A total of 812 miRNAs were detected in the serum exosomes, including 16 upregulated and 14 downregulated. Differentially expressed genes are enriched in the biological process of developmental process and regulation of cellular process, and gathered in pathways such as the signaling pathways regulating pluripotency of stem cells and the Wnt signaling pathway. In the first validation cohort, hsa-miR-4669 (P=0.009) and hsa-miR-4686 (P=0.032) were significantly downregulated in the effective group than the ineffective group, while hsa-miR-3196 (P=0.015) was upregulated. In the second cohort, hsa-miR-4669 level (P<0.0001) was downregulated in the effective group than the ineffective group. In addition, logistic regression revealed that hsa-miR-4669 level was correlated with the visual analogue scale (r=0.323, P=0.001) and total nasal symptoms score (r=0.269, P =0.007). ROC curve highlighted that hsa-miR-4669 level exhibited a reliable accuracy in predicting SCIT efficacy in pediatric AR (AUC=0.785).

CONCLUSION

Serum exosomes derived miRNA were associated with the efficacy of SCIT. Serum exosomes derived hsa-miR-4669 might serve as a novel biomarker for early predicting the response of SCIT in AR children.

9

¿Se relacionan el cáncer y las enfermedades alérgicas?

Allergen immunotherapy, cancer, and immune disorders

El-Qutob D, Matheu V, Fernandez-Caldas E

Curr Opin Allergy Clin Immunol. 2022 Sep 21. Epub ahead of print. PMID: 36165426

PURPOSE OF REVIEW

The purpose of this review is to provide an update on the intriguing relationships between allergies, allergen immunotherapy, cancer, and immune disorders. Allergic diseases and cancer are increasing in incidence and prevalence and a potential relationship, or not, between these diseases have been suggested for many years.

RECENT FINDINGS

Recent findings suggest that there may be some causative effects between certain types of cancer and allergic diseases, as described in the text. Some types of cancer may be more linked to the presence of an allergic disease, than others. However, epigenetic factors, such as tobacco smoke alcohol and toxic substances should also be taken into consideration.

SUMMARY

The association between allergy and cancer is complex and depends on the specific allergy and the specific organ under consideration. Regarding pancreatic cancer, colorectal cancer (CRC), and glioma, all types of allergies were shown to be a protective factor. Conversely, asthma is a risk factor for lung cancer as is atopic dermatitis for skin cancer. Despite extensive research, no definite relationship has been determined, and no clear relationship, either positive or negative, to allergies can be observed. These results should be corroborated with large epidemiological well designed prospective studies due to some weaknesses in the previous investigations.

10

Niveles de polen y gravedad de síntomas en la alergia a artemisia

Ragweed pollen concentration predicts seasonal rhino-conjunctivitis and asthma severity in patients allergic to ragweed

Bonini M, Monti GS, Pelagatti MM, Ceriotti V, Re EE
Sci Rep. 2022 Sep 23;12(1):15921. PMID: 36151263

ABSTRACT

In this work, we investigate the correlation between ragweed pollen concentration and conjunctival, nasal, and asthma symptom severity in patients allergic to ragweed pollen using ambient pollen exposure in the Milan area during the 2014 ragweed season We calculate the pollen/symptom thresholds and we assess the effectiveness of ragweed allergen immunotherapy (AIT). A total of 66 participants allergic to ragweed (Amb a 1) were enrolled in the study and divided into two groups: AIT treated (24) and no AIT treated (42). Pollen counts and daily symptom/medication patient diaries were kept. Autoregressive distributed lag models were used to develop predictive models of daily symptoms and evaluate the short-term effects of temporal variations in pollen concentration on the onset of symptoms. We found significant correlations between ragweed pollen load and the intensity of symptoms for all three symptom categories, both in no AIT treated (τ = 0.341, 0.352, and 0.721; and ρ = 0.48, 0.432, and 0.881; p-value < 0.001) and in AIT treated patients ([Formula: see text]= 0.46, 0.610, and 0.66; and ρ = 0.692, 0.805, and 0.824; p-value < 0.001). In both groups, we observed a positive correlation between the number of symptoms reported and drug use. Mean symptom levels were significantly higher in no AIT treated than in AIT treated patients (p-value < 0.001) for all symptom categories. Pollen concentration thresholds for the four symptom severity levels (low, medium-low, medium-high and high) were calculated. Ragweed pollen concentration is predictive of symptom severity in patients with a ragweed (Amb a 1) allergy. Patients treated with AIT had significantly reduced mean symptom levels compared to those without AIT.

1

Eficacia a corto, largo plazo y sostenido con una ITA de abedul: según mandan las guías

Extrapolating Evidence Based Medicine of AIT into Clinical Practice in the US

Natalija Novak, Margitta Worm, Petra Staubach, Marek Jutel, Angelika Sager, Oliver Pfaar

Clin Transl Allergy. 2022 Oct 55;12(10):e12185. PMID: 36225264

ARTÍCULO DESTACADO

BACKGROUND

Allergen immunotherapy (AIT) is an approved treatment for seasonal respiratory allergic diseases. A depigmented polymerized birch pollen extract for subcutaneous allergen immunotherapy (SCIT) has been demonstrated to be efficacious and safe in patients allergic to birch pollen and its homologous group.

OBJECTIVE

To determine whether SCIT with a birch pollen formulation (5000 depigmented polymerized (DPP) units/mL) shows sustained and long-term efficacy in adults and adolescents with birch-pollen induced allergic rhinitis with or without intermittent asthma.

METHODS

A multicentre (n = 66), double-blind, placebo-controlled Phase III clinical trial was performed in the Czech Republic, Finland, Germany, Latvia, Lithuania, Poland and Russia. Participants were randomized 2:1 to active treatment (birch 5000 DPP/ml) or placebo for three years of SCIT and followed up for two treatment-free years. The primary efficacy endpoint was the EAACI's combined symptom and medication score for rhinoconjunctivitis (CSMSEAACI).

RESULTS

A total of 973 participants were screened and 649 were randomized (active treatment: n = 434; placebo: n = 215). The intention-to-treat analysis of the CSMSEAACI in the overall study population did not demonstrate statistically significant differences in years 1, 2 and 3. In a post-hoc analysis, among the subgroup of patients monosensitized to birch pollen allergen only (n = 200), we observed a statistically significant difference (active treatment vs. placebo) in the CSMSEAACI in year 2, 3 and 5. The AIT's safety profile was good.

CONCLUSIONS

SCIT with a depigmented polymerized birch pollen extract was safe. Sustained and long-term efficacy in years 2, 3 and 5 in monosensitized patients, but not in polysensitized patients was demonstrated. (EudraCT 2012-000414-11).

2

SCIT + tezepelumab para los alérgicos al gato

Effects of combination treatment with tezepelumab and allergen immunotherapy on nasal responses to allergen: a randomized controlled trial

Corren J, Larson D, Altman MC, Segnitz RM, Avila PC, Immune Tolerance Network ITN057AD CATNIP Study Team

J Allergy Clin Immunol. 2022 Oct 9:S0091-6749(22)01333-1. Epub ahead of print. PMID: 36223848

BACKGROUND

Thymic stromal lymphopoietin (TSLP) has been shown to play a central role in the initiation and persistence of allergic responses.

OBJECTIVE

We evaluated whether tezepelumab, a human monoclonal anti-TSLP antibody, improved the efficacy of subcutaneous allergen immunotherapy (SCIT) and promoted the development of tolerance in patients with allergic rhinitis.

METHODS

We conducted a double-blind parallel design trial in patients with cat allergy. A total of 121 patients were randomized to receive either intravenous tezepelumab plus subcutaneous cat SCIT, cat SCIT alone, tezepelumab alone, or placebo for 52 weeks followed by 52 weeks of observation. Nasal allergen challenges (NAC), skin testing, and blood and nasal samples were obtained throughout the study.

RESULTS

At week 52, the NAC-induced total nasal symptom scores (TNSS) (calculated as an area-under-the-curve [AUC 0-1 hr] and as a peak score [peak 0-1 hr] during the first hour after nasal allergen challenge) were significantly reduced in patients receiving tezepelumab/SCIT compared with SCIT alone. At week 104, one year after stopping treatment, the primary endpoint TNSS AUC 0-1hr was not significantly different in the tezepelumab/SCIT group compared to SCIT alone, while TNSS peak 0-1 hr was significantly lower in those receiving combination treatment vs. SCIT. Transcriptomic analysis of nasal epithelial samples demonstrated that treatment with the combination of SCIT/tezepelumab, but neither monotherapy, caused persistent downregulation of a gene network related to type 2 inflammation which was associated with improvement in NAC responses.

CONCLUSIONS

These results suggest that inhibition of TSLP augments the efficacy of SCIT during therapy and may promote tolerance following a one year course of treatment. (ClinicalTrials.gov Identifier: NCT02237196).

3

¿Cómo se correlacionan los síntomas y uso de medicación con la calidad de vida?

Correlation of the combined symptom and medication score with quality of life, symptom severity and symptom control in allergic rhinoconjunctivitis

Palathumpattu B, Pieper-Fürst U, Acikel C, Sahin H, Allekotte S, Singh J, Hess M, Sager A, Müller T, Mösges R

Clin Transl Allergy. 2022 Oct 5;12(10):e12191. PMID: 36225263

BACKGROUND

The European Academy of Allergy and Clinical Immunology recommended the Combined Symptom and Medication Score (CSMS) as primary endpoint in clinical trials on allergen-specific immunotherapy (AIT) in allergic rhinoconjunctivitis. Here, the correlation between the CSMS and the validated standardised Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ(S)), Rhinitis Control Assessment Test (RCAT) and Visual Analogue Scale (VAS) was analysed.

METHODS

Two prospective, multicentre, non-interventional studies on tree pollen, grass pollen and house dust mite allergic patients were performed. The first study comprised 167 patients receiving AIT (AIT population), and the second included 56 patients treated with symptomatic medication only (control population). For up to two seasons (pollen)/exposure periods (house dust mites), participants documented their symptoms and medication intake in a CSMS diary, including VAS. In addition, the standardised RQLQ(S) and the RCAT were completed during study visits.

RESULTS

Comparison between CSMS and RQLQ(S) revealed a positive correlation in the AIT population (r = 0.426) and in the control population (r = 0.569). For CSMS and RCAT, a negative correlation with r = -0.409 (AIT) and r = -0.547 (control) was shown. Positive correlation between CSMS and VAS was also demonstrated with r = 0.585 (AIT) and r = 0.563 (control).

CONCLUSION

These results support the assumption that the CSMS correlates with quality of life, symptom severity and symptom control on the one hand, while the moderate strength of correlations on the other hand mirrors distinctions of the CSMS compared to the assessments used here.

4

La evidencia apoya la ITO con leche de vaca

Oral immunotherapy for Immunoglobulin E-mediated cow's milk allergy in children: A systematic review and meta analysis

Tang L, Yu Y, Pu X, Chen J

Immun Inflamm Dis. 2022 Oct;10(10):e704. PMID: 36169249

BACKGROUND

Cow's milk allergy (CMA) is the most common allergy in infants that decreases the quality of life of patients and their families. Standard treatment for CMA is the strict avoidance of milk; new treatment strategies such as oral immunotherapy (OIT) have been sought for patients with CMA. We aimed to assess the clinical efficacy and safety of OIT in the treatment of children with immunoglobulin E-mediated CMA (IMCMA).

METHODS

We searched all randomized controlled trials in which OIT is used to treat children with IMCMA from five international electronic databases. We estimated a pooled risk ratio (RR) for each outcome using a Mantel-Haenzel fixed-effects model if statistical heterogeneity was low.

RESULTS

Eleven studies were chosen for meta-analysis, including a total of 469 children (242 OITs, 227 controls). One hundred and seventy-six patients (72.7%) in the OIT were desensitized compared with 49 patients (21.6%) in the control group (RR: 7.35, 95% confidence interval (CI): 2.82-19.13, $p < .0001$). The desensitization effect of OIT was particularly significant in children over 3 years old (RR: 18.05, 95% CI: 6.48-50.26, $p < .00001$). Although adverse effects were common, they usually involved mild reactions, but epinephrine use was more common in the OIT group (RR: 7.69, 95% CI: 2.16-27.33, $p < .002$).

OIT can lead to desensitization in the majority of individuals with IMCMA, especially in patients over 3 years old. A major problem of OIT is the frequency of adverse events, although most are mild. OIT may be an alternative treatment in the future.

5

ITO: ¿mejor en niños o en adultos?

Efficacy and safety of food allergy oral immunotherapy in adults

Epstein-Rigbi N, Levy MB, Nachshon L, Koren Y, Katz Y, Goldberg MR, Elizur A

Allergy. 2022 Oct 3. doi: 10.1111/all.15537. Epub ahead of print. PMID: 36190349

BACKGROUND

Oral immunotherapy (OIT) is an emerging method for treating food allergy in children. However, data regarding adults undergoing this process are lacking.

METHODS

We retrospectively analyzed the medical records of patients with food allergy aged ≥17 years who completed OIT treatment between April 2010 and December 2020 at Shamir Medical Center. Data were compared with that of children aged 4 to <11 years and adolescents aged ≥11 to 17 treated during the same time period.

RESULTS

A total of 96 adults at a median age of 22.3 years who underwent OIT for milk (n = 53), peanut (n = 18), sesame (n = 7), egg (n = 5), and tree nuts (n = 13) were analyzed and compared with 1299 children and 309 adolescents. Adults experienced more adverse reactions requiring injectable epinephrine, both during in-clinic up-dosing (49% vs. 15.9% and 26.5% for children and adolescents, respectively, $p < 0.0001$) and during home treatment (22.9% vs. 12.4%, $p = 0.007$ for children, and 17.5%, $p = 0.23$ for adolescents). Most adults (61.5%) were fully desensitized, but the rates of full desensitization were significantly lower than children (73.4%, $p = 0.013$). Significantly more adults (28.3%) undergoing milk OIT failed treatment than children (14.3%, $p = 0.015$) and adolescents (14.1%, $p = 0.022$), while failure rates in adults undergoing OIT for other foods were low (9.3%) and comparable with children and adolescents.

CONCLUSIONS

OIT is successful in desensitizing most adults with IgE-mediated food allergy. Adults undergoing milk OIT are at increased risk for severe reactions and for OIT failure while failure rates in adults undergoing OIT for other foods are low.

6

Avances en el conocimiento de los biomarcadores y mecanismos de tolerancia de la ITO

T. Biomarkers and mechanisms of tolerance induction in food allergic patients drive new therapeutic approaches

Baloh CH, Huffaker MF, Laidlaw

Front Immunol. 2022 Oct 3;13:972103. doi: 10.3389. PMID: 36263023

ABSTRACT

Immunotherapy for food-allergic patients has been effective in inducing desensitization in some populations, but long-term tolerance has remained an elusive target. A challenge facing our field is how to differentiate immune markers that are impacted by immunotherapy from those that are critical biomarkers of tolerance. Data from recent clinical trials have identified several biomarkers and mechanisms for achieving tolerance. These biomarkers include younger age, lower food-specific IgE, lower food component-specific IgE, specific linear epitope profiles, and subsets of food-specific CD4+ T cells. Additional biomarkers under investigation for their relevance in tolerance induction include TCR repertoires, gastrointestinal and skin microbiome, and local tissue immunity. This mini-review highlights recent advances in understanding biomarkers and mechanisms of tolerance induction in food immunotherapy and how these are influencing clinical trial development.

7

Resultados percibidos por pacientes (pediátricos): ¿cómo medirlos?

Development and validation of a tool for the assessment of benefit from treatment of allergic rhinitis in children and adolescents (PBI-AR-K)

Janke TM, Eisner E, Augustin M, Blome C

Allergy Asthma Clin Immunol. 2022 Oct 25;18(1):95. PMID: 36284348

BACKGROUND

Allergic rhinitis (AR) is frequent in children and adolescents and can severely affect their lives. This article describes the development and validation of a questionnaire to assess treatment needs and benefits in children and adolescents, the PBI-AR-K, in a sample of patients receiving grass pollen sublingual immunotherapy.

PATIENTS AND METHODS

The PBI-AR-K was developed based on an open survey including children and adolescents and expert consensus between methodologists, patients, and physicians. The PBI-AR-K assesses patient needs before the treatment and perceived benefit during or at the end of a treatment. A weighted benefit score can be calculated ranging from 0 to 4 (4 = highest possible benefit). The validation was conducted in children (5-12 years) and adolescents (13-17 years) receiving sublingual immunotherapy. Subscales were developed based on factor analysis. Psychometric properties of items and scales were assessed with descriptive statistics, internal consistency, and convergent validity.

RESULTS

The final PBI-AR-K consists of 19 items. For validation, data from 345 patients (mean age 11.1; 60.9% male; n = 223 children; n = 122 adolescents) was analysed. Factor analyses resulted in four subscales for children and three subscales for adolescents. The items with the highest importance ratings were about choice of leisure activities (mean value in children: 3.5) and about being free of AR symptoms (adolescents: 3.3). The weighted PBI-AR-K scores reflected considerable patient-reported benefit (2.08-2.82) in both children and adolescents. Internal consistency of all scales was good or acceptable. In the children's sample, the global scale and three of four subscales were quite consistently correlated with convergent variables, while the subscale 'treatment burden' was significantly correlated only with change in average impairments due to rhinitis symptoms. The adolescents' sample showed more inconsistent results with only change in rhinitis severity being significantly associate with all subscales.

CONCLUSION

The newly developed PBI-AR-K is a reliable and valid questionnaire for use in children; for the use in adolescents, it should be further elaborated.

8

Monosensibilizados vs polisensibilizados: ¿quién responde mejor a una ITA de ácaros?

House dust mite allergen immunotherapy for monosensitized versus polysensitized patients with allergic rhinitis: A systematic review and meta-analysis

Phinyo P, Krikeerati T, Wongyikul P, Lao-Araya M, Thongngarm T

Asian Pac J Allergy Immunol. 2022 Oct 18. doi: 10.12932/AP-190822-1440. Epub ahead of print. PMID: 36278778

BACKGROUND

Most patients with allergic rhinitis are polysensitized. The efficacy of house dust mite (HDM) allergen immunotherapy (AIT) compared between monosensitized and polysensitized patients remains limited.

OBJECTIVE

To systematically review the efficacy and safety of HDM AIT compared between monosensitized and polysensitized patients with allergic rhinitis.

METHODS

We searched PubMed/MEDLINE, Scopus, EMBASE, and the Cochrane central register of Controlled Trials (CENTRAL) until June 2022. The primary outcome was the changes from baseline in total nasal symptom score (TNSS). Secondary outcomes were changes from baseline in total medication score (TMS), combined symptom medication score (CSMS), visual analog scale (VAS), Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) score, immunological parameters, and adverse events (AEs).

RESULTS

Of 13 eligible studies, 10 prospective cohorts, 2 retrospective cohorts, and 1 matched cohort, we identified 10 studies for quantitative synthesis. There were 1,113 patients with allergic rhinitis, 566 with HDM monosensitization and 547 with polysensitization to HDM and other allergens. There was no significant difference in the pooled mean changes of the 2 groups in TNSS (SMD -0.05, 95%CI: -0.22 to 0.11, p = 0.532) and VAS (SMD -0.20, 95%CI: -0.42 to 0.01, p = 0.060) with moderate certainty of evidence. The changes in TMS, CSMS, and RQLQ were similar between the 2 groups with very low certainty of evidence. The AEs were mild and comparable between the 2 groups. The immunological indices remained inconsistent and were not predictive of clinical responses.

CONCLUSIONS

A single HDM AIT similarly improved clinical outcomes in monosensitized and polysensitized patients with allergic rhinitis.

9

Presente y futuro del manejo de la alergia alimentaria

Management of IgE-mediated food allergy in the 21st century

Cafarotti A, Giovannini M, Begìn P, Brough HA, Arasi S

Clin Exp Allergy. 2022 Oct 6. doi: 10.1111/cea.14241. Epub ahead of print. PMID: 36200952

ABSTRACT

The 21st century has seen the propulsion of research in the field of food allergy, which has driven real changes in the clinical approach. Allergen immunotherapy has been recommended for the active management of food allergy. Data have shown promising additional methods of treatment, including biologics. Efforts have been devoted to the risk stratification of food allergy and the standardization of the assessment of food-allergic severity. Alternative routes of administration of epinephrine are under investigation to minimize any mechanical issue and the fear of injections. Evidence-based guidelines have been published by the main international societies in the field of anaphylaxis and food allergy management and new updates are in preparation. In the coming years, treatment options that are currently in pre-clinical or early clinical evaluation will hopefully lead to safe and effective disease-modifying therapies for food allergy in clinical practice. The identification of reliable biomarkers and the standardization of definitions and measurement approaches, alongside a shared decision-making with patients and families, will be key for the development of personalized care and to help minimize the substantial burden of food allergy.

10

La temida esofagitis eosinofílica y la posibilidad de su cribado antes y durante la ITO

Oral immunotherapy and risk of Eosinophilic Esophagitis in children: 15 years' experience

Cristina Morales-Cabeza, Sonsoles Infante, Paula Cabrera-Freitag, Victoria Fuentes-Aparicio, José Manuel Zubeldia, Alberto Álvarez-Perea

J Pediatr Gastroenterol Nutr. 2022 Oct 4. PMID: 36190840 DOI: 10.1097/MPG.0000000000003631

OBJECTIVES

Oral immunotherapy (OIT) an effective treatment for children with persistent food allergy, has concerns about its safety, including Eosinophilic Esophagitis (EoE). The aim of this study was to evaluate the prevalence of EoE in a large cohort of children who underwent OIT in our center. and to determine if there were any clinical, endoscopic or histologic differences depending on the food employed for the OIT.

METHODS

A retrospective study was performed over a 15-year period (2005-2020). Children who underwent cow's milk (CM), egg and/or peanut OIT and developed EoE were included.

RESULTS

607 OIT were carried out (277 CM-OIT, 322 egg-OIT and 8 peanut-OIT). Seventeen patients (2.8%) had a confirmed histologic diagnosis of EoE with a higher prevalence for patients who underwent CM-OIT (3.9%) than egg-OIT (2.2%). Symptoms suggestive of EoE and a confirmed diagnosis occurred at median times of 25 months and 36 months respectively after the build-up phase of the OIT was completed. Choking, abdominal pain and dysphagia were the most frequent symptoms and lamina propria fibrosis was observed in 41.2% of patients. No significant differences in clinical symptoms, endoscopic or histologic findings between patients under CM or egg-OIT were found. One third of patients reported mild symptoms suggestive of EoE before the OIT.

CONCLUSIONS

EoE appears to be a rare but important adverse event that can occur even years after OIT. Validated questionnaires to screen EoE before the OIT and in the follow-up of these patients may be the main tool for an early diagnosis.An infographic is available for this article at: http://links.lww.com/MPG/C952.

BOLETÍN BIBLIOGRÁFICO DE INMUNOTERAPIA

Noviembre 2022

1

El mundo de la alergia y la ITA en EE.UU: del empirismo a la evidencia.

Extrapolating Evidence Based Medicine of AIT into Clinical Practice in the US.

Calderon MA, Casale TB, Nelson HS, Bacharier LB, Bansal P

J Allergy Clin Immunol Pract. 2022 Nov 4:S2213-2198(22)01135-7. doi: 10.1016.

ARTÍCULO DESTACADO

ABSTRACT

Allergy/immunology specialists in the US prescribing allergy immunotherapy (AIT) have placed a heavy value on practical experience and anecdotal evidence rather than research-based evidence. With the extensive research on AIT conducted in the last few decades, the time has come to better implement evidencebased medicine (EBM) for AIT. The goal of this review was to critically assess EBM for debated concepts in US AIT practice for respiratory allergies in the context and quality of today's regulatory standards. Debated topics reviewed were the efficacy and safety of AIT in various subgroups (e.g., polyallergic patients, older patients, patients with asthma, pregnant women), diagnosis topics (e.g., skin prick test vs allergen-specific serum IgE, factors affecting skin prick tests, use of nasal or conjunctival allergen challenges, and telemedicine for diagnosis), and dosing topics (e.g., optimal dosing for subcutaneous immunotherapy and sublingual immunotherapy tablets, US liquid allergen extract history, duration of treatment, biomarkers of efficacy). In addition, EBM for patient-centered AIT issues (e.g., adherence, use of practice guidelines, pharmacoeconomics) and the approach to implementation of AIT EBM in future clinical practice was also addressed. The EBM for each concept was briefly summarized, and when possible, a practical, concise recommendation was given.

2

¿Cómo modula la ITA el sistema inmune?

How the Immune System Responds to Allergy Immunotherapy.

Veneziani I, Landolina N, Ricci B, Rossi O, Moretta L, Maggi E

Biomedicines. 2022 Nov 5;10(11):2825. doi: 10.3390.

ABSTRACT

IgE-mediated diseases represent a highly diversified and multifactorial group of disorders that can deeply impact the patients' quality of life. Currently, allergy immunotherapy (AIT) still remains the gold standard for the management of such pathologies. In this review, we comprehensively examine and discuss how AIT can affect both the innate and the adaptive immune responses at different cell levels and propose timing-scheduled alterations induced by AIT by hypothesizing five sequential phases: after the desensitization of effector non lymphoid cells and a transient increase of IgE (phase 1), high doses of allergen given by AIT stimulate the shift from type 2/type 3 towards type 1 response (phase 2), which is progressively potentiated by the increase of IFN-γ that promotes the chronic activation of APCs, progressively leading to the hyperexpression of Notch1L (Delta4) and the secretion of IL-12 and IL-27, which are essential to activate IL-10 gene in Th1 and ILC1 cells. As consequence, an expansion of circulating memory Th1/Tr1 cells and ILC-reg characterizes the third phase addressed to antagonize/balance the excess of type 1 response (phase 3). The progressive increase of IL-10 triggers a number of regulatory circuits sustained by innate and adaptive immune cells and favoring T-cell tolerance (phase 4), which may also be maintained for a long period after AIT interruption (phase 5). Different administration approaches of AIT have shown a similar tailoring of the immune responses and can be monitored by timely, optimized biomarkers. The clinical failure of this treatment can occur, and many genetic/epigenetic polymorphisms/mutations involving several immunological mechanisms, such as the plasticity of immune responses and the induction/maintenance of regulatory circuits, have been described. The knowledge of how AIT can shape the immune system and its responses is a key tool to develop novel AIT strategies including the engineering of allergen or their epitopes. We now have the potential to understand the precise causes of AIT failure and to establish the best biomarkers of AIT efficacy in each phase of the treatment.

3

Salud digital también en el campo de la alergia.

Real-world data using mHealth apps in rhinitis, rhinosinusitis and their multimorbidities.

Sousa-Pinto B, Anto A, Berger M, Dramburg S, Pfaar O

Clin Transl Allergy. 2022 Nov;12(11):e12208. doi: 10.1002.

ABSTRACT

Digital health is an umbrella term which encompasses eHealth and benefits from areas such as advanced computer sciences. eHealth includes mHealth apps, which offer the potential to redesign aspects of healthcare delivery. The capacity of apps to collect large amounts of longitudinal, real-time, real-world data enables the progression of biomedical knowledge. Apps for rhinitis and rhinosinusitis were searched for in the Google Play and Apple App stores, via an automatic market research tool recently developed using JavaScript. Over 1500 apps for allergic rhinitis and rhinosinusitis were identified, some dealing with multimorbidity. However, only six apps for rhinitis (AirRater, AllergyMonitor, AllerSearch, Husteblume, MASK-air and Pollen App) and one for rhinosinusitis (Galenus Health) have so far published results in the scientific literature. These apps were reviewed for their validation, discovery of novel allergy phenotypes, optimisation of identifying the pollen season, novel approaches in diagnosis and management (pharmacotherapy and allergen immunotherapy) as well as adherence to treatment. Published evidence demonstrates the potential of mobile health apps to advance in the characterisation, diagnosis and management of rhinitis and rhinosinusitis patients.

4

Se revisa al alza el umbral de reacción a la proteína de la leche de vaca.

Informing Risk Management for Patients With Cow's Milk Allergy Based on Threshold Dose Distributions Using Low-Dose Food Challenges.

Katz Y, Melchior M, Elizur A, Nachshon L, Remington BC, Leshno M

J Allergy Clin Immunol Pract. 2022 Nov 12:S2213-2198(22)01189-8. doi: 10.1016.

BACKGROUND

The safe consumption of foods depends on their allergen content in relation to patients' lowest observed adverse effect level (LOAEL) and no observed adverse effect level (NOAEL), as well as other factors. In the case of milk, data on LOAEL and NOAEL are limited and conflicting.

OBJECTIVE

To determine the threshold dose distribution and the lowest individual eliciting dose (ED) for milk in a large group of milk-allergic patients.

METHODS

Individuals with confirmed cow's milk allergy who underwent a diagnostic or pre-oral immunotherapy open milk oral food challenge at the Institute of Allergy, Immunology, and Pediatric Pulmonology at Shamir Medical Center between 2010 and 2015 were included. A subgroup of patients with severe milk allergy underwent a modified challenge with a 90- to 120-minute interval after a starting dose of 0.3 mg cow's milk protein.

RESULTS

A total of 866 participants (193 with diagnostic challenges and 673 with pre-oral immunotherapy challenges) were included in the study. The discrete ED01 and ED05, or values derived in which 1% or 5% of the respective allergic population would be predicted to experience an allergic reaction, were 1.1 to 1.9 and 4.7 to 5.6 mg milk protein, respectively, and values for cumulative doses for ED01 and ED05 were 0.9 to 1.8 and 5.2 to 6.2 mg milk protein, respectively. No patients, including the most severely milk-allergic individuals who underwent the modified challenge, reacted to the first 0.3 mg protein dose.

CONCLUSION

This report provides valuable information about milk NOAELs, LOAELs, and EDs that might assist regulators in decisions about food labeling in general, and milk in particular.

5

Factor H del complemento: posible biomarcador de eficacia en la alergia al Cedro de Japón.

Complement Factor H Is an Early Predictive Biomarker of the Therapeutic Efficacy of Sublingual Immunotherapy for Japanese Cedar Pollinosis.

Yoneda R, Iinuma T, Sakurai D, Kurita J, Arai T, Sonobe Y, Yonekura S, Okamoto Y, Hanazawa T

Pathogens. 2022 Nov 1;11(11):1280. doi: 10.3390

ABSTRACT

Sublingual immunotherapy for Japanese cedar pollinosis can improve the symptoms of allergic rhinitis and modify its natural course. However, sublingual immunotherapy requires a long treatment period and some patients do not respond to treatment. In this study, we aimed to identify biomarkers that could predict the efficacy of sublingual immunotherapy at an early stage. In this study, 40 patients from phase III trials were recruited and divided into good and poor response groups. Using peripheral blood mononuclear cells from before and two months after the start of medication, microarray, discriminant analysis, and realtime polymerase chain reaction were performed to extract candidate genes that could be biomarkers. Furthermore, these genes were validated in 30 patients in general clinical practice. Complement factor H was upregulated in the good response group and downregulated in the poor response group. Complement factor H may be a useful biomarker for predicting the efficacy of sublingual immunotherapy for Japanese cedar pollinosis at early time points after treatment initiation.

6

ITA sublingual vs ITA subcutánea de abedul: ¿cuál es más coste-eficiente?

ITULAZAX® versus Alutard SQ® in the treatment of allergic rhinitis induced by pollen from the birch homologous group: A costminimization modeling analysis from the Danish societal perspective.

Rønborg SM, Grand TS, Brandi H, Pollock RF

Clin Transl Allergy. 2022 Nov;12(11):e12196. doi: 10.1002.

BACKGROUND & AIMS

Allergic rhinitis (AR) is an inflammatory disorder triggered by an allergic immune response to inhaled allergens. Birch pollen is the major allergenic tree pollen in parts of Europe. ITULAZAX® is a sublingual immunotherapy tablet for the treatment of adults with moderate-to severe AR and/or conjunctivitis induced by pollen from the birch homologous group. The aim was to compare the costs of treating AR with ITULAZAX® versus subcutaneous ALUTARD SQ® Betula verrucosa (ALUTARD SQ®) from a Danish societal perspective.

METHODS

A cost-minimization model was developed to capture costs of allergy immunotherapy (AIT), interactions with healthcare professionals (HCPs) in three different care settings (general practice, allergy specialist, and hospital), and indirect costs arising from absenteeism and presenteeism. The cost-minimization analysis was conducted over a 3-year time horizon with costs reported in 2021 Danish Kroner (DKK) and Euros (EUR) based on the European Central Bank 365-day average exchange rate. One-way sensitivity analyses were performed.

RESULTS

The base case analysis showed that the total cost of treatment over 3 years was estimated to be DKK 49,117 (EUR 6598) per patient with ALUTARD SQ®, compared with DKK 30,996 (EUR 4164) with ITULAZAX®, reflecting a cost saving of DKK 18,121 (EUR 2434) per patient with ITULAZAX® over 3 years. Over the 3- year time horizon, costs of AIT were predicted to increase by DKK 17,928 (EUR 2408) with ITULAZAX®, while costs of interactions with HCPs were predicted to decrease by DKK 22,528 (EUR 3027) versus ALUTARD SQ®, more than offsetting the increased cost of ITULAZAX®.

CONCLUSIONS

Given the equivalent effectiveness of the two AIT products and the cost savings with ITULAZAX® versus ALUTARD SQ® from a Danish societal perspective, ITULAZAX® should be considered as a cost-saving alternative to ALUTARD SQ® for the treatment of birch pollen-induced moderate-to-severe AR in adults.

7

Improntas del sistema inmune y ausencia de respuesta mantenida tras ITO de cacahuete

CD8+ T cell differentiation status correlates with the feasibility of sustained unresponsiveness following oral immunotherapy.

Kaushik A, Dunham D, Han X, Do E, Andorf S

Nat Commun. 2022 Nov 4;13(1):6646. doi: 10.1038/s41467-022-34222-8. PMID: 36333296.

ABSTRACT

While food allergy oral immunotherapy (OIT) can provide safe and effective desensitization (DS), the immune mechanisms underlying development of sustained unresponsiveness (SU) following a period of avoidance are largely unknown. Here, we compare high dimensional phenotypes of innate and adaptive immune cell subsets of participants in a previously reported, phase 2 randomized, controlled, peanut OIT trial who achieved SU vs. DS (no vs. with allergic reactions upon food challenge after a withdrawal period; n = 21 vs. 30 respectively among total 120 intent-to-treat participants). Lower frequencies of naïve CD8+ T cells and terminally differentiated CD57+CD8+ T cell subsets at baseline (pre OIT) are associated with SU. Frequency of naïve CD8+ T cells shows a significant positive correlation with peanut-specific and Ara h 2-specific IgE levels at baseline. Higher frequencies of IL-4+ and IFNγ+ CD4+ T cells post-OIT are negatively correlated with SU. Our findings provide evidence that an immune signature consisting of certain CD8+ T cell subset frequencies is potentially predictive of SU following OIT.

8

ITA combinada con omalizumab: beneficios y controversias.

Omalizumab and allergen immunotherapy for respiratory allergies: A mini-review from the Allergen-Immunotherapy Committee of the Italian Society of Pediatric Allergy and Immunology (SIAIP).

Filippo M, Votto M, Caminiti L, Carella F, Castro G

Allergol Immunopathol (Madr). 2022 Nov 1;50(6):47-52. doi: 10.15586.

ABSTRACT

Although currently approved to treat severe asthma and chronic spontaneous urticaria, omalizumab has also been an effective and safe add-on treatment for other allergic diseases. Namely, omalizumab has been proposed to be used as add-on therapy in patients with allergic rhinitis and asthma and undergoing specific allergen immunotherapy (AIT). AIT is the only treatment that modifies the natural history of IgE-mediated diseases. This brief review summarizes the available evidence and controversies on the efficacy and safety of omalizumab combined with specific AIT.

9

Papel preventivo de la ITA en el asma (perenne y estacional)

Allergen immunotherapy effectively reduces the risk of exacerbations and lower respiratory tract infections in both seasonal and perennial allergic asthma: a nationwide epidemiological study.

Woehlk C, Von Bülow A, Ghanizada M, Søndergaard MB, Hansen S, Porsbjerg C

Eur Respir J. 2022 Nov 17;60(5):2200446. doi: 10.1183.

BACKGROUND

Allergic asthma is associated with increased risk of respiratory tract infections and exacerbations. It remains unclear whether this susceptibility is conditioned by seasonal or by perennial allergy.

AIM

To investigate perennial allergy compared with seasonal allergy as a risk factor for lower respiratory tract infections and exacerbations in asthma and whether this risk can be reduced by allergen immunotherapy (AIT).

Methodology

This is a prospective register-based nationwide study of 18-44-year olds treated with AIT during 1995-2014. Based on the type of AIT and use of anti-asthmatic drugs, patients were subdivided into two groups: perennial allergic asthma (PAA) versus seasonal allergic asthma (SAA). Data on antibiotics against lower respiratory tract infections (LRTI) and oral corticosteroids for exacerbations were analysed before starting AIT (baseline) and 3 years after completing AIT (follow-up).

RESULTS

We identified 2688 patients with asthma treated with AIT, of whom 1249 had PAA and 1439 had SAA. At baseline, patients with SAA had more exacerbations (23.8% versus 16.5%, $p \leq 0.001$), but there were no differences in LRTI. During the 3-year follow-up, we observed a highly significant reduction of exacerbations with an average decrease of 57% in PAA and 74% in SAA. In addition, we observed a significant reduction of LRTI in both PAA and SAA: 17% and 20% decrease, respectively.

CONCLUSION

AIT effectively reduced the risk of exacerbations and lower respiratory tract infections in both seasonal and perennial allergic asthma. Perennial allergy is seemingly not a stronger risk factor for respiratory infections and exacerbations than seasonal allergy.

10

Guía de referencia de la ITA para la rinitis alérgica en China.

Chinese Guideline on Allergen Immunotherapy for Allergic Rhinitis: The 2022 Update.

Wang C, Bao Y, Chen J, Chen X, Cheng L, Chinese Society of Allergy (CSA) and Chinese Allergic Rhinitis Collaborative Research Group (C2AR2G)

Allergy Asthma Immunol Res. 2022 Nov;14(6):604-652. doi: 10.4168.

ABSTRACT

In the last few decades, there has been a progressive increase in the prevalence of allergic rhinitis (AR) in China, where it now affects approximately 250 million people. AR prevention and treatment include allergen avoidance, pharmacotherapy, allergen immunotherapy (AIT), and patient education, among which AIT is the only curative intervention. AIT targets the disease etiology and may potentially modify the immune system as well as induce allergen specific immune tolerance in patients with AR. In 2017, a team of experts from the Chinese Society of Allergy (CSA) and the Chinese Allergic Rhinitis Collaborative Research Group (C2AR2G) produced the first English version of Chinese AIT guidelines for AR. Since then, there has been considerable progress in basic research of and clinical practice for AIT, especially regarding the role of follicular regulatory T (TFR) cells in the pathogenesis of AR and the use of allergen-specific immunoglobulin E (sIgE) in nasal secretions for the diagnosis of AR. Additionally, potential biomarkers, including TFR cells, sIgG4, and sIgE, have been used to monitor the incidence and progression of AR. Moreover, there has been a novel understanding of AIT during the coronavirus disease 2019 pandemic. Hence, there was an urgent need to update the AIT guideline for AR by a team of experts from CSA and C2AR2G. This document aims to serve as professional reference material on AIT for AR treatment in China, thus improving the development of AIT across the world.

1

La alergia alimentaria tiene un aliado terapéutico.

Omalizumab in IgE-mediated food allergy: A systematic review and meta-analysis.

Zuberbier T, Wood RA, Bindslev-Jensen C, Fiocchi A, Chinthrajah RS, Worm M, Deschildre A, Fernandez-Rivas M, Santos AF, Jaumont X, Tassinari P

J Allergy Clin Immunol Pract. 2022 Dec 15:S2213-2198(22)01296-X. doi: 10.1016.

ARTÍCULO DESTACADO

BACKGROUND
A growing number of studies have shown encouraging results with omalizumab (OMA) as monotherapy and as an adjunct to oral immunotherapy (OMA+OIT) in patients with single/multiple food allergies.
OBJECTIVES
To evaluate the efficacy and safety of OMA or OMA+OIT in patients with IgE-mediated food allergy.
METHODS
An extensive literature search (inception-December 31, 2020) was performed to identify randomized, controlled, and observational studies that assessed OMA as monotherapy or OMA+OIT in patients with IgE-mediated food allergy.
OUTCOMES
Increase in tolerated dose of foods, successful desensitization, sustained unresponsiveness, immunological biomarkers, severity of allergic reactions to food, quality of life (QoL), and safety. A $P < 0.05$ was considered significant.
RESULTS
In total, 36 studies were included. OMA monotherapy (vs pre-OMA) significantly increased the tolerated dose of multiple foods, increased the threshold of tolerated dose for milk, egg, wheat, and baked milk, improved QoL, and reduced food-induced allergic reactions (all $P < 0.01$). OMA+OIT significantly increased the tolerated dose of multiple foods (vs placebo and pre-OMA), desensitization (vs placebo+OIT and pre-OMA) (all $P \leq 0.01$), and improved QoL (vs pre-OMA) and IgG4 levels (both $P < 0.01$). No major safety concerns were identified.
CONCLUSIONS
In IgE-mediated food allergy, OMA can help patients for consumption of multiple foods and allow for food dose escalation. As an adjunct to OIT, OMA can also support high-dose desensitization and higher maintenance doses. Further studies are warranted to empirically evaluate the effect of OMA and confirm these findings.

2

La “inmunidad entrenada” en el contexto de la alergia.

From trained immunity in allergy to trained immunity-based allergen vaccines.

Martín-Cruz L, Sevilla-Ortega C, Angelina A, Domínguez-Andrés J, Netea MG, Subiza JL, Palomares O

Clin Exp Allergy. 2022 Dec 9. doi: 10.1111.

ABSTRACT
Innate immune cells experience long lasting metabolic and epigenetic changes after an encounter with specific stimuli. This facilitates enhanced immune responses upon secondary exposition to both the same and unrelated pathogens, a process termed trained immunity. Trained immunity-based vaccines (TIbV) are vaccines able to induce innate immune memory, thus conferring heterologous protection against a broad range of pathogens. While trained immunity has been well documented in the context of infections and multiple immune-mediated diseases, the role of innate immune memory and its contribution to the initiation and maintenance of chronic allergic diseases remains poorly understood. Over the last years, different studies attempting to uncover the role of trained immunity in allergy have emerged. Exposition to environmental factors impacting allergy development such as allergens or viruses induces the reprogramming of innate immune cells to acquire a more pro-inflammatory phenotype in the context of asthma or food allergy. Several studies have convincingly demonstrated that prevention of viral infections using TIbV contributes to reduce wheezing attacks in children, which represent a high-risk factor for asthma development later in life. Innate immune cells trained with specific stimuli might also acquire anti-inflammatory features and promote tolerance, which may have important implications for chronic inflammatory diseases such as allergies. Recent findings showed that allergoid-mannan conjugates, which are next generation vaccines for allergen-specific immunotherapy (AIT), are able to reprogram monocytes into tolerogenic dendritic cells by mechanisms depending on metabolic and epigenetic rewiring. A better understanding of the underlying mechanisms of trained immunity in allergy will pave the way for the design of novel trained immunity-based allergen vaccines as potential alternative strategies for the prevention and treatment of allergic diseases.

3

Impacto de una ITO con cacahuete en la calidad de vida de los niños.

Children and caregiver proxy quality of life from peanut oral immunotherapy trials.

Galvin AD, Vereda A, Del Río PR, Muraro A, Jones C, Ryan R, Norval D, Jobrack J, Anagnostou A, Wang J

Clin Transl Allergy. 2022 Dec;12(12):e12213. doi: 10.1002

BACKGROUND

Health-related quality of life (HRQoL) is significantly and substantially reduced in individuals with peanut allergy due to many factors associated with unanticipated or potentially fatal reactions. Further insight on the impact of peanut oral immunotherapy in managing peanut allergy on HRQoL is needed. The aim of this analysis was to assess effects of peanut (Arachis hypogaea) allergen powder-dnfp (PTAH), a biologic drug for peanut oral immunotherapy, on HRQoL from three phase 3 and two follow-on trials of PTAH.

METHODS

HRQoL assessments from participants aged 4-17 in the PALISADE (ARC003), ARC004 (PALISADE follow-on), ARTEMIS (ARC010), RAMSES (ARC007), and ARC011 (RAMSES follow-on) trials were included in this analysis. Responses on the Food Allergy Quality of Life Questionnaire (FAQLQ) and Food Allergy Independent Measure (FAIM) were evaluated by age group and respondent (self or caregiver proxy). Data were analyzed with descriptive statistics and Student t tests.

RESULTS

Baseline FAQLQ and FAIM total scores appeared comparable between PTAH- and placebo-treated participants. Self and caregiver proxy-reported total scores on the FAQLQ for PTAH-treated participants generally improved at trial exit versus baseline; FAIM total scores improved throughout all trials. The tendency for improvement in FAQLQ total scores from baseline for PTAH appeared larger in self versus caregiver proxy-reports. Between treatment groups, PTAH was generally favored in the PALISADE and ARTEMIS trials; differences varied in the RAMSES trial based on age and respondent types.

CONCLUSIONS

PTAH for the management of peanut allergy in children appeared to have a beneficial effect on HRQoL in trials. Improvements were seen despite rigors of trial participation.

4

Inmuno-metabolismo y desarrollo de inflamación alérgica.

Immune Metabolism in TH2 Responses: New Opportunities to Improve Allergy Treatment - Cell Type-Specific Findings (Part 2).

Lin YJ, Goretzki A, Rainer H, Zimmermann J, Schülke S

Curr Allergy Asthma Rep. 2022 Dec 15. doi: 10.1007.

PURPOSE OF REVIEW

Over the last years, we have learned that the metabolic phenotype of immune cells is closely connected to the cell's effector function. Understanding these changes will allow us to better understand allergic disease pathology and improve allergy treatment by modulating immune metabolic pathways. As part two of a two-article series, this review reports on the recent studies investigating the metabolism of the cell types involved in allergies and discusses the initial application of these discoveries in allergy treatment.

RECENT FINDINGS

The cell types involved in allergic reactions display pronounced and highly specific metabolic changes (here discussed for epithelial cells, APCs, ILC2s, mast cells, eosinophils, and Th2 cells). Currently, the first drugs targeting metabolic pathways are tested for their potential to improve allergy treatment. Immune-metabolic changes observed in allergy so far are complex and depend on the investigated disease and cell type. However, our increased understanding of the underlying principles has pointed to several promising target molecules that are now being investigated to improve allergy treatment.

5

Tratamiento de la alergia a huevo y leche: estrategias, seguridad y manejo.

Rostrum: Are There Hidden Dangers Associated with Milk and Egg Dietary Advancement Therapy?

Mack DP, Greenhawt M, Anagnostou A

J Allergy Clin Immunol Pract. 2022 Dec 26:S2213-2198(22)01328-9. doi: 10.1016.

ABSTRACT

Dietary advancement therapies (DAT) constitute a continuum spanning extensively heated item ingestion, progressive milk/egg ladders, and oral immunotherapy (OIT). These represent an evolution in food allergy management from strict avoidance to an active therapy that may modulate the immune system to develop tolerance to particular forms of the allergen. Many egg or milk individuals are tolerant to baked egg/milk at baseline, and regular consumption (at home ingestion) of baked milk or egg is a safe process with potential quality of life and immunologic benefit. Milk and egg ladders, developed for non-IgE mediated allergy, are being increasingly adapted to IgE-mediated allergy as a potentially safe at-home option for gradual dietary advancement. However, data are limited regarding how safe and effective these approaches are, or what patient is best suited for which DAT. It is also unclear if extensively heated allergen consumption and ladders are susceptible to the same patient-specific factors which affect day-to-day tolerance and safety in OIT. Several recent events involving near-fatal or fatal reactions to milk or egg products (all amongst patients with asthma) have highlighted that DATs are not risk-free, and that physician guidance in these therapies is essential. Such guidance may include obtaining informed consent prior to starting any DAT, and instituting the same safe dosing rules for OIT across any form of DAT. This rostrum discusses practical concerns about the safety of DAT, and considerations how clinicians can maximize patient protection while defining the safety and efficacy of real-world implementation of these concepts.

6

La (aprobada) ITO de cacahuete: ¿qué ventajas ofrece?

Peanut (Arachis hypogaea) allergen powder-dnfp for the mitigation of allergic reactions to peanuts in children and adolescents.

Casale TB, Irani AM

Expert Rev Clin Immunol. 2022 Dec 22:1-13. doi: 10.1080.

INTRODUCTION

Peanut allergy can result in severe, sometimes fatal hypersensitivity reactions that place a considerable burden on the lives of patients. This article reviews the first approved immunotherapy for the mitigation of allergic reactions following accidental peanut exposure, peanut (Arachis hypogaea) allergen powder-dnfp (PTAH; Palforzia®, Aimmune Therapeutics).

AREAS COVERED

This article highlights the unmet need for patients with peanut allergy, describes the therapeutic landscape, and reviews the development of and clinical data for PTAH.

EXPERT OPINION

PTAH offers a standardized preparation of peanut allergen, with a tolerability and efficacy profile clearly defined through its robust clinical development and trial program. In children 4-17 years old, PTAH provides a standardized, approved product that many clinicians sought prior to initiating oral immunotherapy. PTAH reduced the likelihood of more severe reactions following exposure to peanut protein; although peanut avoidance remains essential, PTAH will enable more individuals with peanut allergy to participate in activities of daily life with less anxiety.

7

En las alergias potencialmente graves, ¿qué factores impactan en la calidad de vida?

Health-related quality of life in food and venom induced anaphylaxis and role of influencing factors.

Höfer V, Martini M, Dölle-Bierke S, Worm M, Bilò M

Clin Exp Allergy. 2022 Dec 23. doi: 10.1111.

ABSTRACT

The impact on health-related quality of life (HRQL) plays a key role for patients suffering from allergies and anaphylaxis. In this narrative review we review the HRQL in allergic patients suffering from food and venom allergy, both being the most frequent elicitors of severe allergic, potential life threatening reactions and provide an overview on the current knowledge and identified gaps. The data show that for food and venom allergy standardized assessment tools to measure HRQL are available and have been successfully applied. Our analysis shows that multiple factors can modulate HRQL in these patient groups. These include sociodemographic data like patients' age and sex, fear of accidental reactions but also external factors like the social environment and the appreciation of the seriousness of the condition by others. External factors may have a significant impact on HRQL and should be considered in patient-related outcome assessments to avoid biased measurements possibly affecting the results. The assessment of the quality of life in the context of specific immunotherapy should consider lifestyle factors and ideally, the individual change in HRQL should be measured. Although there are many data indicating a negative impact on HRQL in food allergic children and their caregivers, limited data are existing from adults with food allergy and venom allergic patients from all age groups. Also, the use of standardized questionnaires should be extended to allow for a better comparability of results between studies. Therefore, translation to additional languages is necessary. Taken together, the eliciting allergen, the severity of the allergic disease but moreover multiple external factors impact the outcome in HRQL and should be considered in HRQL assessment.

8

Evidencia en vida real con un alergoide monomérico carbamilado.

Real-Life Effectiveness of Subcutaneous Immune Therapy with Carbamylated Monomeric Allergoids on Mite, Grass, and Pellitory Respiratory Allergy: A Retrospective Study.

Di Gioacchino M, Della Valle L, Mangifesta R, Lumaca A, Cipollone F

J Clin Med. 2022 Dec 12;11(24):7384. doi: 10.3390.

BACKGROUND

Real-life studies are encouraged to evaluate the effectiveness and safety of allergen immunotherapy (AIT). In this context, a retrospective cohort study was conducted to assess the effectiveness and safety of carbamylated monomeric allergoid subcutaneous immunotherapy (MA SCIT), along with patient satisfaction.

METHODS

A total of 291 patients with rhinoconjunctivitis with or without asthma with inhalant (house dust mite, grass, and pellitory) allergies were enrolled in this study. Perceived efficacy and perceived satisfaction with MA-SCIT, symptom score by VAS, ARIA classification of rhinitis, drug consumption, number of asthma worsening episodes, and asthma symptom control were evaluated by questionnaires before, after one year, at the end of treatment, and after one or two years of MA-SCIT.

RESULTS

The overall symptom score significantly decreased over the years of MA-SCIT, irrespective of specific sensitization ($p < 0.01$). There was a substantial amelioration of rhinitis severity, with a significant reduction ($p < 0.01$) in drug use. A significant reduction was observed in the asthma symptom VAS score and asthma-worsening episodes requiring systemic steroids. None of the patients reported any severe adverse reactions. Finally, 90% of the patients reported full satisfaction with the treatment.

CONCLUSIONS

The study showed that AIT with carbamylated monomeric allergoids of grass, pellitory, and mites was effective and well tolerated by patients.

9

Pauta convencional vs pauta agrupada: la seguridad, a prueba.

Risk of anaphylaxis in cluster versus standard subcutaneous multi-allergen immunotherapy.

Chen JH, Orden T, Wang J, Sowho M, Tversky JR

Ann Allergy Asthma Immunol. 2022 Dec 12:S1081-1206(22)01993-7. doi: 10.1016.

BACKGROUND

Cluster schedules for subcutaneous allergen immunotherapy require significantly fewer injections, but there have been conflicting reports regarding the risk of systemic reaction.

OBJECTIVE

To compare the incidence of systemic reactions during the build-up stages of multi-allergen standard versus cluster immunotherapy.

METHODS

Data on systemic reactions were collected prospectively from 91 adult, urban patients who underwent either standard or cluster allergen immunotherapy at the Johns Hopkins Allergy and Asthma Center between 2014-2022. Systemic reactions were recorded during build-up phase and compared for both protocols using Pearson's chi-square, Fisher exact test, and multivariate logistic regression models.

RESULTS

Overall, systemic reaction rates were 21% for patients in the standard schedule and 37% for patients in the cluster immunotherapy schedule which was not statistically different (P = 0.084). However, the systemic reaction rate for each individual injection was 0.69% per injection in the standard protocol and 2.29% per injection in the cluster schedule (IRR = 3.3). 100% of all systemic reactions in both groups occurred in the second half of the build-up phase. Multivariate regression showed that the target prescription PNU and the number of allergens in the treatment vial did not influence systemic reaction rates (OR = 1.00 and 1.06 respectively).

CONCLUSION

The overall incidence of systemic reaction was not statistically different for cluster and standard allergen immunotherapy protocols. However, since cluster patients received about half the number of injections, the risk for systemic reaction per individual injection is more than 3 fold higher than that of standard immunotherapy.

10

Factores de riesgo que limitan el uso de la ITO.

Factors Associated with Home Epinephrine-Treated Reactions During Peanuts and Tree-nuts Oral Immunotherapy.

Nachshon L, Schwartz N, Levy MB, Goldberg MR, Epstein-Rigbi N, Katz Y, Elizur A

Ann Allergy Asthma Immunol. 2022 Dec 9:S1081-1206(22)01971-8. doi: 10.1016.

BACKGROUND

Home reactions requiring epinephrine administration, a marker of their severity, restrict the widespread use of oral immunotherapy (OIT) but their risk-factors are largely unknown.

OBJECTIVE

To identify risk factors for such reactions during OIT to most allergenic foods.

METHODS

All patients who began OIT for peanut, tree nuts, sesame or egg allergy at the Shamir Medical Center between April 2010 and January 2020 were enrolled. Patients were instructed to use their epinephrine auto injectors during reactions consisting of severe abdominal pain, significant shortness of breath, or lethargy, or whenever in uncertainty of reaction severity. Patients with and without home epinephrine-treated reactions (HETRs) were compared.

RESULTS

A total of 757 OIT treatments to peanut (n=346), tree nuts (n=221; walnut n=147, cashew n=57, hazelnut n=16, almond n=1), sesame (n=115) and egg (n=75) were administered to 644 patients. Eighty-three (10.9%) patients experienced HETRs. The highest rate of HETRs was experienced during walnut (20.4%) or hazelnut (25%) OIT, followed by peanut (9.8%), sesame (6.1%), egg (6.7%) and cashew (5.3%) OIT. Risks factors for HETRs included a reaction treated in an ER (p=0.0048) before starting OIT, and a reaction treated with epinephrine during in-clinic induction (p<0.0001). Significantly less patients (73.6%) with, compared to those without (88.3%) HETRs achieved full desensitization (p=0.001), but only a few patients with HETRs (8.4%) failed treatment.

CONCLUSION

Previous reaction severity is the main predictor for HETRs during OIT. These reactions are more frequent during walnut and hazelnut OIT compared to other foods studied. Most patients experiencing HETRs achieved desensitization.