1

¿Lo sabemos ya todo acerca de la ITO?

Mechanisms of oral immunotherapy.

Barshow SM, Kulis MD, Burks AW, Kim EH

Clin Exp Allergy. 2021 Jan 8. doi: 10.1111/cea.13824. Epub ahead of print. PMID: 33417257.

ARTÍCULO DESTACADO

ABSTRACT

Food allergy presents a significant global health concern with up to 10% of the population affected in developed nations and a steadily increasing prevalence. In many cases, particularly with peanut, tree nut and shellfish, food allergy is a lifelong and potentially life-threatening diagnosis. While no 'cure' for IgE-mediated food allergy exists, oral immunotherapy (OIT) is a promising treatment modality with the peanut OIT drug Palforzia (Aimmune Therapeutics) the only treatment for food allergy that is currently approved by the United States Food and Drug Administration. OIT primarily induces a state of desensitization with only a minority of subjects achieving sustained unresponsiveness, a state of limited clinical remission that appears to be immunologically distinct from natural tolerance. Early humoural changes during OIT include an initial increase in allergen-specific IgE, which eventually decreases to below baseline levels as OIT progresses, and a gradual increase in allergen-specific IgA and IgG4 that continues throughout the course of OIT. Basophil hyporesponsiveness and decreased skin prick test wheal size are observed within the first year of OIT, and persistence after completion of therapy has been associated with sustained unresponsiveness. In the T-cell compartment, there is an initial expansion followed by a decline in the number and activity of T helper 2 (TH 2) cells, the latter of which may be dependent on an expansion of IL-10-producing cells, including regulatory T-cells. Our understanding of the immunomodulatory effects of OIT continues to evolve, with new technologies such as single-cell transcriptional profiling and antibody epitope analysis allowing for more detailed study of T-cell and B-cell responses to OIT. In this review, we present evidence to illustrate what is currently known about the immunologic changes induced by OIT, explore potential mechanisms and emphasize knowledge gaps where future research is needed.

2

ITA y eosinofilia gastrointestinal: ¿Qué las une?

Eosinophilic gastrointestinal disorders and allergen immunotherapy: lights and shadows.

Votto M, De Filippo M, Caminiti L, Carella F, de Castro G, Landi M et al

Pediatr Allergy Immunol. 2021 Jan 27. doi: 10.1111/pai.13458. Epub ahead of print.

ABSTRACT

Allergic diseases, such as IgE-mediated food allergy, asthma and allergic rhinitis, are relevant health problems worldwide and show an increasing prevalence. Therapies for food allergies are food avoidance and the prompt administration of intramuscular epinephrine in anaphylaxis occurring after accidental exposure. However, allergen immunotherapy (AIT) is being investigated as a new potential tool for treating severe food allergies. Effective oral immunotherapy (OIT) and epicutaneous immunotherapy (EPIT) induce desensitization and restore immune tolerance to the causal allergen. While immediate side effects are well known, the long-term effects of food AIT are still underestimated. In this regard, eosinophilic gastrointestinal disorders (EGIDs), mainly eosinophilic esophagitis, have been reported as putative complications of OIT for food-allergy and sublingual immunotherapy (SLIT) for allergic asthma and rhinitis. Fortunately, these complications are usually reversible and the patient recovers after AIT discontinuation. This review summarizes current knowledge on the possible causative link between eosinophilic gastrointestinal disorders and AIT, highlighting recent evidence and controversies.

3

¿Inmunoterapia para todos? Depende...

A randomized trial of subcutaneous allergy immunotherapy in inner-city asthmatic children <4 years of age.

de Vos G, Viswanathan S, Pichardo Y, Nazari R, Jorge Y, Ren Z et al

Ann Allergy Asthma Immunol. 2021 Jan 5:S1081-1206(20)31271-0. doi: 10.1016/j.anai.2020.12.016. Epub ahead of print.

BACKGROUND

Allergic sensitization to environmental allergens in the first years of life is a strong predictor of asthma morbidity in children. Allergy immunotherapy can improve asthma and allergy outcomes, but its efficacy in atopic, inner-city children < 4 years of age with recurrent wheeze has not yet been established.

OBJECTIVE

The objective of this study was to determine if subcutaneous allergy immunotherapy improves asthma in a population of U.S. inner-city children when started at < 4 years of age.

METHODS

In a randomized controlled, open-label phase I/II single center trial in the Bronx, New York, 58 children with recurrent wheeze or physician-diagnosed asthma were randomized to receive asthma standard of care treatment with or without a 3-year course of multiple allergen subcutaneous immunotherapy.

RESULTS

23 children in the control group and 27 children in the immunotherapy group began the study. 20 of 27 children commencing immunotherapy completed at least 2 years of immunotherapy. There was no difference in asthma medication and symptom scores between the treatment or control groups over time. Similarly, naso-ocular symptoms and allergy medication use were similar in both groups over time. Nevertheless, asthma related quality of life improved in the immunotherapy group compared to the control group (p=0.03).

CONCLUSION

With the exception of asthma related quality of life, allergy immunotherapy was ineffective in improving asthma outcomes in this population of inner-city children < 4 years of age. These findings suggest that the effects of allergy immunotherapy depend on population specific factors and highlight the importance of precise predictors of immunotherapy efficacy.

4

Revolución en la ITA: tecnología VLP.

Bioengineering of Virus-like Particles for the Prevention or Treatment of Allergic Diseases.

Pechsrichuang P, Namwongnao S, Jacquet A

Allergy Asthma Immunol Res. 2021 Jan;13(1):23-41

ABSTRACT

Recent findings on the mechanism of allergen-specific immunotherapy (AIT) have revisited the role of immunoglobulin G (IgG) as the development of specific blocking IgG antibodies appeared critical for the successful suppression of T-helper 2 (Th2)-biased allergic responses. Consequently, any form of molecular AIT-promoting potent allergen-specific neutralizing antibodies would be preferred to conventional administration of allergen extracts. The potent immunogenicity of virus-like particles (VLPs) could be harnessed for that purpose. The particle size (20-200 nm) optimizes uptake by antigen-presenting cells as well as lymphatic trafficking. Moreover, the display of antigens in repetitive arrays promotes potent B cell activation for the development of sustained antibody responses. The presentation of self-antigens on the particle surface was even capable to break B cell tolerance. In this review, we describe the immunomodulatory properties of the 3 VLP-based strategies designed so far for the treatment of allergic disease: VLP packaged with CpG motifs as well as chimeric particles displaying pro-Th2/Th2 cytokines or allergens (full-length or B cell epitopes).

5

Crónica de los vacunados con venenos.

Long-term impact of hymenoptera venom immunotherapy on clinical course, immune parameters, and psychosocial aspects.

Adelmeyer J, Pickert J, Pfützner W, Möbs C

Allergol Select. 2021 Jan 26;5:57-66.

BACKGROUND

Venom immunotherapy (VIT) is highly efficient in subjects suffering from IgE-mediated allergy to hymenoptera venom (HV), and VIT results in substantial improvement of quality of life (QoL). However, VIT-induced tolerance may be lost over time after cessation of treatment, putting patients at risk of re-sting anaphylaxis.

MATERIALS AND METHODS

To study the effect of VIT on maintenance of HV tolerance we evaluated the natural history of 54 patients who were treated with VIT up to 29 years ago, with a special focus on re-stings and their subsequent course. Furthermore, we analyzed HV-specific IgE, IgG, and IgG4 antibody titers. Finally, we assessed the long-term impact of VIT on various psychosocial aspects like dealing with hymenoptera exposures, daily life activities, self-assurance, and personal environment.

RESULTS

29 (53.7%) subjects experienced at least one re-sting after stopping VIT, with 23 (79%) showing no systemic reaction (SR). Eleven of these (37.9%) took emergency drugs as a safety measurement. Six individuals (21%) showed loss of tolerance experiencing an anaphylactic reaction. No difference in HV-specific IgE, IgG4, or IgG antibody concentrations was noticed among the different patients. Subjects who tolerated a re-sting without applying emergency drugs felt least affected in their social-behavioral leisure activities when hymenoptera were around or by anxiety for new stings.

CONCLUSION

VIT leads to long-term tolerance in the majority of HV-allergic patients, however, ~ 1/5 may lose protection over time, arguing for continued follow-up on VIT-treated subjects and keeping them equipped with an emergency kit. Notably, VIT also results in a lasting, strong impact on self-assurance and sense of well-being in individuals who tolerated a re-sting without employing emergency drugs, which emphasizes the need to use them only in case of systemic symptoms after stopping successful VIT.

6

Ácaros y Alternaria: ¿mezclamos?

A preliminary study to investigate effectiveness of a mixed extract of Dermatophagoides sp. house dust mites and Alternaria sp. mold.

El-Qutob D, Raducan I, Mencia G

Eur Ann Allergy Clin Immunol. 2021 Jan 8. doi: 10.23822/EurAnnACI.1764-1489.185. Epub ahead of print.

BACKGROUND AND OBJECTIVES

Although the administration of single-allergen extracts is recommended, there are polysensitized patients who require a different strategy. This study evaluates the effectiveness of an extract containing a mixture of house dust mites (HDM) and mold allergens in polysensitized patients with asthma and/or rhinitis.

METHODS

Using validated questionnaires, we assessed asthma and rhinitis control and quality of life (QOL) of patients that received a combined immunotherapy of HDM and mold in routine clinical practice.

RESULTS

39 polysensitized patients with asthma and/or rhinitis were included. After 6 months of follow up, asthma control increased significantly from baseline and was maintained at 12 months. However, QOL of asthma patients did not change significantly from baseline to month 6 or 12, but at month 12, 57.9% of them improved their score and 5.3% maintained the same. On the other hand, QOL of 76.9% patients with rhinitis improved significantly at both 6 and 12 months.

CONCLUSIONS

In this preliminary study, the administration of immunotherapy based on the combination of allergens from HDM and mold, besides being effective, also allows an increase in the quality of life of patients with asthma and/or rhinitis.

7

Acelerando algunas pautas.

Accelerated Dose Escalation with 3 Injections of an Aluminum Hydroxide-Adsorbed Allergoid Preparation of 6 Grasses Is Safe for Children and Adolescents with Moderate to Severe Allergic Rhinitis.

Bovermann X, Ricklefs I, Vogelberg C, Klimek L, Kopp MV
Int Arch Allergy Immunol. 2021 Jan 27:1-11. doi: 10.1159/000512561. Epub ahead of print.

ABSTRACT

A high-dose, accelerated escalation schedule during subcutaneous allergen-specific immunotherapy (AIT) is safe and well-tolerated in adults. However, there are no data in children and adolescents. The aim of the present trial was to assess safety and tolerability of an accelerated dose escalation schedule of an AIT with a grass pollen allergoid in children and adolescents with moderate to severe seasonal rhinoconjunctivitis in a multicenter, open-label, randomized phase II trial. The dose escalation scheme for patients in the One Strength Group included 3 injections with 1 strength B (10,000 TU/mL), whereas the dose escalation scheme for the Standard group included 7 injections with 2 strengths A (1,000 TU/mL) and B (10,000 TU/mL) of an allergoid grass pollen preparation. Overall, n = 50 children (n = 25 in each group; mean age 8.9 + 1.54 years) and n = 37 adolescents (n = 20 and n = 17; 14.2 + 1.62 years) were randomized. For all patients, the mean treatment duration was 59.4 days in the One Strength group and 88.6 days in the Standard group. Treatment-emergent adverse events (TEAEs) related to AIT were reported in 52 and 40% in children and 35 and 35.3% in adolescents, respectively. Systemic allergic reactions occurred in about 5% of our patients and were reported in more patients of the One Strength group (6.7 vs. 2.4%). All systemic reactions were classified as WAO Grade 1. Accelerated high-dose escalation with an aluminum hydroxide-adsorbed grass pollen allergoid can be initiated with a safety and tolerability profile comparable to the standard dose escalation schedule in children and adolescents with allergic rhinitis with or without asthma.

8

El (complejo) manejo de la ITO en el día a día de la consulta.

Integrating oral immunotherapy into clinical practice.

Leonard SA, Laubach S, Wang J
J Allergy Clin Immunol. 2021 Jan;147(1):1-13.

ABSTRACT

In 2020, the first food allergy treatment, an oral immunotherapy (OIT) product for peanut allergy, was approved by the Food and Drug Administration, and a peanut epicutaneous immunotherapy patch was under review. As food allergy therapies become available and widespread, allergy offices will need to adjust practices to be able to offer their patients these new treatments. OIT is an intensive therapy that requires commitment from patients and their families, and open communication with the practice is paramount. OIT may not be the right therapy for every patient, and although identifying good candidates is still an area rich for research opportunity, experience from cohorts and clinical trials provides some insight. It is important to understand the scope of practice for each member of the OIT team based on state regulations for a particular location. Staffing and space will likely dictate how many patients at an individual office could be on active OIT at one time. Emergency medications, supplies, and protocols must be in place. Screening, scheduling, visit procedures, monitoring, home dosing, dose modifications, safety precautions, adverse reactions, and maintenance will be addressed in this article. Finally, adjunct therapies under investigation will be reviewed.

9

Un “porqué” inmunológico de la respuesta clínica a la ITA.

Induction of IL-10-producing type 2 innate lymphoid cells by allergen immunotherapy is associated with clinical response.

Golebski K, Layhadi JA, Sahiner U, Steveling-Klein EH, Lenormand MM, Li RCY et al
Immunity. 2021 Jan 7:S1074-7613(20)30541-0. doi: 10.1016/j.immuni.2020.12.013. Epub ahead of print.

BACKGROUND

The role of innate immune cells in allergen immunotherapy that confers immune tolerance to the sensitizing allergen is unclear. Here, we report a role of interleukin-10-producing type 2 innate lymphoid cells (IL-10+ ILC2s) in modulating grass-pollen allergy. We demonstrate that KLRG1+ but not KLRG1- ILC2 produced IL-10 upon activation with IL-33 and retinoic acid. These cells attenuated Th responses and maintained epithelial cell integrity. IL-10+ KLRG1+ ILC2s were lower in patients with grass-pollen allergy when compared to healthy subjects. In a prospective, double-blind, placebo-controlled trial, we demonstrated that the competence of ILC2 to produce IL-10 was restored in patients who received grass-pollen sublingual immunotherapy. The underpinning mechanisms were associated with the modification of retinol metabolic pathway, cytokine-cytokine receptor interaction, and JAK-STAT signaling pathways in the ILCs. Altogether, our findings underscore the contribution of IL-10+ ILC2s in the disease-modifying effect by allergen immunotherapy.

10

La necesidad de romper el círculo vicioso.

House dust mites-driven allergic rhinitis: could its natural history be modified?

Ciprandi G, Tosca MA
Expert Rev Clin Immunol. 2021 Jan 31:1-6. doi: 10.1080/1744666X.2021.1879642. Epub ahead of print.

INTRODUCTION

Allergic rhinitis (AR) is the most common IgE-mediated disease. House dust mites (HDMs)-sensitization is the main cause of AR. HDM-driven AR is characterized by a typical natural history consisting of possible progression to asthma. Allergen Immunotherapy (AIT) is, at present, a unique treatment to modify the natural history of allergic diseases. Tablets AIT (TAIT) represents a new era in AIT. There is evidence that TAIT could prevent asthma in AR patients.

AREAS COVERED

The literature search methodology was based on the articles cited by PubMed from 1980 to 2020. AIT's rationale is to restore an immunological and, consequently, clinical tolerance toward the causal allergen. The progression from rhinitis to asthma may be influenced by a relevant risk factor, such as the persistent type 2 inflammation of airways. HDMs are perennial allergens and allergen exposure is the condicio sine qua non to maintain inflammation. AIT could modify the progression toward asthma restoring physiologic immune response to the causal allergen and consequently dampening type 2 inflammation.

EXPERT OPINION

Patients with HDM-driven AR are susceptible to develop asthma over time. Many studies explored this topic. Cross-sectional and longitudinal studies identified some markers which predict the risk of developing asthma. They include bronchial airflow limitation, bronchial hyperresponsiveness, type 2 inflammation, and rhinitis duration. TAIT could block this progression by acting on this vicious circle. Future studies should explore this issue using adequate methodology.

1

Eficaz en el matraz y efectivo “en vivo”.

Allergen immunotherapy: the growing role of observational and randomised trial “Real-World Evidence”.

Paoletti G, DiBona D, Chu DK, Firinu D, Heffler E, Agache I et al
Allergy. 2021 Feb 14. doi: 10.1111/all.14773. Epub ahead of print.

ARTÍCULO DESTACADO

ABSTRACT

Although there is a considerable body of knowledge about allergen immunotherapy (AIT), there is a lack of data on the reliability of real-world evidence (RWE) in AIT and consequently, a lack of information on how AIT effectively works in real life. To address the current unmet need for an appraisal of the quality of RWE in AIT, the European Academy of Allergy and Clinical Immunology Methodology Committee recently initiated a systematic review of observational studies of AIT, which will usethe RELEVANT tool and the Grading of Recommendations Assessment, Development and Evaluation approach (GRADE) to rate the quality of the evidence base as a whole. The next step will be to develop a broadly applicable, pragmatic “real-world” database using systematic data collection.Based on the current RWE base,and perspectives and recommendations of authorities and scientific societies, a hierarchy of RWE in AIT is proposed, which places pragmatic trials and registry data at the positions of highest level of evidence. There is a need to establish more AIT registries that collect data in a cohesive way, using standardised protocols. This will provide an essential source of real-world data that can be easily shared, promoting evidence-based research and quality improvement in study design and clinical decision-making.

2

Coste-efectividad de la ITA: magnitud y alcance.

Pharmacoeconomics of allergy immunotherapy versus pharmacotherapy.

Cox L
Expert Rev Clin Immunol. 2021 Feb 28:1-13. doi: 10.1080/1744666X.2021.1886079. Epub ahead of print.

INTRODUCTION

The purpose of this review is to evaluate the cost-effectiveness of allergy immunotherapy (AIT) in the treatment of allergic rhinitis, asthma, and other allergic conditions.

AREAS COVERED

An extensive search of the PubMed and Medline database (January 1996 up to June of 2020) was conducted using the search terms allergy immunotherapy, pharmacoeconomics, cost-effectiveness, allergic rhinitis, and asthma. Studies were included if they included information on the economics of AIT in comparison to pharmacotherapy in the treatment of allergic rhinitis or asthma either as actual costs or based on theoretical models. Systematic reviews were included if they included information about the cost-effectiveness of AIT.Most clinical trials found significant cost-savings with AIT. The cost-effective time-point ranged from a few months to several years after treatment initiation.. Cost savings were demonstrated as early as 3 months after treatment initiation and were as great as 80% less than SDT in some studies.

EXPERT OPINION

There is strong evidence in the collective literature that AIT is cost-effective as compared to SDT alone. The magnitude of AIT’s cost-effectiveness is likely underestimated because most of the studies considered during treatment costs and not AIT’s long-term benefits or preventive/prophylactic effects or its impact on co-morbid conditions.

3

Biomarcadores y eficacia: ¿novedades?

Changes in Immunologic Indicators During Allergen-Specific Immunotherapy for Allergic Rhinitis and Determinants of Variability: A Systematic Review and Meta-analysis of Randomized Controlled Trials.

Jiang Z, Xiao H, Liu S, Meng J
Am J Rhinol Allergy. 2021 Feb 25:1945892421999649. doi: 10.1177/1945892421999649.

BACKGROUND

To date, there are no generally recognized biomarkers for allergen immunotherapy (AIT) and even the changes in immunological indicators during AIT are inconsistent in different publications.

OBJECTIVE

This study was conducted to quantify the immunological changes that occur during AIT and identify the determinants of heterogeneity.

METHODS

Randomized controlled trials of AIT published in the past 10 years were searched in Medline, Embase and Cochrane CENTRAL. Data on immunological indicators were extracted, and the characteristics of the included studies were collected. Meta-analysis and meta-regression were conducted for each indicator. The study was registered on the PROSPERO website (CRD42020176127).

RESULTS

We reviewed 1898 studies. Forty-six studies met the inclusion criteria, and 31 studies were included in the quantitative analyses. Subset analyses by time demonstrated that serum allergen-specific IgE (sIgE) of AIT patients increased in the first 12 months, then decreased and became slightly lower than that of control patients. Allergen-specific IgG4 (sIgG4) was elevated in the AIT group during and after treatment. IgE-blocking factor (IgE-BF) was increased and IgE-facilitated allergen binding (IgE-FAB) was reduced in AIT patients. Both of them of the 2 factors were associated with clinical efficacy in the multivariate regression analysis. sIgE/sIgG4 decreased in AIT patients, while there was no change in total IgE.

CONCLUSION

The levels of serum sIgE and sIgG4 during AIT showed a time-dependent pattern. IgE-BF and IgE-FAB should be further investigated as biomarkers for predicting and monitoring AIT efficacy.

4

Mejorando el arsenal terapéutico del alergólogo.

Peptide allergen-specific immunotherapy for allergic airway diseases-State of the art.

Wraith DC, Krishna MT

Clin Exp Allergy. 2021 Feb 2. doi: 10.1111/cea.13840. Epub ahead of print.

ABSTRACT

Allergen-specific immunotherapy (AIT) is the only means of altering the natural immunological course of allergic diseases and achieving long-term remission. Pharmacological measures are able to suppress the immune response and/or ameliorate the symptoms but there is a risk of relapse soon after these measures are withdrawn. Current AIT approaches depend on the administration of intact allergens, often comprising crude extracts of the allergen. We propose that the challenges arising from current approaches, including the risk of serious side-effects, burdensome duration of treatment, poor compliance and high cost, are overcome by application of peptides based on CD4+ T cell epitopes rather than whole allergens. Here we describe evolving approaches, summarize clinical trials involving peptide AIT in allergic rhinitis and asthma, discuss the putative mechanisms involved in their action, address gaps in evidence and propose future directions for research and clinical development.

5

ITA con panalérgenos: ¿sí o no?

Pru p 3 Sublingual Immunotherapy in Patients with Lipid Transfer Protein Syndrome: Is It Worth?

Beitia JM, Vega Castro A, Cárdenas R, Peña-Arellano MI

Int Arch Allergy Immunol. 2021 Feb 15:1-8. doi: 10.1159/000512613. Epub ahead of print.

BACKGROUND

Lipid transfer proteins (LTPs) syndrome is an important cause of multiple plant food allergy in the Mediterranean area. The effectiveness of sublingual immunotherapy (SLIT) with the LTP Pru p 3 extract has been little investigated in the real-world setting. This study aimed to investigate the outcome of Pru p 3 SLIT in real-life patients with LTP syndrome with/without concurrent reactions to peanut and/or nuts.

METHODS

This was a prospective real-life study including all patients diagnosed with LTP allergy and treated with Pru p 3 SLIT between 2011 and 2018 in a tertiary hospital in Spain. Patients underwent open oral food challenge (OFC) tests for unpeeled peach and nuts/peanuts 1 year after the treatment started to assess food tolerance. A control group of patients diagnosed with LTP allergy who refused treatment with immunotherapy were included. Severity of symptoms and diet avoidance was recorded in both groups.

RESULTS

Twenty-nine patients with a median age of 24.7 years (range 5.5-43.1) were included: 100% were allergic to fruit; 72%, to peanut and/or nuts; 19 had a history of severe systemic reactions. Seven patients discontinued therapy; 3 (10%), due to adverse events. One year after SLIT start, 16 (73%) patients had negative OFC to peach; 95%, after 2 years; 69% had negative OFC to nuts/peanuts. The control group included 13 patients: 53.8% experienced reactions with new foods; severity of symptoms increased significantly ($p < 0.001$), and diet restrictions were maintained in this group.

CONCLUSION

SLIT with Pru p 3 shows a good safety profile, and avoid dietary restrictions in patients with LTP syndrome treated in the real-life setting.

6

Las preguntas de moda en ITA y asma.

Recent Advances in Allergen-Specific Immunotherapy as Treatment for Allergic Asthma: A Practical Overview.

Tabar AI, Delgado J, González-Mancebo E, Arroabarren E, Soto Retes L, Domínguez-Ortega J, Spanish Allergy and Clinical Immunology Scientific Society (SEAIC)

Int Arch Allergy Immunol. 2021 Feb 25:1-19. doi: 10.1159/000513811.

ABSTRACT

The Global Initiative for Asthma Report updated in 2019 stated that potential benefits of allergen immunotherapy (AIT), compared to pharmacological and avoidance options, must be weighed against the risk of adverse effects and the inconvenience and cost of the prolonged course of therapy in asthma. Thus, with the aim of clarifying some aspects with regard to the possible use of AIT in allergic asthma treatment armamentarium, a group of expert allergists from the Spanish Allergy and Clinical Immunology Scientific Society (SEAIC), particularly from the Immunotherapy and Asthma Interest Groups developed a frequently asked questions in clinical practice. This document updates relevant topics on the use of AIT in asthma and could facilitate physician clinical decisions and improve health outcomes for individual patients.

7

Leche, harinas y ejercicio.

Exercise-induced allergic reactions after achievement of desensitization to cow's milk and wheat.

Kubota S, Kitamura K, Matsui T, Takasato Y, Sugiura S, Ito K

Pediatr Allergy Immunol. 2021 Feb 19. doi: 10.1111/pai.13479. Epub ahead of print.

BACKGROUND

We have previously reported that more than half of the patients who achieved desensitization after wheat rush oral immunotherapy (OIT) developed exercise-induced allergic reaction on desensitization (EIARD). However, data on EIARDs after slow OIT are lacking. Therefore, this study aimed to investigate the results of exercise provocation tests (EPTs) in patients after slow OIT for cow's milk and wheat allergies.

METHODS

This was a retrospective chart review of 87 EPTs in 74 patients. The EPTs were performed in patients who were desensitized to at least 6,600 mg cow's milk protein or 5,200 mg wheat protein with slow OIT and were identified to be at a high risk of EIARDs. EPTs were performed after ingestion of the maximum desensitization dose. The patients' clinical characteristics and symptoms were analyzed.

RESULTS

The EPT results were positive for cow's milk in 49% (21/43) of the patients and for wheat in 48% (15/31) of the patients. There was no significant difference in the clinical characteristics between the EIARD-positive and EIARD-negative groups. The specific IgE (sIgE) levels before OIT and the reduction rates of sIgE before and after OIT did not correlate with the outcomes of the EPTs. Among the EIARD-positive patients, 13 patients (cow's milk, n=7; wheat, n=6) underwent a second EPT, and the EIARD disappeared in 8 patients (cow's milk, n=4; wheat, n=4).

CONCLUSION

EIARDs were observed after slow OIT for cow's milk and wheat. Further research into the predictive factors of EIARDs in these patients is needed to understand its clinical manifestations.

8

Lo último en mediadores antiinflamatorios locales.

Allergen-specific immunotherapy induces the suppressive secretoglobin 1A1 in cells of the lower airways.

Zissler UM, Jakwerth CA, Guerth F, Lewitan L, Rothkirch S, Davidovic M

Allergy. 2021 Feb 2. doi: 10.1111/all.14756. Epub ahead of print.

BACKGROUND

While several systemic immunomodulatory effects of allergen-specific immunotherapy (AIT) have been discovered, local anti-inflammatory mechanisms in the respiratory tract are largely unknown. We sought to elucidate local and epithelial mechanisms underlying allergen-specific immunotherapy in a genome-wideapproach.

METHODS

We induced sputum in hayfever patients and healthy controls during the pollen peak season and stratified patients by effective allergen-immunotherapy or as untreated. Sputum was directly processed after induction and subjected to whole transcriptome RNA microarray analysis. Nasal secretions were analyzed for Secretoglobin1A1(SCGB1A1) and IL-24 protein levels in an additional validation cohort at three defined time points during the three-year course of AIT. Subsequently, RNA was extracted and subjected to an array-based whole transcriptome analysis.

RESULTS

AIT inhibited pro-inflammatory CXCL8, IL24 and CCL26mRNA expression, while SCGB1A1, IL7, CCL5, CCL23 and WNT5BmRNAs were induced independently of the asthma status and allergen season. In our validation cohort, local increase of SCGB1A1 occurred concomitantly with the reduction of local IL-24 in upper airways during the course of AIT. Additionally, SCGB1A1 was identified as a suppressor of epithelial gene expression.

CONCLUSION

AIT induces a yet unknown local gene expression footprint in the lower airwaysthat on one hand appears to be a result of multiple regulatory pathways and on the other hand reveals SCGB1A1 as novel anti-inflammatory mediator of long-term allergen specific therapeutic intervention in the local environment.

9

La nanotecnología al rescate.

Role of nanostructures in allergy: diagnostics, treatments,and safety.

Mayorga C, Perez-Inestrosa E, Rojo J, Ferrer M, Montañez MI

Allergy. 2021 Feb 9. doi: 10.1111/all.14764. Epub ahead of print.

BACKGROUND

Nanotechnology is science, engineering, and technology conducted at the nanoscale, which is about 1 to 100 nanometers. It has led to the development of nanomaterials, which behave very differently from materials with larger scales and can have a wide range of applications in biomedicine. The physical and chemical properties of materials of such small compounds depend mainly on the size, shape, composition, and functionalisation of the system. Nanoparticles, carbon nanotubes, liposomes, polymers, dendrimers, nanogels, among others, can be nanoengineeried for controlling all parameters, including their functionalisation with ligands, which provide the desired interaction with the immunological system, i.e. dendritic cell receptors to activate and/or modulate the response, as well as specific IgE, or effector cell receptors. However, undesired issues related to toxicity and hypersensitivity responses can also happen and would need evaluation. There are wide panels of accessible structures, and controlling their physico-chemical properties would permit obtaining safer and more efficient compounds for clinical applications goals, either in diagnosis or treatment.The application of dendrimericantigens, nanoallergens and nanoparticles in allergy diagnosis is very promising since it can improve sensitivity by increasing specific IgE binding, mimicking carrier proteins, or enhancing signal detection. Additionally, in the case of immunotherapy, glycodendrimers, liposomes, polymers, and nanoparticles have shown interest,behaving as platforms of allergenic structures, adjuvants or protectors of allergen from degradation or having a depot capacity.Taken together, the application of nanotechnology to allergy shows promising facts facing important goals related to the improvement of diagnosis as well as specific immunotherapy.

10

Hablemos de seguridad en niños.

Subcutaneous Allergen-Specific Immunotherapy Is Safe in Pediatric Patients with Allergic Rhinitis.

F Pavon-Romero, DE Larenas-Linnemann, K Eloisa Xochipa Ruiz , F Ramirez-Jimenez, LM Teran

Int Arch Allergy Immunol. 2021 Feb 19;1-9. doi: 10.1159/000513158.

INTRODUCTION

Subcutaneous allergen-specific immunotherapy (SCIT) is one of the main cornerstones in the treatment of allergic rhinitis in pediatric patients. It has demonstrated symptoms and quality of life improvement, but it is not exempt from adverse reactions (ADVrs). Nevertheless, there are a few reports that have evaluated their safety. Our objective was to evaluate the ADVr to SCIT in pediatric patients.

METHODS

We reviewed 786 clinical records with SCIT from 2005 to 2018, comparing the clinical characteristics of patients with ADVrs with SCIT versus a group of a similar number of patients who completed SCIT (control group, CG). The analysis of ADVrs was according to the World Allergy Organization (WAO) 2010 grading system by frequency analysis, survival curve, and log rank.

RESULTS

Of 786 patients, 106 (13.4%) presented ADVrs, and the patients with ADVr had sensitivity and immunotherapy with at least 2 allergens versus CG $p < 0.001$, containing a combination of standardized and nonstandardized allergens ($p = 0.003$). The ADVrs were in the buildup phase ($p < 0.001$). The survival curve showed that 50% had some reaction at 12 weeks of SCIT. The most frequent ADVr was grade 1 in 73/106 patients (68.8%) and grade 2 in 33/106 (31.1%). The log-rank analysis between the grades of the WAO grading system showed a statistically significant difference ($p = 0.02$).

CONCLUSION

The SCIT is safe in pediatric patients. The ADVrs are infrequent, grade 1 being the most reported; however, at >12 weeks, the risk of ADVrs that involve 2 organs systems increases.

1

El (gran) poder del efecto placebo

Placebo effects in allergen immunotherapy-An EAACI Task Force Position Paper

Pfaar O, Agache I, Bergmann KC, Bindslev-Jensen C, Bousquet J, Creticos PS, et al.

Allergy. 2021 Mar;76(3):629-47

ARTÍCULO DESTACADO

ABSTRACT

The placebo (Latin "I will please") effect commonly occurs in clinical trials. The psychological and physiological factors associated with patients' expectations about a treatment's positive and negative effects have yet to be well characterized, although a functional prefrontal cortex and intense bidirectional communication between the central nervous system and the immune system appear to be prerequisites for a placebo effect. The use of placebo raises certain ethical issues, especially if patients in a placebo group are denied an effective treatment for a long period of time. The placebo effect appears to be relatively large (up to 77%, relative to pretreatment scores) in controlled clinical trials of allergen immunotherapy (AIT), such as the pivotal, double-blind, placebo-controlled (DBPC) randomized clinical trials currently required by regulatory authorities worldwide. The European Academy of Allergy and Clinical Immunology (EAACI) therefore initiated a Task Force, in order to better understand the placebo effect in AIT and its specific role in comorbidities, blinding issues, adherence, measurement time points, variability and the natural course of the disease. In this Position Paper, the EAACI Task Force highlights several important topics regarding the placebo effect in AIT such as a) regulatory aspects, b) neuroimmunological and psychological mechanisms, c) placebo effect sizes in AIT trials, d) methodological limitations in AIT trial design and e) potential solutions in future AIT trial design. In conclusion, this Position Paper aims to examine the methodological problem of placebo in AIT from different aspects and also to highlight unmet needs and possible solutions for future trials.

2

La alergia al gato vislumbra un nuevo aliado terapéutico

Passive Prophylactic Administration with a Single Dose of Anti-Fel d 1 Monoclonal Antibodies REGN1908-1909 in Cat Allergen-Induced Allergic Rhinitis: A Randomized, Double-blind, Placebo Controlled Trial

Shamji MH, Singh I, Layhadi JA, Ito C, Karamani A, Kouser L, et al.

Am J Respir Crit Care Med. 2021 Mar 2. doi: 10.1164/rccm.202011-4107OC. Epub ahead of print.

RATIONALE

Sensitization to Felis domesticus allergen 1 (Fel d 1) contributes to persistent allergic rhinitis and asthma. Existing treatment options for cat allergy, including allergen immunotherapy (AIT) are only moderately effective, and AIT has limited use due to safety concerns.

OBJECTIVES

To explore the relationship among the pharmaokinteic, clinical, and immunological effects of REGN1908-1909 (anti-Fel d 1 monoclonal antibodies) in patients after treatment.

METHODS

Patients received REGN1908-1909 (n=36) or placebo (n=37) in a phase 1b study. Fel d 1-induced basophil and IgE-facilitated allergen binding responses were evaluated at baseline and days 8, 29 and 85. Cytokine and chemokine levels in nasal fluids were measured. REGN1908-1909 inhibition of allergen-IgE binding in patient serum was evaluated.

MEASUREMENTS AND MAIN RESULTS

Peak serum drug concentrations were concordant with maximal observed clinical response. The anti-Fel d 1 IgE/cat-dander IgE ratio in pretreatment serum correlated with Total Nasal Symptom Score improvement. The allergen neutralizing capacity of REGN1908-1909 was observed in serum and nasal fluid, and was detected in an inhibition assay. Type-2 cytokines (IL-4, IL-5 and IL-13) and chemokines (CCL17/TARC, CCL5/RANTES) in nasal fluid were inhibited in REGN1908-1909-treated patients compared to placebo (all $P < 0.05$); IL-13 and IL-5 levels correlated with TNSS improvement. Ex vivo assays demonstrated that REGN1908 and REGN1909 combined was more potent than each alone for inhibiting FcεRI- and FcεRII (CD23)-mediated allergic responses and subsequent T-cell activation.

CONCLUSION

Single passive dose administration of Fel d 1-neutralizing IgG antibodies improved nasal symptoms in cat-allergic patients, and was underscored by suppression of FcεRI-, FcεRII- and Th2-mediated allergic responses.

3

ITA como prevención de asma: ventana de oportunidad

Preventive Effect of Allergen Immunotherapy on Asthma and New Sensitizations

Gradman J, Halken S

J Allergy Clin Immunol Pract. 2021 Mar 18:S2213-2198(21)00314-7. doi: 10.1016/j.jaip.2021.03.010. Epub ahead of print

ABSTRACT

Allergen immunotherapy (AIT) is a disease-modifying treatment for some IgE-mediated allergic diseases with the potential to have important preventive effects. Children with allergic rhinitis have a high risk of developing asthma, and treating allergic rhinitis with AIT may interfere with disease progression and prevent onset of asthma. Although the evidence is limited due to relatively few and heterogeneous studies, data nevertheless suggest that AIT has a preventive effect on development of asthma especially in children with rhinitis due to grass pollen allergy. AIT may also affect the development of new sensitizations. Both the degree of sensitization and the specific sensitization pattern may influence future disease severity and development of comorbidities. Hitherto, the indication for AIT for prevention of development of asthma in grass/birch pollen allergic children has been the same as for treatment of allergic rhinitis. Probably, AIT should be applied in the early stage of the allergic disease to have the greatest preventive effect on disease progression. Consequently, in the future, the potential preventive effects should influence the timing of initiating AIT. The window of opportunity to prevent asthma may primarily exist in young children with mild symptoms and a low degree of sensitization.

4

Los alérgicos a las LTPs no lo tienen (nada) fácil

European Academy of Allergy & Clinical Immunology (EAACI) Task Force: Non-specific Lipid Transfer Protein Allergy Across Europe. The diagnosis and management of allergic reactions in patients sensitized to non-specific lipid transfer proteins.

Skypala IJ, Bartra J, Ebo DG, Antje Faber M, Fernández-Rivas M, Gomez F, et al

Allergy. 2021 Mar 2. doi: 10.1111/all.14797. Epub ahead of print.

ABSTRACT

Sensitization to one or more non-specific lipid transfer proteins (nsLTPs), initially thought to exist mainly in southern Europe, is becoming accepted as a cause of allergic reactions to plant foods across Europe and beyond. The peach nsLTP allergen Pru p 3 is a dominant sensitizing allergen and peaches a common food trigger, although multiple foods can be involved. A frequent feature of reactions is the requirement for a cofactor (exercise, alcohol, non-steroidal anti-inflammatory drugs, Cannabis sativa) to be present for a food to elicit a reaction. The variability in the food and cofactor triggers makes it essential to include an allergy-focused diet and clinical history in the diagnostic workup. Testing on suspected food triggers should also establish whether sensitization to nsLTP is present, using purified or recombinant nsLTP allergens such as Pru p 3. The avoidance of known trigger foods and advice on cofactors is currently the main management for this condition. Studies on immunotherapy are promising, but it is unknown whether such treatments will be useful in populations where Pru p 3 is not the primary sensitizing allergen. Future research should focus on the mechanisms of cofactors, improving diagnostic accuracy and establishing the efficacy of immunotherapy.

5

El papel de las nuevas tecnologías en el mundo de la alergia

The role of mobile health technologies in stratifying patients for AIT and its cessation. The ARIA-EAACI perspective.

Bousquet J, Jutel M, Pfaar O, Fonseca JA, Agache I, Czarlewski W, et al.

J Allergy Clin Immunol Pract. 2021 Mar 1:S2213-2198(21)00240-3. doi: 10.1016/j.jaip.2021.02.035. Epub ahead of print.

ABSTRACT

Allergen immunotherapy (AIT) is a proven therapeutic option for the treatment of allergic rhinitis and/or asthma. Many international or national practice guidelines have been produced, but the evidence-based method varies and they do not usually propose care pathways. The present paper considers the possible role of mHealth in AIT for allergic rhinitis/asthma. There are no currently available validated biologic biomarkers that can predict AIT success, and mHealth biomarkers have some relevance. In the current paper, the following aspects will be discussed: patient stratification for AIT, symptom medication scores for the follow-up of patients, clinical trials as well as the approach of the European Academy of Allergy and Clinical Immunology.

6

Biomarcadores en ITA: el tema de moda

Immunological Responses and Biomarkers for Allergen-Specific Immunotherapy Against Inhaled Allergens.

Shamji MH, Layhadi JA, Sharif H, Penagos M, Durham SR

Allergy Clin Immunol Pract. 2021 Mar 26:S2213-2198(21)00363-9. doi: 10.1016/j.jaip.2021.03.029. Epub ahead of print.

ABSTRACT

Long-term efficacy that occurs with allergen immunotherapy of proven value is associated with decreases in IgE-dependent activation of mast cells and tissue eosinophilia. This suppression of type 2 immunity is accompanied by early induction of regulatory T cells, immune deviation in favor of TH1 responses, and induction of local and systemic IgG, IgG4, and IgA antibodies. These "protective" antibodies can inhibit allergen-IgE complex formation and consequent mast cell triggering and IgE-facilitated TH2-cell activation. Recent studies have highlighted the importance of innate responses mediated by type 2 dendritic cells and innate lymphoid cells in allergic inflammation. These cell types are under the regulation of cytokines such as thymic stromal lymphopoietin and IL-33 derived from the respiratory epithelium. Novel subsets of regulatory cells induced by immunotherapy include IL-35-producing regulatory T cells, regulatory B cells, a subset of T follicular cells (TFR cells), and IL-10-producing group 2 innate lymphoid cells. These mechanisms point to biomarkers that require testing for their ability to predict clinical response to immunotherapy and to inform novel approaches for better efficacy, safety, and long-term tolerance.

7

Dermatitis atópica y alergia a ácaros: ¿ITA sí?

Analysis of the long-term efficacy and safety of subcutaneous immunotherapy for atopic dermatitis.

Zhou J, Chen S, Song Z

Allergy Asthma Proc. 2021 Mar 1;42(2):e47-e54

INTRODUCTION

Atopic dermatitis (AD) is a chronic and relapsing inflammatory skin disease characterized by severe pruritus and eczematous skin lesions. Subcutaneous immunotherapy (SCIT) refers to repeated contact with gradually increasing doses of allergen extracts, which improve patient tolerance to such allergens and controls, or reduces allergic symptoms. This study aimed to explore the long-term efficacy and safety of SCIT for patients with AD sensitized to house-dust mite (HDM).

METHODS

We conducted a retrospective analysis of 378 patients with HDM-sensitized AD. Among these patients, 164 received SCIT plus pharmacotherapy for 3 years (SCIT group) and the other 214 patients received only pharmacotherapy (non-SCIT group). The scoring atopic dermatitis (SCORAD) and pruritus visual analog scale (VAS) scores, laboratory test results, and adverse effects were recorded.

RESULTS

The SCORAD and pruritus VAS scores significantly decreased in the SCIT group. Also, the SCIT group showed higher reduction ratios of SCORAD and pruritus VAS scores than those observed in the non-SCIT group at 3 years after treatment initiation. The risk of development of new sensitization was higher in the non-SCIT group than in the SCIT group (relative risk 1.92 [95% confidence interval {CI}, 1.30-2.85]; $p < 0.05$). The eosinophil count of the participants significantly differed in the complete response (CR) group ($p < 0.05$) but not in the non-CR group ($p = 0.098$). However, the serum total immunoglobulin E value was not significantly reduced ($p = 0.204$). Of 8421 injections given to the patients, 231 injections (2.74%) showed adverse effects during the treatment period.

CONCLUSION

Three years of SCIT can significantly reduce the severity and pruritus of moderate-to-severe AD with HDM sensitization. Patients who are multisensitized can also benefit from HDM SCIT. Patients can achieve long-term effects, such as prevention of neoallergen sensitization and inhibition of the allergy march.

8

ITA subcutánea: cada vez, más segura

Risk factors for fatal and nonfatal reactions to immunotherapy (2008-2018): post-injection monitoring and severe asthma.

Epstein TG, Murphy-Berendts K, Liss GM, Bernstein DI

Ann Allergy Asthma Immunol. 2021 Mar 19:S1081-1206(21)00187-3. doi: 10.1016/j.anai.2021.03.011. Epub ahead of print.

BACKGROUND

Subcutaneous allergen immunotherapy (SCIT) is highly effective but risks exist.

OBJECTIVE

Identify practices that influence systemic allergic reactions (SRs) to SCIT, and SCIT-associated infections.

METHODS

ACAAI/AAAAI members completed an annual survey of SCIT-related SRs of varying severity (2008-2018). Injection-related infections were queried (2014-2018). Strategies to enforce post-injection waiting times, and to reduce risks from asthma/severe asthma were queried (2016-2018).

RESULTS

Data were gathered on 64.5 million injection visits. Ten confirmed fatalities occurred since 2008, including 3 new fatalities since 2017. One fatal reaction occurred per 7.2 million injection visits (2008-2018). No infections occurred. Practices that tracked the time after injections, and required checking out with office personnel, had significantly lower total ($p<0.0001$), Grade 3 (severe) ($p<0.0008$) and Grade 4 (very severe) SRs ($p<0.0001$). Having more asthmatics on SCIT was associated with more Grade 3 SRs ($p<0.02$). Not prescribing SCIT in uncontrolled asthmatics was associated with fewer Grade 3 SRs ($p=0.02$). Having more severe asthmatics on SCIT was associated with more total, Grade 1, and Grade 2 SRs ($p<0.0001$); 50% of Grade 3 and 4 SRs occurred in severe asthmatics.

CONCLUSION

SCIT- related fatalities have declined since 2008, with a slight increase in recent years. SCIT is not associated with an increased risk of infections. Tracking the time after injections and checking out with office staff confers significantly lower risks of severe SRs. Asthma, and especially severe asthma, are major risk factors for severe and fatal SRs. Strategies that reduce risks for asthmatics, such as not prescribing SCIT to uncontrolled asthmatics, may lower risks.

9

ITA sublingual con Bet v 1 como alérgeno de referencia: ¿qué pasa con sus homólogos?

IgE-cross-blocking antibodies to Fagales following sublingual immunotherapy with recombinant Bet v 1.

Grilo J, Kitzmüller C, Aglas L, Sánchez Acosta G, Vollmann U, et al

Allergy. 2021 Mar 16. doi: 10.1111/all.14817. Epub ahead of print

BACKGROUND

Evidence has accumulated that birch pollen immunotherapy reduces rhinoconjunctivitis to pollen of birch-homologous trees. Therapeutic efficacy has been associated with IgE-blocking IgG antibodies. We have recently shown that sera collected after sixteen weeks of sublingual immunotherapy with recombinant Bet v 1 (rBet v 1-SLIT)display strongIgE-blocking bioactivity for Bet v 1. Here, we assessedwhetherrBet v 1-SLIT-induced IgG antibodiesdisplay cross-blocking activity to related allergensin Fagalespollen.

METHODS

IgE, IgG1 and IgG4 reactivity to recombinantBet v 1, Aln g 1, Car b 1, Ost c 1, Cor a 1, Fag s 1, Cas s 1, and Que a 1 were assessed in pre- and post-SLIT samplesof 17 individuals by ELISA. A basophil inhibition assay using stripped basophils re-sensitized with a serum pool containing high Bet v 1-specific IgElevels was established and used to assess CD63 expression in response toallergens after incubation with pre-SLIT or post-SLIT samples.IgG1 and IgG4 wasdepleted from post-SLIT samples to assess its contribution toIgE-cross-blocking.

RESULTS

rBet v 1-SLIT boostedcross-reactive IgE antibodies and induced IgG1 and IgG4 antibodieswith inter- and intra-individuallydiffering reactivity tothe homologs. Highly variablecross-blocking activitiesof post-SLIT samples to the different allergens werefound. IgG1 and IgG4 antibodies displayed cross-blocking activity with individual variance.

CONCLUSIONS

Our mechanistic approach suggested that immunotherapy with the reference allergen Bet v 1 induces individual repertoires of cross-reactive IgG1 and IgG4 antibodies. The cross-blocking bioactivity of these antibodies was also highly variable and neither predictable from protein homology nor IgE-cross-reactivity.

10

Rinitis alérgica, ITA y ahorro de costes

Real-word evidence costs of allergic rhinitis and allergy immunotherapy in the commercially insured United States population.

Joseph P Tkacz, Karen Rance, Douglas Waddell, Mark Aagren, Eva Hammerby

Curr Med Res Opin. 2021 Apr 2;1-15. doi: 10.1080/03007995.2021.1903848. Online ahead of print.

OBJECTIVE

To assess total and allergic rhinitis (AR)-related helthcare cost among AR patients residing in the United States with a focus on patients persisting wiht AIT.

METHODS

AR patients were identified in the IBM MarketScan database between 1 January 2014 to 31 March 2017. Patients receiving allergy immunotherapy (AIT) were identified with relevant billing codes (earliest AIT claim = index date); non-AIT patients were identified with claims containing a diagnosis code for AR (earliest AR claim = index date). AIT patients reaching 25+ injection claims were analyzed as a separate maintenance cohort. All patients were required to have continuous enrollment for 12 months preceding and following index.

RESULTS

A total of 2,334,530 AR patients were included; 103,207 had at least 1 AIT claim, with 45,279 (43.9%) of these patients reaching maintenance, and 24,640 AIT patients (23.9%) never presenting a single injection claim. Compared to non-AIT patients, patients initiating AIT presented higher rates of baseline comorbidities, including asthma (30.1% vs. 7.5%) and conjunctivitis (21.7% vs. 4.4%). During the follow-up period, patients reaching the maintenance phase of AIT incurred lower total costs than the overall AIT cohort ($10,431±$16,606 vs. $11,612±$24,797), and also presented lower follow-up hospitalization costs ($698±$7,248 vs. $1,281±$12,991) and total medical costs ($7950±$13,844 vs. $8989±$22,019).

CONCLUSIONS

Continued efforts are needed to increase patient awareness of available options and adherence to AIT, along with reducing wastage. Despite AIT patients presenting fairly progressed disease at the time of treatment initiation, this therapy remains an economical treatment option, as it was not accompanied by substantial increases in overall healthcare expenditure, and may promote positive societal impacts beyond the direct medical costs.What is known on this topicThe prevalence of allergic diseases has increased over the past 50 years and affects between 10-30% of the world population.Allergic rhinitis (AR) poses a significant economic burden in the form of both direct and indirect costsAllergy immunotherapy (AIT) is the only treatment option able to modify the underlying course of the disease.What this study addsSpecific all-cause and AR-related healthcare costs decreased following the initiation of AIT among patients diagnosed with AR, with the largest decreases observed among AIT patients reaching the maintenance phase of treatment, while non-AIT patients showed increases in all categories assessed over a similar follow-up period.Cost decreases among AIT patients were observed despite increased levels of comorbidities compared to non-AIT patients, as the AIT cohort presented elevated rates of atopic dermatitis (7.1% vs. 2.7%), conjunctivitis (21.7% vs. 4.4%), asthma (30.1% vs. 7.5%), and chronic sinusitis (22.6% vs. 4.9%).An analysis of patients' index subcutaneous AIT consultation revealed substantial variability in the initial treatment costs, with nearly 20% of paid amounts exceeding $1,000; given nearly 1 in 4 AIT patients who get AIT mixed never came back for their first injection, this highlights an opportunity to target frontloaded billing practices and the timing of mixing/injection as an area to minimize healthcare waste.

1

La clave está en la IgA

Differential Induction of Allergen-specific IgA Responses following Timothy Grass Subcutaneous and Sublingual Immunotherapy.

Shamji MH, Larson D, Eifan A, Scadding GW, Qin T, Lawson K, et al.
J Allergy Clin Immunol. 2021 Apr 2:S0091-6749(21)00552-2. doi: 10.1016/j.jaci.2021.03.030. Epub ahead of print

ARTÍCULO DESTACADO

INTRODUCTION
There is no detailed comparison of allergen-specific immunoglobulin responses following sublingual (SLIT) and subcutaneous (SCIT) immunotherapy.
OBJECTIVE
To compare nasal and systemic Timothy grass pollen (TGP)-specific antibody responses during two years of SCIT and SLIT and one year after treatment discontinuation in a double-blind, double-dummy, placebo-controlled trial.
METHODS
Nasal fluid and serum were obtained yearly (per-protocol population, n=84). TGP-specific IgA1, IgA2, IgG4, IgG and IgE were measured in nasal fluids by ELISA. TGP-specific IgA1, IgA2 and Phl p1, 2, 4, 5b, 6, 7, 11 and 12 IgE and IgG4 were measured in sera by ELISA and ImmunoCAP, respectively.
RESULTS
At years 2 and 3, TGP-IgA1/2 in nasal fluid were elevated in SLIT compared to SCIT (4.2 and 3.0-fold for IgA1, 2.0 and 1.8-fold for IgA2, respectively; all P<.01). TGP-IgA1 in serum was elevated in SLIT compared to SCIT at years 1, 2, and 3 (4.6, 5.1, and 4.7-fold, respectively; all P<.001). Serum TGP-IgG was higher in SCIT compared to SLIT (2.8-fold) at year 2. Serum TGP-IgG4 was higher in SCIT compared to SLIT at years 1, 2, and 3 (10.4, 27.4, and 5.1-fold, respectively; all P<.01). Serum IgG4 to Phl p1, 2, 5b and 6 were increased at years 1, 2 and 3 in SCIT and SLIT compared to placebo (Phl p1: 11.8 and 3.9-fold; Phl p2: 31.6 and 4.4-fold; Phl p5b: 135.5 and 5.3-fold; Phl p6: 145.4 and 14.7-fold, respectively, all at year 2 when levels peaked; P<.05). IgE to TGP in nasal fluid increased in the SLIT group at year 2 but not year 3 compared to SCIT (2.8-fold; P=.04) and placebo (3.1-fold; P=.02). IgA to TGP and IgE and IgG4 to TGP-components stratified participants according to treatment group and clinical response.
CONCLUSION
The observed induction of IgA1/2 in SLIT and IgG4 in SCIT suggest key differences in the mechanisms of action.

2

Ácaros y virus: ¿cómo se relacionan?

RNA viruses in the house dust mite Dermatophagoidespteronyssinus, detection in environmental samples and in commercial allergen extracts used for in vivo diagnosis.

Vidal-Quist JC, Vidal C, Escolar F, Lambrecht B, Rombauts S, Hernández-Crespo P
Allergy. 2021 Apr 29. doi: 10.1111/all.14884. Epub ahead of print

BACKGROUND
Allergy to house dust mites (HDM), the most important source of indoor allergens worldwide, is diagnosed and treated using natural extracts from cultures that can contain immunoactive components from the HDM microbiome, including mite-infecting viruses.
OBJECTIVE
Discovery and characterization of RNA viruses from Dermatophagoides pteronyssinus, followed by detection in different mite-derived sources.
METHODS
Viruses were assembled after in silicometatranscriptomic analysis of D.pteronyssinus RNA samples, visualized by electron microscopy, and RNA detected by direct RT-PCR or data mining. Mite culture performance was evaluated in vivo.
RESULTS
Seven RNA viruses were identified in our laboratory stock colony. Picornavirus-like viral particles were detected in epithelial cells of the digestive system and in fecal pellets. Most of these viruses could be persistently transmitted to an inbred virus-free colony by inoculating fecal material from the stock colony. Upon viral infection, no significant effect could be seen on mite population growth. Transcriptomic screening confirmed the presence of homolog sequences to these viruses in independent laboratory stocks of D. pteronyssinus and in other Astigmata mites. Noteworthy, RNA from most of the viruses could be detected by RT-PCR on house dust samples, reference standards, and/or commercial diagnostic D. pteronyssinus extracts.
CONCLUSIONS
Our results show that viral infections are common and widespread in D. pteronyssinus, both in natural and culture-based growth conditions. Potential effects on the mites themselves and consequences towards allergenicity in humans whether exposed naturally or after immunotherapy are discussed.

3

Seguridad de una nueva ITA con abedul

Safety of the SQ Tree Sublingual Immunotherapy Tablet: Pooled safety analysis of clinical trials

Biedermann T, Couroux P, Greve TM, Mäkelä M

Allergy. 2021 Apr 27. doi: 10.1111/all.14882. Epub ahead of print

BACKGROUND

The standardised quality (SQ) tree sublingual immunotherapy (SLIT)-tablet has recently been approved for treatment of tree pollen allergy. Health care workers should be provided with detailed safety data for clinical use.

OBJECTIVE

To assess the tolerability and safety of the SQ tree SLIT-tablet (12 SQ-Bet)in adults and adolescents.

METHODS

Safety data were pooled fromthree double-blinded, randomized, placebo-controlled trials (2 phase-II/1 phase-III) including adults and adolescents 12-65 years with allergic rhinitis and/orconjunctivitis treated before and during one pollen season once-daily with 12 SQ-Bet (n=471) or placebo (n=458): EudraCTno:2012-000031-59; NCT02481856; EudraCT 2015-004821-15.

RESULTS

The most frequently reported investigational medicinal product(IMP)-related AEs with 12 SQ-Bet were oral pruritis (39% of subjects)and throat irritation (29%).IMP-related AEs were mainly mild or moderate in severity,and the majority resolved without treatment and did not lead to treatment interruption/discontinuation. With 12 SQ-Bet, oral pruritus was more frequent among subjects with pollen food syndrome (PFS) (45%) than without PFS (29%).The 12 SQ-Bet did not seem to induce an increased risk of asthma: 7 events were reported in 7 subjects with 12 SQ-Bet and 11 in 10 subjects with placebo. No differences were seen in the risk of moderate to severe IMP-related AEs regardless of age, PFS status and asthma medical history.

CONCLUSIONS

The 12 SQ tree SLIT-tablet was well tolerated in tree pollen allergic subjects with no major safety concerns detected.This safety profile supports daily at-home sublingual administration once the first dose is tolerated when administered under medical supervision.

4

Los venenos y la mastocitosis en Estados Unidos

Prevalence of mastocytosis and hymenoptera venom allergy in the United States.

Schuler CF 4th, Volertas S, Khokhar D, Yuce H, Chen L, Baser O, et al.

J Allergy Clin Immunol. 2021 Apr 22:S0091-6749(21)00652-7. doi: 10.1016/j.jaci.2021.04.013. Epub ahead of print

BACKGROUND

Background: Mastocytosis is a risk factor for hymenoptera venom anaphylaxis (HVA). Current guidelines recommend measuring tryptase in HVA patients and that those with mastocytosis pursue lifelong venom immunotherapy (VIT). Available data on HVA and mastocytosis largely derives from European single-center studies and the prevalence of HVA with and without mastocytosis in the United States (US) is unknown.

OBJECTIVE

We sought to determine the prevalence of HVA and mastocytosis in the US using an insurance claims database and evaluate the impact oo determine the prevalence of HVA and mastocytosis in the US using an insurance claims database and evaluate the impact of mastocytosis on VIT in HVA patients in a US cohort.

METHODS

The IBM Watson Database, consisting of insurance claims from approximately 27 million US patients in 2018, was queried to identify patients with HVA and/or mastocytosis. Further, a retrospective study of 161 patients undergoing VIT between 2015 - 2018 at the University of Michigan (U-M) was conducted.

RESULTS

In the IBM Watson Database, the prevalence of HVA was 167 per 100,000 (0.167%) and the prevalence of mastocytosis 10 per 100,000 (0.010%) overall and 97 per 100,000 (0.097%) among those with HVA. Mastocytosis showed a 9.7-fold increase among HVA patients versus the general population. In the U-M cohort, 2.6% of VIT patients had mastocytosis. Tryptase level did not correlate with venom reaction severity but was higher in patients with systemic VIT reactions.

CONCLUSIONS

We observed a lower US HVA prevalence than previously reported. Mastocytosis was more common in US HVA patients, though at lower rates than previously reported. In VIT patients there was no correlation between tryptase level and reaction severity.

5

Una posible (y novedosa) relación entre la coagulación y la respuesta a la ITSL

Increased Thrombin-Activatable Fibrinolysis Inhibitor in Response to Sublingual Immunotherapy for Allergic Rhinitis.

Yoshida K, Takabayashi T, Imoto Y, Sakashita M, Kato Y, Narita N, at al.

Laryngoscope. 2021 Apr 12. doi: 10.1002/lary.29563. Epub ahead of print.

OBJECTIVES/HYPOTHESIS

The objective of this study was to determine the role of thrombin-activatable fibrinolysis inhibitor (TAFI) as a candidate biomarker for therapeutic efficacy of sublingual immunotherapy (SLIT) and to identify the role of TAFI in the pathogenesis of allergic rhinitis (AR).

STUDY DESING

Retrospective cohort study and laboratory study.

METHODS

Serum was collected from patients with allergies to Japanese cedar pollen before, during, and after treatment with SLIT. We measured the levels of immunoreactive TAFI, C3a, and C5a in serum by enzyme-linked immunosorbent assay (ELISA) and assessed their relative impact on a combined symptom-medication score. We also examined the impact of TAFI on mast cells and fibroblasts in experiments performed in vitro.

RESULTS

Serum levels of TAFI increased significantly in response to SLIT. By contrast, serum C3a levels decreased significantly over time; we observed a significant negative correlation between serum levels of TAFI versus C3a and symptom-medication score. Mast cell degranulation was inhibited in response to TAFI, as it was the expression of both CCL11 and CCL5 in cultured fibroblasts.

CONCLUSIONS

High serum levels of TAFI may be induced by SLIT. TAFI may play a critical protective role in pathogenesis of AR by inactivating C3a and by inhibiting mast cell degranulation and chemokines expression in fibroblasts.

6

La monitorización de los alérgicos al huevo

Relationship between the outcome of low-dose egg oral immunotherapy and the fold-difference levels of allergen-specific IgE and IgG4 in serum.

Maeta A, Takaoka Y, Kameda M, Takahashi K

Asian Pac J Allergy Immunol. 2021 Apr 18. doi: 10.12932/AP-100620-0877. Epub ahead of print

BACKGROUND

There are no indices to monitor desensitization by low-dose egg oral immunotherapy (eOIT).

OBJECTIVE

We aimed to examine the relationship between desensitization by low-dose eOIT and the changes in allergen-specific immunoglobulin E (IgE) and IgG4 levels.

METHODS

We carried out low-dose eOIT in 31 patients with severe egg allergy in our previous two studies. After 4 months of treatment, the patients with no observed allergic symptoms in response to the open hard-boiled egg white challenge tests were classified as the negative group, and the remaining patients, the positive group. The fold-difference levels were calculated using 10 Log (Titer after eOIT/Titer before eOIT).

RESULTS

Results: The 28 patients who completed eOIT with sufficient serum collected before and after eOIT were analyzed. The median fold-difference levels of ovomucoid-specific IgE in the negative and positive groups were 0.819 and 0.953, respectively (P = 0.082). The median fold-difference levels of ovalbumin-specific IgG4 in the negative and positive groups were 2.01 and 1.29, respectively (P = 0.057). In the receiver-operating characteristic curves, the area under the curves of fold-difference ovomucoid-specific IgE and ovalbumin-specific IgG4 were 0.701 and 0.719, respectively. The challenge positive predictive values of fold-difference ovomucoid-specific IgE and ovalbumin-specific IgG4 were 83.8% (cut-off point: 0.934) and 77.8% (cut-off point: 1.87), respectively. Moreover, the challenge positive predictive value in patients with both 0.934 < ovomucoid-specific IgE and ovalbumin-specific IgG4 <1.87 was 100%.

CONCLUSIONS

The fold-difference levels of allergen-specific IgE and IgG4 in serum are considered useful for monitoring desensitization by low-dose OIT.

7

ITO con cacahuete en la vida real

Peanut oral immunotherapy in a pediatric allergy clinic: patient factors associated with clinical outcomes.

Guarnieri KM, Slack IF, Gadoury-Lévesque V, Eapen AA, Andorf S, Lierl MB

Ann Allergy Asthma Immunol. 2021 Apr 8:S1081-1206(21)00266-0. doi: 10.1016/j.anai.2021.04.003. Epub ahead of print.

BACKGROUND

Additional information is needed to inform optimal patient selection, expected outcomes, and treatment endpoints for clinical peanut oral immunotherapy (OIT).

OBJECTIVE

We analyzed a real-world peanut OIT cohort to provide insight into these questions.

METHODS

Records were reviewed for 174 children undergoing peanut OIT at a pediatric allergy clinic. Patient age, peanut skin prick test, peanut-specific IgE (sIgE) results, and inclusion of additional foods in OIT were analyzed for correlations with OIT outcomes.

RESULTS

To date, 144 patients have achieved maintenance dosing, 50 of whom transitioned to ad lib twice-weekly peanut ingestion. Thirty discontinued OIT. Fortyseven patients who underwent multi-food OIT had no significant difference in reactions or time to reach maintenance compared to those on peanut OIT alone. Age at initiation inversely correlated with achievement of maintenance: 92% of patients 0.5-<5 years, 81% of those 5-<11 years, and 70% of those 11-<18 years reached and continued maintenance (P=0.013). Baseline peanut-sIgE level positively correlated with number of reactions during updosing (P=0.0004) and maintenance (P=0.0048), though was not significantly different in patients achieving successful maintenance versus those who discontinued OIT (P=0.098). Sixty-six percent of patients experienced ≥1 adverse reaction during OIT. Of those on ad lib peanut ingestion, 2 reported mild reactions after lapses in peanut consumption.

CONCLUSION

Clinical peanut OIT has similar outcomes to research protocols. OIT can be successful in older children and those with high peanut-sIgE levels, though these factors impact outcomes. Clinical and laboratory criteria can guide successful transition to intermittent ad lib peanut consumption.

8

ITSC vs ITSL: ¿quién gana?

Subcutaneous Versus Sublingual Immunotherapy for Adults with Allergic Rhinitis: A Systematic Review with Meta-Analyses.

Tie K, Miller C, Zanation AM, Ebert CS Jr

Laryngoscope. 2021 Apr 30. doi: 10.1002/lary.29586. Epub ahead of print.

OBJECTIVES

To determine whether subcutaneous immunotherapy (SCIT) or sublingual immunotherapy (SLIT) better improves patient outcomes and quality of life for adults with allergic rhinitis or rhinoconjunctivitis (AR/C) with or without mild to moderate asthma.

METHODS

Systematic review methodology was based on the Cochrane Collaboration handbook and Preferred Reporting Items for Systematic Reviews and Meta-analyses. Four databases (PubMed, Cochrane Library, EMBASE, and Web of Science) were queried from inception to July 30, 2020. Two independent reviewers screened potentially relevant studies and assessed risk of bias. Outcomes of interest were symptom score (SS), medication score (MS), combined symptom medication score (CSMS), and Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ). Meta-analyses with an adjusted indirect comparison were conducted in RevMan 5.4.1.

RESULTS

Seven SCIT versus SLIT randomized controlled trials (RCTs) demonstrated no significant differences for any outcomes, but insufficient data precluded direct meta-analysis. For the adjusted indirect comparison, 46 RCTs over 39 studies were included for SCIT versus placebo (n = 13) and SLIT versus placebo (n = 33). Statistically significant results favoring SCIT were found for SS (standardized mean difference [SMD] = 0.40; 95% confidence interval [CI] = 0.31-0.49), MS (SMD = 0.26; 95% CI = 0.14-0.39), CSMS (SMD = 0.42; 95% CI = 0.17-0.67), and RQLQ (MD = 0.24; 95% CI = 0.04-0.44). Statistically significant results favoring SLIT were found for SS (SMD = 0.42; 95% CI = 0.32-0.53), MS (SMD = 0.40; 95% CI = 0.28-0.53), CSMS (SMD = 0.37; 95% CI = 0.29-0.45), and RQLQ (MD = 0.32; 95% CI = 0.20-0.43). No significant differences were found between SCIT and SLIT for SS (SMD = -0.02; 95% CI = -0.15 to 0.11), MS (SMD = -0.14; 95% CI = -0.31 to 0.03), CSMS (SMD = 0.05; 95% CI = -0.21 to 0.31), or RQLQ (MD = -0.08; 95% CI = -0.31 to 0.15).

CONCLUSION

SCIT and SLIT are comparably effective treatments for adults with AR/C. More RCTs analyzing SCIT versus SLIT are needed to directly compare the two

9

¿Pruebas cutáneas intradérmicas con aeroalérgenos?

Intradermal Testing Doubles Identification of Allergy among 110 Immunotherapy-Responsive Patients with Eustachian Tube Dysfunction.

Hurst DS, Gordon BR, McDaniel AB, Poe DS.

Diagnostics (Basel). 2021 Apr 24;11(5):763.

ABSTRACT

The purpose of this study was to determine whether the sensitivity advantage of intradermal dilutional testing (IDT) is clinically relevant in patients with obstructive Eustachian tube dysfunction (ETD) or otitis media with effusion (OME). This retrospective, private-practice cohort study compared the sensitivity of skin prick tests (SPT) vs. IDT in 110 adults and children with suspected allergy and OME. Primary outcome measure was symptom resolution from allergy immunotherapy (AIT). IDT identified 57% more patients as being allergic, and 8.6 times more reactive allergens than would have been diagnosed using only SPT. Patients diagnosed by IDT had the same degree of symptom improvement from immunotherapy, independent of allergen sensitivity (66% by SPT vs. 63% by IDT; p = 0.69, not different). Low-sensitivity allergy tests, which may fail to identify allergy in over two thirds of children aged 3 to 15 as being atopic, or among 60% of patients with ETD, may explain why many physicians do not consider allergy as a treatable etiology for their patient's OME/ETD. IDT offers superior sensitivity over SPT for detecting allergens clinically relevant to treating OME/ETD. These data strongly support increased utilization of intradermal testing and invite additional clinical outcome studies.

10

ITA y adherencia: los efectos secundarios de la pandemia

Subcutaneous Allergen Immunotherapy in Children: Real Life Compliance and Effect of COVID-19 Pandemic on Compliance.

Aytekin ES, Soyer Ö, Şekerel BE, Şahiner ÜM.

Int Arch Allergy Immunol. 2021 Apr 22:1-6. doi: 10.1159/000514587. Epub ahead of print.

BACKGROUND

Subcutaneous allergen immunotherapy (SCIT) is an effective treatment for allergic rhinitis, asthma, and venom allergy. Compliance is essential for SCIT to obtain maximal benefit as it is a long-term treatment.

OBJECTIVES

This study aimed to determine the level of real-life SCIT compliance in pediatric patients and the associated factors. Additional aims were to determine how SCIT compliance was affected by the COVID-19 pandemic and why some patients dropped out SCIT.

METHOD

Pediatric patients diagnosed with allergic rhinitis, allergic asthma, or venom allergy that received SCIT between September 2012 and July 2020 were analyzed.

RESULTS

The study included 201 children (66.7% male) with a median (interquartile range) age of 12.8 years (9.4-15.2) at the time of the first SCIT injection. The overall compliance rate before COVID-19 pandemic was 86.1%. Short SCIT follow-up time and venom anaphylaxis were found to be risk factors for drop out. The leading causes of drop outs were moving to another city/country (32.1%), symptom improvement (17.8%), treatment ineffectiveness (14.2%), and adverse reactions (14.2%). Among the 108 patients that were still receiving SCIT during the COVID-19 pandemic, 31 (28.7%) dropped out the therapy. The most frequent reasons for drop-out were fear of being infected with COVID-19 (35.4%) and thinking that the AIT practise stopped due to COVID-19 pandemic (29%). Male gender and older age were found to be the independent risk factors for drop-out of SCIT.

CONCLUSIONS

Real life compliance in children was found 13.9% and it was higher than adults. Nearly one-third of children dropped out during the CO-VID-19 pandemic. Male gender and older age are associated with SCIT drop-out during the COVID-19 pandemic.

1

Alérgicos a veneno de abeja: ¿quién tiene más riesgo?

Biomarkers of the Severity of Honeybee Sting Reactions and the Severity and Threshold of Systemic Adverse Events During Immunotherapy.

Kopač P, Custovic A, Zidarn M, Šilar M, Šelb J, Bajrović N, et al.

J Allergy Clin Immunol Pract. 2021 May 4:S2213-2198(21)00507-9

BACKGROUND

A biomarker that could identify individuals at high risk for severe honeybee sting allergic reaction and/or systemic adverse events (SAEs) during venom immunotherapy (VIT) would improve the management of patients with honeybee (HB) venom allergy.

OBJECTIVE

To identify biomarkers for risk of severe sting reactions or SAEs during VIT.

METHODS

We recruited 332 patients undergoing HB VIT. We ascertained predictors of the severity of the field-sting reaction and the severity and threshold of SAEs during VIT. We assessed the use of cardiovascular medications; baseline serum tryptase (BST) levels; specific IgEs to HB venom, rApi m 1, and rApi m 10; and basophil activation test (BAT) response.

RESULTS

: Significant and independent predictors of a severe HB field-sting reaction were age (P = .008), an absence of skin symptoms (P = .001), BST (P = .014), and BAT response at an HB venom concentration of 0.1 μg/mL (P = .001). Predictors of severe SAEs during HB VIT were age (P = .025), BST (P = .006), and BAT response (P = .001). BAT response was also an individual and significant predictor of any SAEs and SAEs at a low cumulative allergen dose (median, 55 μg) during VIT build-up (P < .001). The use of β-blockers and angiotensin-converting-enzyme inhibitors and specific IgE levels were not associated with the severity of HB field-sting reactions or VIT SAEs.

CONCLUSIONS

BST and basophil activation are independent risk factors for severe HB sting anaphylaxis and SAEs during HB VIT. BAT response was the best biomarker for any SAEs and a lower threshold of SAEs during HB VIT. These risk factors can help guide recommendations for VIT and overcome systemic reactions to HB VIT.

2

¿Qué se le exige a una ITA de calidad en la alergia a alimentos?

Regulatory Requirements for the Quality of Allergen Products for Allergen Immunotherapy of Food Allergy

Englert L, Mahler V, Bonertz A.

Curr Allergy Asthma Rep. 2021 May 10;21(5):32.

PURPOSE OF REVIEW

Medicinal products for allergen immunotherapy (AIT) of food allergies have gained enormous momentum in recent years. With this new class of products entering marketing authorization procedures, compliance to regulatory requirements becomes a critical element. Here, an overview is provided on specific requirements and aspects concerning the quality control and manufacturing of these products.

RECENT FINDINGS

Recent developments in the field of AIT for food allergies are divers, including products for oral, epicutaneous, and subcutaneous application, most notably targeting egg, milk, and peanut allergy. As the source materials for food AIT product are typically produced for food consumption and not for medicinal purposes, unique challenges arise in the manufacturing processes and controls of these medicinal products. Individual approaches are needed to assure acceptable quality, including control of relevant quantitative and qualitative characteristics. Major characteristics for quality verification include determination of protein content, total allergenic activity, and major allergen content. The applied manufacturing processes need to be established such that relevant process parameters are kept within justified limits and consistency of produced batches is assured. Allergen products for food AIT present specific challenges with respect to quality aspects that differentiate them from other commonly available AIT products. While established regulation is available and provides clear guidance for most aspects, other issues require consideration of new and individual settings relevant here. Consequently, as experience grows, respective amendments to currently available guidance may be needed.

3

Lo que ocurre a nivel celular con la ITA: inicio y mantenimiento (no es lo mismo)

An exhausted phenotype of TH 2 cells is primed by allergen exposure, but not reinforced by allergen-specific immunotherapy.

Wang SH, Zissler UM, Buettner M, Heine S, Heldner A, Kotz S, et al.

Allergy. 2021 May 9. doi: 10.1111/all.14896. Epub ahead of print.

BACKGROUND

Studies show that proallergic TH 2 cells decrease after successful allergen-specific immunotherapy (AIT). It is likely that iatrogenic administration of allergens drives these cells to exhaustion due to chronic T-cell receptor stimulation. This study aimed to investigate the exhaustion of T cells in connection with allergen exposure during AIT in mice and two independent patient cohorts.

METHODS

OVA-sensitized C57BL/6J mice were challenged and treated with OVA, and the development of exhaustion in local and systemic TH 2 cells was analyzed. In patients, the expression of exhaustion-associated surface markers on TH 2 cells was evaluated using flow cytometry in a cross-sectional grass pollen allergy cohort with and without AIT. The treatment effect was further studied in PBMC collected from a prospective long-term AIT cohort.

RESULTS

The exhaustion-associated surface markers CTLA-4 and PD-1 were significantly upregulated on TH 2 cells upon OVA aerosol exposure in OVA-allergic compared to non-allergic mice. CTLA-4 and PD-1 decreased after AIT, in particular on the surface of local lung TH 2 cells. Similarly, CTLA-4 and PD-1 expression was enhanced on TH 2 cells from patients with allergic rhinitis with an even stronger effect in those with concomitant asthma. Using an unbiased Louvain clustering analysis, we discovered a late-differentiated TH 2 population expressing both markers that decreased during up-dosing but persisted long term during the maintenance phase.

CONCLUSIONS

This study shows that allergen exposure promotes CTLA-4 and PD-1 expression on TH 2 cells and that the dynamic change in frequencies of exhausted TH 2 cells exhibits a differential pattern during the up-dosing versus the maintenance phases of AIT.

4

Lo último sobre ITA sublingual: ¡pólenes y ácaros a examen!

Recent Development on the use of SLIT tablets for Allergic Rhinitis

Susan Waserman, Anita Shah, Ernie Avilla

Ann Allergy Asthma Immunol. 2021 May 21;S1081-1206(21)00381-1. doi: 10.1016/j.anai.2021.05.020. Online ahead of print.

OBJECTIVE

Allergic rhinitis (AR) is an IgE-mediated inflammatory condition that causes symptoms of sneezing, nasal congestion, rhinorrhea, and nasal itch. Although subcutaneous immunotherapy (SCIT) for the treatment of AR has been in use and well established as a treatment modality, sublingual immunotherapy (SLIT) is increasingly considered to be the safer and more convenient alternative. Thus, the objective of this review is to describe recent findings pertaining to the use of SLIT tablets (SLIT-T) for AR.

STUDY SELECTION

A total of 11 RCTs were selected for full-text review and included in the analysis. All studies investigated the use of SLIT on patients with seasonal allergic rhinitis (4 tree pollen studies, 1 grass pollen study, 1 Japanese Cedar) or perennial allergic rhinitis (3 house dust mite studies).

DATA SOURCE

A database search (PubMed.gov) for articles published between January 1 st, 2017 to February 9 th, 2021 was conducted using the following key words: "allergic rhinitis", AND-ed "sublingual immunotherapy". Included were randomized placebocontrolled trials (RCTs). Other experimental designs studies were excluded.

RESULTS

Our review of 7 recently published randomized placebo-controlled trials with 2348 subjects receiving SLIT, reported increased efficacy, safety, supportive immunological parameters (IgE and IgG4 levels pre- and post-treatment levels) and improved quality of life. All studies excluded subjects with overlapping seasonal or perennial allergens, a history of moderate to severe, uncontrolled asthma or reduced lung function.

CONCLUSION

Our review highlights that SLIT is a safe and effective treatment that significantly reduces symptoms and medication requirements in allergic rhinitis, and improved quality of life.

5

110 años de inmunoterapia

One Hundred Ten Years of Allergen Immunotherapy: A Broad Look Into the Future.

Pfaar O, Creticos PS, Kleine-Tebbe J, Canonica GW, Palomares O, Schülke S

J Allergy Clin Immunol Pract. 2021 May;9(5):1791-1803. doi: 10.1016/j.jaip.2020.12.067

ABSTRACT

Allergen immunotherapy (AIT) is the only disease-modifying treatment option for patients with type 1-mediated allergic diseases such as allergic rhinitis/rhinoconjunctivitis with/without allergic asthma. Although many innovations have been developed since the first clinical report of Noon et al in 1911, the improvement of clinical efficacy and tolerability of this treatment is still an important unmet need. Hence, much progress has been made in the characterization of the cell types, cytokines, and intracellular signaling events involved in the development, maintenance, and regulation of allergic reactions, and also in the understanding of the mechanisms of tolerance induction in AIT. This comprehensive review aims to summarize the current innovative approaches in AIT, but also gives an outlook on promising candidates of the future. On the basis of an extensive literature review, integrating a clinical point of view, this article focuses on recent and future innovations regarding biologicals, allergen-derived peptides, recombinant allergens, "Toll"-like receptor agonists and other adjuvants, and novel application routes being developed for future AIT.

6

Rinitis alérgica perenne, ITA con ácaros y células Th2A

Decrease in CD38+ TH2A cell frequencies following immunotherapy with house dust mite tablet correlates with humoral responses.

Luce S, Batard T, Bordas-Le Floch V, Le Gall M, Mascarell L

Clin Exp Allergy. 2021 May 3. doi: 10.1111/cea.13891. Epub ahead of print.

BACKGROUND

In line with evidence for a role of pathogenic TH2A in seasonal allergies, we previously showed that individuals suffering from food allergy exhibited a decrease in circulating TH2A cells following multi-food immunotherapy. Herein, we aim to confirm the decline of TH2A cells in individuals undergoing house dust mite immunotherapy (HDM-AIT) and extend our observation to a new subset of CD38 expressing activated TH2A cells.

METHODS

The frequencies of TH2A and CD38+ TH2A cells were analysed by flow cytometry in blood cells from 182 Japanese HDM-allergic individuals included in a 1-year clinical trial assessing the efficacy of HDM tablets. Interrelationship between these cellular responses and humoral mite-specific IgE and IgG4 levels was further explored.

RESULTS

A decrease in TH2A cells was observed in both active and placebo groups. Interestingly, CD38+ TH2A cell frequencies significantly decreased only in active groups. In younger individuals (16-30 years), both TH2A and CD38+ TH2A cells were significantly reduced in active groups but not in the placebo group. Significant inverse correlations were observed in the course of HDM-AIT between changes in TH2A or CD38+ TH2A frequencies and IgG4 antibody levels.

CONCLUSIONS

We confirm the value of monitoring TH2A cell frequencies in allergic individuals and extend this observation to perennial allergy to HDM. We highlight the interest of CD38 to better identify the subset of TH2A cell down-regulated by AIT. Finally, correlated cellular and humoral responses observed in immunoreactive individuals stress that coordinated pathways occur in the adaptive responses during AIT.

7

El efecto de la premedicación con antihistamínicos

Antihistamine Premedication Improves Safety and Efficacy of Allergen Immunotherapy.

Wang L, Wang C, Lou H, Zhang L

Ann Allergy Asthma Immunol. 2021 May 27:S1081-1206(21)00415-4. doi: 10.1016/j.anai.2021.05.023. Epub ahead of print.

BACKGROUND

Allergen immunotherapy (AIT)-associated adverse events are a major concern for safety and efficacy of AIT. Presently, there is no consensus to whether antihistamine premedication could improve such conditions.

OBJECTIVE

To identify the superiority of antihistamine pretreatment in AIT.

METHODS

A comprehensive literature search for randomized controlled trials (RCTs) reporting the effects of antihistamine premedication on safety and efficacy of AIT was performed in MEDLINE, Embase and Cochrane Library databases. Safety was assessed according to the number of patients reporting systemic adverse reactions (SARs; the primary outcome), efficacy according to the number of patients achieving target maintenance dose (TMD) and sustained unresponsiveness (SU) to allergen.

RESULTS

Eleven RCTs (including 609 patients) satisfied the inclusion criteria for the meta-analysis. All premedication protocols were temporary. Pooled analysis demonstrated that compared to control patients, significantly fewer antihistaminepretreated patients reported total and moderate-to-severe SARs (OR= 0.36; 95%CI, 0.23 to 0.56, P<0.05; and OR= 0.20; 95%CI, 0.06 to 0.74, P<0.05; respectively), as well as total and moderate-to-severe SAR episodes (OR= 0.42; 95%CI: 0.34 to 0.53, P<0.05; and OR= 0.09; 95%CI: 0.01 to 0.50, P<0.05; respectively). Similarly, antihistamine pretreatment significantly increased the number of patients achieving TMD (OR= 2.94; 95%CI: 1.72 to 5.03, P<0.05), but not SU (OR= 1.65; 95%CI: 0.77 to 3.54, P=0.2), compared with the control group. Subgroup analysis according to different allergens and dose escalating approaches also displayed superiority of antihistamine pretreatment over control.

CONCLUSION

Antihistamine premedication can significantly improve safety and efficacy of AIT by reducing frequency and severity of SAR and increasing TMD.

8

¿Qué aporta el diagnóstico molecular a la práctica clínica habitual?

Molecular allergology and its impact in specific allergy diagnosis and therapy.

Barber D, Diaz-Perales A, Escribese MM, Kleine-Tebbe J, Matricardi P, Ollert M, et al.

Allergy. 2021 May 31. doi: 10.1111/all.14969. Epub ahead of print.

ABSTRACT

Progressive knowledge of allergenic structures resulted in a broad availability of allergenic molecules for diagnosis. Component resolved diagnosis allowed a better understanding of patient sensitization patterns, facilitating allergen immunotherapy decisions. In parallel to the discovery of allergenic molecules, there was a progressive development of a regulation framework that affected both in vitro diagnostics and Allergen Immunotherapy products. With a progressive understanding of underlying mechanisms associated to Allergen immunotherapy and an increasing experience of application of molecular diagnosis in daily life, we focus in analyzing the evidences of the value provided by molecular allergology in daily clinical practice, with a focus on Allergen Immunotherapy decisions.

9

El (gran) potencial de las cámaras de exposición

Technical standards in allergen exposure chambers worldwide - an EAACI Task Force Report.

Pfaar O, Bergmann KC, Bonini S, Compalati E, Domis N, de Blay F, et al.

Allergy. 2021 May 24. doi: 10.1111/all.14957. Epub ahead of print.

ABSTRACT

Allergen exposure chambers (AECs) can be used for controlled exposure to allergenic and non-allergenic airborne particles in an enclosed environment, in order to (i) characterize the pathological features of respiratory diseases and (ii) contribute to and accelerate the clinical development of pharmacological treatments and allergen immunotherapy for allergic disease of the respiratory tract (such as allergic rhinitis, allergic rhinoconjunctivitis, and allergic asthma). In the guidelines of the European Medicines Agency for the clinical development of products for allergen immunotherapy (AIT), the role of AECs in determining primary endpoints in dose-finding Phase II trials is emphasized. Although methodologically insulated from the variability of natural pollen exposure, chamber models remain confined to supporting secondary, rather than primary, endpoints in Phase 3 registration trials. The need for further validation in comparison with field exposure is clearly mandated. On this basis the European Academy of Allergy and Clinical Immunology (EAACI) initiated a Task Force in 2015 charged to gain a better understanding of how AECs can generate knowledge about respiratory allergies and can contribute to the clinical development of treatments. Researchers working with AECs worldwide were asked to provide technical information in eight sections: (i) dimensions and structure of the AEC, (ii) AEC staff, (iii) air flow, air processing, and operating conditions, (iv) particle dispersal, (v) pollen/particle counting, (vi) safety and non-contamination measures, (vii) procedures for symptom assessments, (viii) tested allergens/substances and validation procedures. On this basis, a minimal set of technical requirements for AECs applied to the field of allergology is proposed.

10

Prescribir ITA al percibir riesgo de asma

Allergen immunotherapy for house dust mite-induced rhinitis: prescriptive criteria.

Ridolo E, Incorvaia C, Ciprandi G

Acta Biomed. 2021 May 12;92(2):e2021194.

ABSTRACT

Allergic rhinitis (AR) is a very common disease. In most cases, therapy is based on symptomatic drugs, while allergen immunotherapy (AIT), which is the only one to act on the cause of the disease, is reserved for patients with a greater burden of disease. In particular, the possible evolution towards asthma substantiates the use of AIT, but requires the availability of diagnostic indices related to the risk of developing asthma. We analyzed the available literature on risk factors for onset of asthma in patients with AR, including bronchial hyperresponsiveness, uncovering by respiratory function tests of airway impairment, measurement of fractioned exhaled nitric oxide, given IgE sensitization pattern, and respiratory infections detected by nasal mucus samples or by particular microbiomes. Most of these risk predictors have been investigated too little or do not have consistent results, while various studies have confirmed that early bronchial impairment in AR patients, particularly concerning small airways, should be considered as prescriptive criteria for AIT.

1

La calidad los estudios observacionales se pone a prueba

Allergen immunotherapy for respiratory allergy: Quality appraisal of observational comparative effectiveness studies using the REal Life Evidence AssessmeNt Tool. An EAACI methodology committee analysis

Di Bona D, Paoletti G, Chu DK, Pepys J, Macchia L, Heffler E, et al.

Clin Transl Allergy. 2021 Jun 14;11(4):e12033. doi: 10.1002/clt2.12033.

ARTÍCULO DESTACADO

BACKGROUND

Observational comparative effectiveness studies in allergen immunotherapy (AIT) represent an important evidence source answering research questions that can be challenging to obtain from randomized controlled trials (RCTs), such as long-term benefits of AIT, the effects on asthma prevention and the onset of new allergen sensitizations. However, observational studies are prone to several sources of bias, which limit their reliability.The REal Life Evidence AssessmeNt Tool (RELEVANT) was recently developed to assist in quality appraisal of observational comparative research to enable identification of useful nonrandomized studies to be considered within guideline development.

OBJECTIVE

To systematically appraise the quality of published observational comparative AIT studies using RELEVANT.

METHODS

Observational studies comparing AIT to pharmacotherapy for respiratory allergies, assessing as outcome measures reduction of symptoms and/or medication use reduction, were retrieved by computerized bibliographic searches. According to RELEVANT, a failure to meet any one of primary items (background, design, measures, analysis, results, discussion/interpretation, and conflict of interest) represents a critical flaw, significantly undermining the validity of the study results.

RESULTS

The 14 studies identified supported the benefit of AIT in real-life, which persists after treatment discontinuation. However, none of them met all the 7 primary RELEVANT criteria. The main defects were reported in the design (28.6% of studies), measures and analysis (64.3% of studies), and results (78.6% of studies) items, due to selection bias and lack of methods for adjusting controls. Half of the studies did not report on conflict of interest.

CONCLUSION

There is a need for more robust observational research in AIT. RELEVANT appears as an easy-to-use and sensitive tool for quality appraisal in AIT studies.

2

El papel crucial de Pol d 1

Prevalence of Pol d 1 sensitization in Polistes dominula allergy and its diagnostic role in vespid double-positivity

Maria Beatrice Bilò, Matteo Martini, Patrizia Bonadonna, Barbara Cinti, Mirella Da Re, Oretta Gabrielli, Francesco Olivieri, Valeria Salgarolo, Giovanna Zanoni, Danilo Villalta

J Allergy Clin Immunol Pract. 2021 Jun 16;S2213-2198(21)00660-7. doi: 10.1016/j.jaip.2021.05.033. Online ahead of print.

BACKGROUND

Stings by Polistes species frequently cause allergic reactions. However, standard allergy diagnostics are often unable to differentiate between primary sensitization and cross-reactivity, in case of Vespula/Polistes double-sensitization, because Antigen 5 is the only Polistes venom molecule currently available in diagnostics (Pol d 5).

OBJECTIVE

The objectives of this study were to evaluate the frequency of Phospholipase A1 in Polistes venom allergy (Pol d 1) and its diagnostic role in vespid allergy.

METHODS

Component resolved diagnostics was performed in patients with Vespid allergic reactions who resulted positive to Polistes venom. A prevalence analysis was performed, and the diagnostic accuracy of Pol d 1 evaluated for detection of primary Polistes sensitization, in double-sensitized patients.

RESULTS

Blood samples were collected from 132 patients. Pol d 1 was present in 97-100% of the 128 Polistes-positive patients, and it was frequently involved in case of positivity to one single Polistes molecule (48% in double- and 80% in mono-sensitized patients). Furthermore, Pol d 1 was positive in 95% of Pol d 5 negative subjects. The diagnostic accuracy of Pol d 1 was good (folded type: AUC=87%, 82% sensitivity and 77% specificity at the best cut-off of 5.773), and even better if used in combination with the whole extract ratio (AUC= 99%, 91% sensitivity and 100% specificity).

CONCLUSION

The study shows that Pol d 1 is the most frequent Polistes allergen in Italian patients, and it can distinguish Polistes primary sensitizations with a good diagnostic accuracy, supporting its use in clinical practice.

3

Alérgicos que abandonan la ITA: cuántos, por qué y el efecto de la pandemia

Real-life adherence to subcutaneous immunotherapy: What has changed in the era of the COVID-19 pandemic.

Koca Kalkan I, Ates H, Aksu K, Yesilkaya S, Topel M, Cuhadar Ercelebi D, et al.

World Allergy Organ J. 2021 Jul;14(7):100558.

BACKGROUND

Allergen immunotherapy (AIT) must be continued for 3 years, to achieve a long-term modifying effect. Adherence is a key to ensure effectiveness. The objective of this study was, first of all, to evaluate the adherence with subcutaneous immunotherapy (SCIT) and to identify the main causes of SCIT withdrawal in real-life practice in our clinic. Secondly, we also aimed to investigate to what extent the COVID-19 pandemic altered our SCIT receiving patients' treatment adherence behaviors and the factors that affected their decisions.

METHODS

Retrospective analysis of the medical records of patients ages ≥18 years, who had started SCIT in January 2014 or later until September 2020 in our department for the diagnosis of allergic rhinitis, allergic asthma or venom allergy, were included in the study. Adherence was determined as the accomplishment of 3 years of SCIT.

RESULTS

A total of 124 patients (72 female [58.1%]; median age, 35 [19-77] years) were included. The adherence rate to SCIT in our tertiary center's real-life setting was 56.25% with a follow-up duration of 3 years before COVID-19 pandemic. Dose modification, defined as reducing patient's planned SCIT dose due to a systemic allergic/large local reaction or missed injection, and its frequency, which is the number of dose adjustments done throughout the SCIT, was found to be the only factor related to nonadherence. But with the pandemic only in 6 months, among 63 patients receiving SCIT, 15 patients (23.81%) dropped out, and the most common reason was fear of being infected with COVID-19 virus during receiving SCIT in hospital (93.33%). The only independent predictor of drop-out during the COVID-19 pandemic was short duration of AIT ($p = 0.012$). When we compare the dropped-out cases before and after the start of pandemic, AIT duration was significantly shorter in pandemic period ($p = 0.005$).

CONCLUSION

Adherence rate to SCIT in our real-world setting study was 56.25% before the COVID-19 pandemic. Our results indicated that patients requiring dose modification were more prone to be non-adherent. Approximately one quarter of patients dropped-out with the start of pandemic, almost all due to fear of being infected during receiving SCIT in hospital. Since short SCIT follow-up time was found to be the only risk factor for drop-out during the COVID-19 pandemic, we believe that patients who are in the early phases of their treatment should be observed more closely and their concerns should be answered by their doctors.

4

Los beneficios de la ITA intralinfática y sus (todavía) limitaciones

Intralymphatic immunotherapy for allergic rhinoconjunctivitis: a systematic review and meta-analysis.

Hoang MP, Seresirikachorn K, Chitsuthipakorn W, Snidvongs K

Rhinology. 2021 Jun 1;59(3):236-244

BACKGROUND

Intralymphatic immunotherapy (ILIT) is a new route of allergen-specific immunotherapy. Data confirming its effect is restricted to a small number of studies.

Methodology

A systematic review with meta-analysis was conducted. The short-term (less than 24 weeks), medium-term (24-52 weeks), and long-term (more than 52 weeks) effects of ILIT in patients with allergic rhinoconjunctivitis (ARC) were assessed. The outcomes were combined symptom and medication scores (CSMS), symptoms visual analog scale (VAS), disease-specific quality of life (QOL), specific IgG4 level, specific IgE level, and adverse events.

RESULTS

Eleven randomized controlled trials and 2 cohorts (483 participants) were included. Compared with placebo, short term benefits of ILIT for seasonal ARC improved CSMS, improved VAS and increased specific IgG4 level but did not change QOL or specific IgE level. Medium-term effect improved VAS. Data on the long-term benefit of ILIT remain unavailable and require longer term follow-up studies. There were no clinical benefits of ILIT for perennial ARC. ILIT was safe and well-tolerated.

CONCLUSION

ILIT showed short-term benefits for seasonal ARC. The sustained effects of ILIT were inconclusive. It was well tolerated.

5

¿Qué hacemos con los “no muy alérgicos” a alimentos?

Managing Food Allergy When the Patient Is Not Highly Allergic.

Sicherer SH, Abrams EM, Nowak-Wegrzyn A, Hourihane JO

J Allergy Clin Immunol Pract. 2021 Jun 5:S2213-2198(21)00608-5

ABSTRACT

Few patients with food allergy are "highly allergic," meaning they always have severe reactions and always react to very small amounts of allergen. Standard medical approaches for allergy management have focused on the safety and lifestyle modifications this group truly needs, but consequently families with food allergy are typically advised to strictly avoid any exposure to their implicated allergens. Most food-allergic subjects are actually not reactive to very low doses, and many never experience severe reactions. There are also notable conditions where a different care plan is already commonly offered: patients with pollen-related food allergy syndrome, with food-associated exercise-induced anaphylaxis, and with resolving or mild milk or egg allergy might be advised to ingest the allergens in specific circumstances with detailed instructions. Because oral immunotherapy and allergy prevention by early exposure have emphasized alternatives to strict avoidance, there is increasing interest in prospects to forego strict avoidance in those with food allergy. For patients with a high threshold of reactivity (low-dose tolerant, high-dose mildly reactive), there may be options such as allowing the ingestion of products with precautionary allergen labels, allowing dietary indiscretions with small amounts of the allergen, or even encouraging ingestion of subthreshold amounts with therapeutic intent. These practices have not been extensively studied and could be considered controversial. If these approaches are considered, shared decision making is needed in discussing them with patients and families. This review considers the potential approaches to those who are "not highly allergic": the risks, benefits, shared decision making, and research needs.

6

Monosensibilizados vs polisensibilizados y el debate sobre la composición de la ITA

Clinical effectiveness of house dust mite immunotherapy in mono- versus poly-sensitised patients with allergic rhinitis: a systematic review and meta-analysis.

Kim JY, Hwang D, Jang M, Rhee CS, Han DH

Rhinology. 2021 Jun 28. doi: 10.4193/Rhin20.588. Epub ahead of print.

ABSTRACT

Selecting an appropriate allergen-specific immunotherapy (AIT) regimen for polysensitised allergic rhinitis (AR) patients is challenging for clinicians. Although previous studies showed comparable effectiveness of single-allergen AIT with house dust mite (HDM) extract between monosensitised and polysensitised AR patients, there is no systematic review and meta-analysis demonstrating the comparable effectiveness of HDM AIT. In this meta-analysis, we analysed nine studies to compare the clinical effectiveness of HDM AIT. The primary outcome was nasal symptom score and secondary outcomes were medication and quality of life scores. The changes in nasal symptom score after HDM AIT did not significantly differ between monosensitised and polysensitised patients. The clinical effectiveness of HDM AIT regarding medication and quality of life score was not significantly different between monosensitised and polysensitised patients). In conclusion, single-allergen AIT with HDM extract showed comparable clinical effectiveness between polysensitised and monosensitised patients with AR.

7

¿Qué intervenciones mejoran la calidad de vida de los alérgicos a alimentos?

Improvement in Health-Related Quality of Life in Food-Allergic Patients: A Meta-analysis.

Cao S, Borro M, Alonzi S, Sindher S, Nadeau K, Chinthrajah RS

J Allergy Clin Immunol Pract. 2021 Jun 2:S2213-2198(21)00607-3

BACKGROUND

Food allergy (FA) is a growing global problem that can affect patients' health-related quality of life (HRQoL) owing to increased anxiety as well as social and economic restrictions. Interventions such as oral food challenges (OFCs) and oral immunotherapy (OIT) have been shown to improve HRQoL. However, meta-analyses and systematic synthesis of these data are lacking.

OBJECTIVE

To review and quantitatively synthesize potential benefits of interventions (OIT and OFC) systematically to address FA to a variety of foods.

METHODS

We conducted a systematic search through PubMed and Cochrane Medical Library databases and performed a meta-analysis focusing on studies assessing changes in HRQoL after OIT and/or OFCs in FA participants and caregivers from 2010 to July 2020. Random effects model and I2 statistics were used to assess overall intervention effects and heterogeneity across studies.

RESULTS

We included 13 publications in this meta-analysis (OIT = 7; OFCs = 6). Mean change in HRQoL scores after OIT and OFCs was -1.25 ($P < .001$) and -0.78 ($P = .052$), with a significant I2 of 87% ($P < .001$) and 90% ($P < .001$), respectively. Five OIT studies found significant improvements in HRQoL in the OIT group compared with the placebo group, with an overall standardized mean difference of -0.56 ($P = .007$; I2 = 42%, $P = .099$).

CONCLUSIONS

This meta-analysis showed that in FA patients, both OIT and OFCs are associated with an improvement in HRQoL. Well-designed and long-term HRQoL studies are necessary to ascertain sustained benefits of OIT and OFCs.

8

Parámetros inmunológicos que nos dan una pista sobre la respuesta a la ITA

Immunological parameters as biomarkers of response to MicroCrystalline Tyrosine-adjuvanted mite immunotherapy

Justicia JL, Padró C, Roger A, Moreno F, Rial MJ, Parra A, et al.

World Allergy Organ J. 2021 Jun 6;14(6):100545

BACKGROUND

Despite the effectiveness of allergen immunotherapy (AIT), some patients are unresponsive for reasons still unknown; yet validated response biomarkers remain unavailable.

OBJECTIVE

To analyze immunological parameters as biomarkers to monitor and predict clinical response to a MicroCrystalline Tyrosine-adjuvanted house dust mite (HDM) AIT in patients with allergic rhinitis (AR).

METHODS

Observational, prospective, multicenter study including adult patients (aged 18-65 years) with AR, with and without asthma, sensitized to the HDM Dermatophagoides pteronyssinus (DP) and prescribed Acarovac Plus® DP 100% in the routine practice. Serum concentrations of total IgE, specific IgE, specific IgG4, IL-4, IL-5, IL-10, IL-13, and IFN-γ were compared between baseline and 12 months after AIT. The relationship between patients' baseline immunological profiles and classification as low, high, and non-responders and between their sensitization profile to DP allergens and effectiveness were analyzed.

RESULTS

Of 141 patients recruited, 118 (mean [SD] age of 33.6 [9.5] years) were evaluable. One year after treatment, Der p 1-specific IgE, DP-specific IgG4, and IL-10 increased by a mean (SD) of 3.4 (13.6) kU/L ($p = 0.016$), 0.43 (0.55) mg/L ($p < 0.0001$), and 1.35 (7.56) pg/mL ($p = 0.033$), respectively. Non-responders showed increased baseline levels of IL-13 compared to high responders ($p = 0.037$). Changes in effectiveness variables between baseline and after AIT were similar regardless of the sensitization profile.

CONCLUSION

Non-responsive patients to AIT showed increased baseline IL-13 concentrations, suggesting its value as prognostic biomarker. DP-specific AIT increased Der p 1-specific IgE, DP-specific IgG4, and IL-10 concentrations in patients with AR. All patients benefited from treatment regardless of their sensitization profile to major DP allergens.

9

¿Qué sabemos de la ITO con trigo?

Wheat oral immunotherapy

Leeds S, Liu EG, Nowak-Wegrzyn A

Curr Opin Allergy Clin Immunol. 2021 Jun 1;21(3):269-277.

PURPOSE OF REVIEW

The prevalence of food allergy is increasing on a global scale, and therefore increased attention is being paid to specific food allergy epidemiology and management. There has been a large amount of progress made in the last decade on human trials of wheat oral immunotherapy (WOIT).

RECENT FINDINGS

To date, there has been one multicenter, double-blind, randomized controlled trial of WOIT, one randomized, noncontrolled trial of WOIT, and several smaller, nonrandomized clinical trials of WOIT. WOIT trials are generally limited by smaller sample sizes, affecting the demographic skew of evaluated patients. In addition, there is minimal standardization of efficacy and safety outcomes between trial protocols, making head-to-head comparison challenging. However, some common themes emerge. The majority of WOIT regimens result in successful desensitization, and success is more likely with higher maintenance dosing for longer periods of time. Limited studies have looked at sustained unresponsiveness in WOIT. WOIT can induce allergic reactions, including anaphylaxis, but more severe reactions often have an associated augmenting factor, such as exercise. Lower maintenance doses likely are associated with less severe reactions, and food modification and/or adjunct therapeutics may also decrease the risk of reactions.

SUMMARY

WOIT trials are ongoing and will optimize updosing protocols and maintenance doses to improve efficacy and safety.

10

La investigación sobre alergia al cacahuete sigue su curso (a pesar de la pandemia)

Emerging developments in the forefront of peanut oral immunotherapy.

Pepper AN, Sriaroon P, Casale TB

Curr Opin Allergy Clin Immunol. 2021 Jun 1;21(3):263-268.

PURPOSE OF REVIEW

Despite the COVID-19 pandemic, progress continued in the field of peanut oral immunotherapy over the past 12 to 18 months. Of importance, the first oral immunotherapy product for the treatment of peanut allergy was approved by the US Food and Drug Administration in January 2020.

RECENT FINDINGS

Suggested modifications to the practice of oral immunotherapy, some of which may have lasting impacts, were circulated as a result of the pandemic. New advances in pathophysiology, sustained unresponsiveness, quality of life, safety, and cost effectiveness were also published.

SUMMARY

During 2020, COVID-19 influenced the daily practice of allergy and immunology, with peanut oral immunotherapy being no exception. However, clinicians now have a FDA-approved treatment option for peanut allergy in children, a welcome development for a difficult disease. Future research is needed to clarify several knowledge deficits surrounding the best use of peanut OIT.

1

La ITA a lo largo de un siglo

One hundred and ten years of Allergen Immunotherapy: A journey from empiric observation to evidence.

Pfaar O, Bousquet J, Durham SR, Kleine-Tebbe J, Larché M, Roberts G, et al.

Allergy. 2021 Jul 27. doi: 10.1111/all.15023. Epub ahead of print.

ARTÍCULO DESTACADO

ABSTRACT

One hundred and ten years after Noon's first clinical report of the subcutaneous application of allergen extracts, allergen immunotherapy (AIT) has evolved as the most important pillar of the treatment of allergic patients. It is the only disease-modifying treatment option available and the evidence for its clinical efficacy and safety is broad and undisputed. Throughout recent decades, more insights into the underlying mechanisms, in particular the modulation of innate and adaptive immune responses, have been described. AIT is acknowledged by worldwide regulatory authorities, and following the regulatory guidelines for product-development, AIT products are subject to a rigorous evaluation before obtaining market authorization. Knowledge and practice are anchored in international guidelines, such as the recently published series of the European Academy of Allergy and Clinical Immunology (EAACI). Innovative approaches continue to be further developed with the focus on clinical improvement by e.g., the usage of adjuvants, peptides, recombinants, modification of allergens, new routes of administration, and the concomitant use of biologicals. In addition, real-life data provide complementary and valuable information on the effectiveness and tolerability of this treatment-option in the clinical routine. New mobile health technologies and big-data approaches will improve daily treatment convenience, adherence and efficacy of AIT. However, the current coronavirus disease 2019 (COVID-19) pandemic has also had some implications for the feasibility and practicability of AIT. Taken together, AIT as the only disease modifying therapy in allergic diseases, has been broadly investigated over the past 110 years laying the path for innovations and further improvement.

2

El cacahuete y el Estudio PALISADE: más allá del primer año de tratamiento

Open-label follow-on study evaluating the efficacy, safety, and quality of life with extended daily oral immunotherapy in children with peanut allergy.

Fernandez-Rivas M, Vereda A, Vickery BP, Sharma V, Nilsson C, Muraro A, et al.

Allergy. 2021 Jul 28. doi: 10.1111/all.15027. Epub ahead of print.

BACKGROUND

The benefit of daily administration of Peanut (Arachis hypogaea) Allergen Powder-dnfp (PTAH)-formerly AR101-has been established in clinical trials, but limited data past the first year of treatment are available. This longitudinal analysis aimed to explore the impact of continued PTAH therapeutic maintenance dosing (300 mg/day) on efficacy, safety/tolerability, and food allergy-related quality of life.

METHODS

We present a subset analysis of PALISADE-ARC004 participants (aged 4-17 years) who received 300 mg PTAH daily for a total of ~1.5 (Group A, n=110) or ~2 years (Group B, n=32). Safety assessments included monitoring the incidence of adverse events (AEs), accidental exposures to food allergens, and adrenaline use. Efficacy was assessed by double-blind, placebo-controlled food challenge (DBPCFC); skin prick testing; peanut-specific antibody assays; and Food Allergy Quality of Life Questionnaire (FAQLQ) and Food Allergy Independent Measure (FAIM) scores.

RESULTS

Continued maintenance with PTAH increased participants' ability to tolerate peanut protein: 48.1% of completers in Group A (n=50/104) and 80.8% in Group B (n=21/26) tolerated 2000 mg peanut protein at exit DBPCFC without dose-limiting symptoms. Immune biomarkers showed a pattern consistent with treatment-induced desensitisation. Among PTAH-continuing participants, the overall and treatment related exposure-adjusted AE rate decreased throughout the intervention period in both groups. Clinically meaningful improvements in FAQLQ and FAIM scores over time suggest a potential link between increased desensitisation as determined by the DBPCFC and improved quality of life.

CONCLUSIONS

These results demonstrate that daily PTAH treatment for peanut allergy beyond 1 year leads to an improved safety/tolerability profile and continued clinical and immunological response.

3

Buenas noticias para los alérgicos al gato

Passive Prophylactic Administration with a Single Dose of Anti-Fel d 1 Monoclonal Antibodies REGN1908-1909 in Cat Allergen-induced Allergic Rhinitis: A Randomized, Double-Blind, Placebo-controlled Clinical Trial.

Shamji MH, Singh I, Layhadi JA, Ito C, Karamani A, Kouser L, et al.

Am J Respir Crit Care Med. 2021 Jul 1;204(1):23-33.

RATIONALE

Sensitization to Fel d 1 (Felis domesticus allergen 1) contributes to persistent allergic rhinitis and asthma. Existing treatment options for cat allergy, including allergen immunotherapy, are only moderately effective, and allergen immunotherapy has limited use because of safety concerns.

OBJECTIVES

To explore the relationship among the pharmacokinetic, clinical, and immunological effects of anti-Fel d 1 monoclonal antibodies (REGN1908-1909) in patients after treatment.

METHODS

Patients received REGN1908-1909 (n = 36) or a placebo (n = 37) in a phase 1b study. Fel d 1-induced basophil and IgE-facilitated allergen binding responses were evaluated at baseline and Days 8, 29, and 85. Cytokine and chemokine concentrations in nasal fluids were measured, and REGN1908-1909 inhibition of allergen-IgE binding in patient serum was evaluated.

MEASUREMENTS AND MAIN RESULTS

Peak serum drug concentrations were concordant with maximal observed clinical response. The anti-Fel d 1 IgE/cat dander IgE ratio in pretreatment serum correlated with Total Nasal Symptom Score improvement. The allergen-neutralizing capacity of REGN1908-1909 was observed in serum and nasal fluid and was detected in an inhibition assay. Type 2 cytokines (IL-4, IL-5, and IL-13) and chemokines (CCL17/TARC, CCL5/RANTES [regulated upon activation, normal T-cell expressed and secreted]) in nasal fluid were inhibited in REGN1908-1909-treated patients compared with placebo ($P < 0.05$ for all); IL-13 and IL-5 concentrations correlated with Total Nasal Symptom Score improvement. Ex vivo assays demonstrated that REGN1908 and REGN1909 combined were more potent than each alone for inhibiting FcεRI- and FcεRII (CD23)-mediated allergic responses and subsequent T-cell activation.

CONCLUSIONS

A single, passive-dose administration of Fel d 1-neutralizing IgG antibodies improved nasal symptoms in cat-allergic patients and was underscored by suppression of FcεRI-, FcεRII-, and T-helper cell type 2-mediated allergic responses. Clinical trial registered with www.clinicaltrials.gov (NCT02127801).

4

Pacientes y personal sanitario, la seguridad de la ITA en vuestras manos

Systemic reactions to subcutaneous allergen immunotherapy: real-world cause and effect modelling.

Aue A, Ho J, Zhu R, Kim H, Jeimy S

Allergy Asthma Clin Immunol. 2021 Jul 6;17(1):65

BACKGROUND

Subcutaneous immunotherapy (SCIT) is an effective treatment for allergic rhinoconjunctivitis. However, adverse events, including life-threatening systemic reactions, may occur. The purpose of this project is to identify risk factors for systemic reactions to SCIT and to provide practice-based solutions using a quality improvement (QI) framework.

METHODS

A QI initiative was performed in a hospital-based, Canadian Allergy clinic administering SCIT in a 12-month period.

RESULTS

A total of 4242 injections of SCIT were performed over a period of 12 months. Of these, 10 injections resulted in a systemic reaction requiring epinephrine administration (i.e., an incidence of 1 in 424 injections, or 0.24%). Eight patients had at least one documented risk factor for a systemic reaction, and six had multiple risk factors. Major risk factors included seasonal exacerbation of allergic rhinitis, uncontrolled asthma, and an error in route of administration. All reactions occurred with the highest allergen extract concentration.

CONCLUSION

This QI initiative highlights the need for improved patient and health care practitioner education and pre-administration screening. We suggest several considerations for SCIT administration: provide patients with written information on safety; screen patients before injections, including a review of treatment plan adherence and asthma control; adjust dosing to slow down buildup of the most concentrated immunotherapy extract, particularly in high risk patients; and apply additional safety measures in patients with multiple risk factors.

5

La ITA intralinfática se abre camino

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

Werner MT, Bosso JV

Allergy Asthma Proc. 2021 Jul 1;42(4):283-292

BACKGROUND

Only a fraction of patients with allergic rhinitis receive allergen-specific immunotherapy (AIT). AIT is most commonly delivered subcutaneously in a series of injections over 3-5 years. Common obstacles to completing this therapy include cost and inconvenience. Intralymphatic immunotherapy (ILIT) has been proposed as a faster alternative, which requires as few as three injections spaced 4 weeks apart.

OBJECTIVE

This systematic review and meta-analysis evaluated the current evidence that supports the use of ILIT for allergic rhinitis.

METHODS

Clinical trials were identified in the published literature by using an electronic search strategy and were evaluated by using a risk of bias tool. Treatment outcome (symptom scores, medication scores, and combined symptom and medication scores) and provocation testing results (nasal provocation and skin-prick testing) were included in a meta-analysis of standardized mean difference with subgrouping by using a random-effects model. Overall adverse event rates were tabulated, and overall risk ratios were calculated by using a random-effects model.

RESULTS

We identified 17 clinical trials that met eligibility criteria. The standardized mean difference of ILIT on the symptom and medication score was -0.72 (95% confidence interval [CI], -0.98 to -0.46; $p < 0.0001$) (n = 10). The standardized mean difference of ILIT on nasal provocation and skin-prick testing was -1.00 (95% CI, -1.38 to -0.61; $p < 0.0001$) (n = 7) and -0.73 (95% CI, -0.99 to -0.47; $p < 0.0001$) (n = 7), respectively. No statistically significant heterogeneity was detected. The overall adverse event rate was 39.5% for ILIT and 23.5% for placebo. Also, 98.4% of adverse events were mild.

CONCLUSION

Our meta-analysis demonstrated that ILIT was safe, conferred desensitization to seasonal and nonseasonal allergens, alleviated allergic rhinitis symptoms, and reduced medication use. A larger randomized, double-blind, placebo controlled trial will be necessary for wider adaptation of this form of AIT.

6

ITA subcutánea vs tabletas: ¿Cuál deberíamos elegir, económicamente hablando?

Sublingual immunotherapy tablet: a cost-minimizing alternative in the treatment of tree pollen-induced seasonal allergic rhinitis in Canada

Anne K Ellis, Rémi Gagnon, Eva Hammerby, Julia Shen, Sheena Gosain

Allergy Asthma Clin Immunol. 2021 Jul 8;17(1):66. doi: 10.1186/s13223-021-00565-y.

BACKGROUND

A cost-minimization analysis (CMA) was performed to evaluate the economic implications of introducing the SQ Tree sublingual immunotherapy (SLIT)-tablets marketed as ITULATEK® (Health Canada regulatory approval in April 2020) for the treatment of pollen-induced (birch, alder and/or hazel) seasonal allergic rhinitis in Canada (Ontario and Quebec), where Tree Pollen subcutaneous immunotherapy (SCIT) is already an available treatment option.

METHODS

A CMA was deemed appropriate and was based on the assumption that the SQ Tree SLIT-tablets have comparable efficacy to Tree Pollen SCIT. A societal perspective was adopted in the model, including relevant costs of medications, costs of health care services, and productivity losses. The time horizon in the model was three years, which corresponds to a minimal treatment course of allergy immunotherapy. Resource use and costs were based on published sources, where available, and validated by Canadian specialist clinicians (allergists) in active practice in Ontario and in Quebec, where applicable. A discount rate of 1.5% was applied in accordance with the Canadian Agency for Drugs and Technologies in Health (CADTH) guidelines. To assess the robustness of the results, scenario analyses were performed by testing alternative assumptions for selected parameters (e.g., Tree Pollen SCIT resource use, discount rates, number of injections, annual SCIT dosing with maintenance injections, and nurse time support), to evaluate their impact on the results of the analysis.

RESULTS

The direct costs, including the drug costs, and physician services costs, for three years of treatment, were similar for both SQ Tree SLIT-tablets vs. Tree Pollen SCIT in both Ontario and Quebec ($2799.01 and $2838.70 vs. $2233.76 and $2266.05 respectively). However, when the indirect costs (including patient's travel expenses and lost working hours) are included in the model, total savings for the treatment with SQ Tree SLIT-tablets of $1111.79 for Ontario and $1199.87 for Quebec were observed. Scenario analyses were conducted and showed that changes in assumptions continue to result in the savings of SQ Tree SLIT- tablets over Tree Pollen SCIT.

CONCLUSIONS

The CMA indicates that SQ Tree SLIT-tablets are a cost-minimizing alternative to Tree Pollen SCIT when considered from a societal perspective in Ontario and Quebec.

7

La nueva promesa de los biomarcadores

Circulating MIF Associated With Disease Severity and Clinical Response of Sublingual Immunotherapy in House Dust Mite-Induced Allergic Rhinitis.

Xie S, Zhang H, Wang F, Xie Z, Jiang W, Gao K

Front Pharmacol. 2021 Jul 8;12:681724.

BACKGROUND

Macrophage migration inhibitory factor (MIF) is described as a pro-inflammatory cytokine involved in many inflammatory and allergic disorders, but the role of MIF in allergic rhinitis (AR) remains poorly clarified. The aim of this study was to investigate the association between circulating MIF levels and house dust mite (HDM)-induced AR, and evaluate MIF as a potential biomarker in reflecting disease severity and predicting the clinical response of sublingual immunotherapy (SLIT) in HDM-induced AR patients.

METHODS

In this study, we enrolled 160 persistent HDM-induced AR patients (AR group), including 48 mild AR patients (MAR group) and 112 moderate-severe AR patients (MSAR group), and 77 healthy controls (HC group). Circulating levels of MIF were measured by ELISA, and the relationship between MIF concentrations and disease severity was assessed. In the MSAR group, 106 patients were assigned to receive SLIT for 3 years. At the end of the study, patients were categorized into good response group and poor response group, and associations between clinical variables or biomarkers and clinical response were analyzed by the multivariate regression analysis.

RESULTS

The concentrations of serum MIF were significantly higher in AR patients than in HCs, especially in those with MSAR. Moreover, circulating MIF levels were positively correlated with TNSS, VAS, serum HDM-specific IgE, total IgE, blood eosinophil count, and blood eosinophil percentage (all $p < 0.05$). Eighty MSAR patients finally completed SLIT, 45 patients obtained good response, and 35 patients resulted in poor response. The serum levels of MIF were significantly lower in the good-response group than in the poor-response group ($p < 0.001$). The receiver operating characteristic analysis for MIF showed good accuracy for predicting clinical response of SLIT (area under the curve = 0.877, $p < 0.001$). The multivariate regression analysis demonstrated that serum MIF was an independent factor for SLIT responsiveness.

CONCLUSION

Serum MIF appeared to be an important biological indicator in reflecting disease severity and an independent predictor for clinical responsiveness of SLIT in HDM-induced AR patients.

8

Reacciones locales exageradas y predicción de riesgo

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

Simsek IE, Aydogan M

Asian Pac J Allergy Immunol. 2021 Jul 11. Epub ahead of print.

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.

9

¿Cómo de eficaz será la combinación de ITO con huevo + probiótico?

Study protocol of a phase 2, dual-centre, randomised, controlled trial evaluating the effectiveness of probiotic and egg oral immunotherapy at inducing desensitisation or sustained unresponsiveness (remission) in participants with egg allergy compared with placebo (Probiotic Egg Allergen Oral Immunotherapy for Treatment of Egg Allergy: PEAT study).

Loke p, Chebar Lozinsky A, Orsini F, Wong LS, Leung AS, Tham EH, et al

BMJ Open. 2021 Jul 7;11(7):e044331.

INTRODUCTION

Egg allergy is the most common food allergy in children but recent studies have shown persistence or delayed resolution into adolescence. As there is currently no effective long-term treatment, definitive treatments that improve quality of life and prevent fatalities for food allergies are required. We have previously shown that a novel treatment comprising a combination of the probiotic Lactobacillus rhamnosus CGMCC 1.3724 with peanut oral immunotherapy (OIT) is highly effective at inducing sustained unresponsiveness, with benefit persisting to 4 years after treatment cessation in the majority of initial treatment responders. In this study, we plan to extend the probiotic food OIT platform to another allergen, namely egg. We describe the protocol for a phase 2, dual-centre, randomised, controlled trial evaluating the effectiveness of probiotic and egg OIT at inducing desensitisation or sustained unresponsiveness (remission) in participants with egg allergy compared with placebo.

METHODS AND ANALYSIS

80 participants aged 5-30 years of age with current egg allergy confirmed by double-blind placebo-controlled food challenge at study screening will be recruited from Australia and Singapore. There are two intervention arms-probiotic and egg OIT (active) or placebo. Interventions are administered once daily for 18 months. The primary outcome is the proportion of participants who attain 8-week sustained unresponsiveness in the active group versus placebo group.

ETHICS AND DISSEMINATION

This study has been approved by the Human Research Ethics Committees at the Royal Children's Hospital (HREC 2019.082) and the National Healthcare Group Domain Specific Review Board (2019/00029). Results will be published in peer-reviewed journals and disseminated via presentations at international conferences.

10

Gravedad de los síntomas en la alergia a alimentos: en busca del consenso

Improving severity scoring of food-induced allergic reactions: a global “Best-Worst Scaling” exercise

Aisling Stafford, Joan Bartra, Antony Aston, En Clare Mills, Montserrat Fernandez-Rivas, Paul J Turner

J Allergy Clin Immunol Pract. 2021 Jul 19;S2213-2198(21)00789-3. doi: 10.1016/j.jaip.2021.06.056. Online ahead of print.

BACKGROUND

There is no current consensus on assigning severity to food-induced allergic reactions, for example to assess the efficacy of allergen immunotherapy. Existing severity scores lack the capability to discriminate between non-anaphylaxis reactions of different severities. Attempts are ongoing to develop a more discriminatory score, which should ideally be data-driven and validated in multiple cohorts.

OBJECTIVE

To undertake an exercise using 'Best-Worst Scaling' (BWS) to define a potential 'gold standard' against which severity scoring of food-induced allergic reactions can be refined.

METHODS

Methods: We undertook a global survey to better understand how healthcare professionals rate the severity of food-induced allergic reactions, using BWS methodology. Respondents were given a number of patient case vignettes describing real-world allergic reactions, and asked to select the pair that, in their opinion, reflected the maximum difference in severity. Responses were then modelled and a "preference" score (representing severity) determined for each scenario. Scenarios were also scored using existing published scoring systems, and the scores compared to the BWS score using Spearman's R correlation and Cohen's kappa. Given the differences in definitions of anaphylaxis globally, we also evaluated differences in BWS ranking depending on the geographical location of respondents.

RESULTS

334 complete responses were received, 183 (55%) from Europe and 65 (20%) from North America. Perception of severity of some reactions appeared to be affected by geographical location. The comparison of BWS ranking with current grading systems identified significant issues that varied from one grading system to another, such as prominence to some symptoms e.g. vomiting which skew grading when using scoring systems not designed for food allergy. In general, current scoring systems poorly discriminate against more mild symptoms and often overestimate their severity.

CONCLUSION

These data provide a methodology free of user scale bias to help define a potential, consensus-driven gold-standard which can be used to guide and validate the development of improved grading systems to score food induced allergic symptoms, and highlight areas for education where there is potential to mis-categorize severity.

1

En duda la eficacia de la ITA intralinfática

Efficacy and safety of intralymphatic immunotherapy in allergic rhinitis: A systematic review and meta-analysis

Nor Rahimah Aini, Norhayati Mohd Noor, Mohd Khairi Md Daud, Sarah K Wise, Baharudin Abdullah

Clin Transl Allergy. 2021 Aug 17;11(6):e12055. doi: 10.1002/clt2.12055. eCollection 2021 Aug.

ARTÍCULO DESTACADO

BACKGROUND

Intralymphatic immunotherapy (ILIT) is a potential treatment option for allergic rhinitis (AR). We aimed to determine the efficacy (primary outcomes) and safety (secondary outcomes) of ILIT in treating patients with AR.

METHODS

An electronic literature search was performed using MEDLINE and Cochrane Central Register of Controlled Trials CENTRAL (from their inception to December 2020). A random-effects model was used to estimate the pooled prevalence with 95% confidence intervals. This study is registered with PROSPERO (CRD42019126271).

RESULTS

We retrieved a total of 285 articles, of which 11 satisfied our inclusion criteria. There were 452 participants with age ranged from 15 to 58 years old. Intralymphatic immunotherapy was given in three doses with intervals of four weeks between doses in 10 trials. One trial gave three and six doses with an interval of two weeks. Both primary and secondary outcomes showed no difference between ILIT and placebo for all trials. There was no difference in the combined symptoms and medication score (SMD -0.51, 95% CI -1.31 to 0.28), symptoms score (SMD -0.27, 95% CI -0.91 to 0.38), medication score (SMD -6.56, 95% CI -21.48 to 8.37), rescue medication (RR 12.32, 95% CI 0.72-211.79) and the overall improvement score (MD -0.07, 95% CI -2.28 to 2.14) between ILIT and placebo. No major adverse events noted.

CONCLUSIONS

Intralymphatic immunotherapy possibly has a role in the treatment of AR patients. This review found it is safe but not effective, which could be contributed by the high variation amongst the trials. Future trials should involve larger numbers of participants and report standardized administration of ILIT and outcome measures.

2

Dupilumab como adyuvante

Short-Term Subcutaneous Allergy Immunotherapy and Dupilumab are Well Tolerated in Allergic Rhinitis: A Randomized Trial.

Corren J, Saini SS, Gagnon R, Moss MH, Sussman G, Jacobs J, et al.

J Asthma Allergy. 2021 Aug 16;14:1045-1063.

BACKGROUND

Subcutaneous immunotherapy (SCIT) has been proven as an effective therapy against some allergens for seasonal allergic rhinitis (SAR) patients unresponsive to intranasal corticosteroids and/or antihistamines but carries risk of systemic allergic reactions. Dupilumab blocks the shared receptor component for interleukin-4 and interleukin 13, key and central drivers of type 2 inflammation in multiple diseases.

OBJECTIVE

To evaluate the efficacy and safety of SCIT+dupilumab vs SCIT alone.

METHODS

This phase 2a, multicenter, double-blind, placebo-controlled parallel-group study conducted in 103 adults with grass pollen-induced SAR (NCT03558997) randomized patients 1:1:1:1 to SCIT, dupilumab (300 mg every 2 weeks), SCIT+dupilumab, or placebo. SCIT was administered using an 8-week cluster protocol followed by 8 weeks of maintenance injections. Primary endpoint was change from pre-treatment baseline in area under the curve (AUC) in total nasal symptom score (TNSS) 0-1 h following nasal allergen challenge (NAC) with timothy grass extract at Week 17.

RESULTS

Although 16 weeks of treatment with SCIT+dupilumab did not significantly improve TNSS AUC (0-1 h) following NAC at Week 17 vs SCIT (least squares mean -56.76% vs -52.03%), a higher proportion of SCIT+dupilumab treated patients (61.5%) achieved SCIT maintenance dose vs SCIT (46.2%). A lower proportion of SCIT+dupilumab-treated patients (7.7%) required epinephrine rescue treatment vs SCIT (19.2%). There were significantly fewer withdrawals in the SCIT+dupilumab group than in the SCIT group (n = 2 [7.7%] vs n = 8 [30.8%]; P = 0.0216); the majority of SCIT group withdrawals were due to SCIT-related intolerability, compared with no discontinuations from the SCIT+dupilumab group.

CONCLUSION

In SAR patients, 16 weeks of SCIT+dupilumab may improve SCIT tolerability but did not incrementally reduce post-allergen challenge nasal symptoms compared with SCIT alone.

3

ITA subcutánea y sublingual cara a cara

Efficacy of subcutaneous and sublingual immunotherapy for house dust mite allergy: a network meta-analysis-based comparison.

Kim JY, Jang MJ, Kim DY, Park SW, Han DH

: J Allergy Clin Immunol Pract. 2021 Aug 28:S2213-2198(21)00924-7. doi: 10.1016/j.jaip.2021.08.018. Epub ahead of print.

BACKGROUND

Meta-analyses comparing the efficacy of sublingual immunotherapy (SLIT) and subcutaneous immunotherapy (SCIT) for house dust mite (HDM) allergy are lacking.

OBJECTIVE

To compare the efficacy of SLIT drops, SLIT tablets, and SCIT in patients with perennial allergic rhinitis (AR) through network analysis.

METHODS

Frequentist network meta-analyses estimated the standardized mean difference (SMD) across the three immunotherapy modalities on AR symptom and medication score data from double-blind randomized clinical trials (DBRCTs). Random effects models were investigated.

RESULTS

Twenty-six DBRCTs were included in this meta-analysis for the symptom score, and 18 DBRCTs were included for the medication score. In the direct pairwise meta-analysis, significant reduction of the symptom score was observed for all immunotherapy modalities as compared to the placebo: pooled SMDs of -0.461 (95% CI, -0.795 to -0.127) for SLIT-drop, -0.329 (95% CI, -0.426 to -0.231) for SLIT-tablet, and -1.669 (95% CI, -2.753 to -0.585) for SCIT. For the medication score, significant reduction was observed for all the modalities. In network meta-analysis, the clinical efficacy of SCIT based on the symptom score was greater than SLIT-drop or SLITtablet (SMD: -0.697, 95% CI, -1.105 to -0.288 and SMD: -0.819, 95% CI, -1.242 to -0.397). However, there was no significant difference in the symptom score between SLIT-drop and SLIT-tablet.

CONCLUSION

This study demonstrated the clinical efficacy of all HDM immunotherapy modalities and suggested that SCIT may be more effective than SLIT drop or tablet in controlling symptoms of allergic rhinitis.

4

¿ITA intralinfática como refuerzo tras ITA subcutánea?

High dose pollen intralymphatic immunotherapy: Two RDBPC trials question the benefit of dose increase

Hellkvist L, Hjalmarsson E, Weinfeld D, Dahl Å, Karlsson A, Westman M, et al.

Allergy. 2021 Aug 11. doi: 10.1111/all.15042. Epub ahead of print

BACKGROUND

The same dosing schedule, 1000 SQ-U times three, with one-month intervals, have been evaluated in most trials of intralymphatic immunotherapy (ILIT) for the treatment of allergic rhinitis (AR). The present studies evaluated if a dose escalation in ILIT can enhance the clinical and immunological effects, without compromising safety.

METHODS

Two randomized double-blind placebo-controlled trials of ILIT for grass pollen-induced AR were performed. The first included 29 patients that had recently ended 3 years of SCIT and the second contained 39 not previously vaccinated patients. An up-dosage of 1000-3000-10,000 (5000 + 5000 with 30 minutes apart) SQ-U with 1 month in between was evaluated.

RESULTS

Doses up to 10,000 SQ-U were safe after recent SCIT. The combined symptom-medication scores (CSMS) were reduced by 31% and the grass-specific IgG4 levels in blood were doubled. In ILIT de novo, the two first patients that received active treatment developed serious adverse reactions at 5000 SQ-U. A modified updosing schedule; 1000 3000-3000 SQ-U appeared to be safe but failed to improve the CSMS. Flow cytometry analyses showed increased activation of lymph nodederived dendritic but not T cells. Quality of life and nasal provocation response did not improve in any study.

CONCLUSION

Intralymphatic immunotherapy in high doses after SCIT appears to further reduce grass pollen-induced seasonal symptoms and may be considered as an add-on treatment for patients that do not reach full symptom control after SCIT. Up-dosing schedules de novo with three monthly injections that exceeds 3000 SQ-U should be avoided.

5

Reactividad cruzada en alérgicos a ácaros e ITA: continua la controversia

The effect of immunotherapy on cross-reactivity between house dust mite and other allergens in house dust mite -sensitized patients with allergic rhinitis.

Zhao L, Zhang Y, Zhang S, Zhang L, Lan F

Expert Rev Clin Immunol. 2021 Aug 18:1-7. doi: 10.1080/1744666X.2021.1968834. Epub ahead of print

INTRODUCTION

House dust mite (HDM) is a main perennial allergen causing allergic rhinitis (AR). It has been shown that HDM cross-reacts with a variety of other allergens. Presently, allergen-specific immunotherapy (AIT) is an effective way for management of mono-sensitized HDM+ AR patients. However, management approaches to polysensitized HDM-sensitized AR patients are not standardized yet.

AREAS COVERED

This article reviews the data available in the literature for cross-reactivity between HDM and inhalant or food allergens, the diagnosis of cross reactivity in HDM-sensitized AR patients, and the effect of immunotherapy on cross-reactivity in HDM-sensitized AR patients; which may help to develop effective therapeutic strategies for management of polysensitized HDM-sensitized AR patients in the future.

EXPERT OPINION

Pan-allergen proteins such as tropomyosin, arginine kinase (AK), glutathione S-transferase (GST), and hemocyanin are responsible for cross-reactivity between HDM and other allergens. To distinguish genuine or cross-reactive sensitization, molecular- or component resolved diagnosis is suggested to apply in HDMsensitized AR patients. The effect of HDM immunotherapy to treat the associated cross reactivity in HDM-sensitized AR patients is still contradictory, and might be dependent on the degree of homology between two allergens. Furthermore, targeting tropomyosin might be a promising way to treat HDM patients with allergen crossreactivity.

ABBREVIATIONS

AIT: allergen specific immunotherapy; AK: arginine kinase; AR: allergic rhinitis; CRD: component-resolved diagnostics; Der f: Dermatophagoides farina; Derp: Dermatophagoides pteronyssinus; EAACI: European Academy of Allergy and Clinical Immunology; GST: glutathione S-transferase; GWAS: genomewide association study; HDM: house dust mite; IgE: immunoglobulin E; RAST: radioallergosorbent test; sIgE: specific IgE; SIT: specific immunotherapy; SCIT: subcutaneous immunotherapy; SLIT: sublingual immunotherapy; SPT: skin prick test.

6

La vida real con sus ventajas e inconvenientes

Real-life studies in allergen immunotherapy.

Passalacqua G, Bagnasco D

Curr Opin Allergy Clin Immunol. 2021 Aug 1;21(4):361-367.

PURPOSE OF REVIEW

Real-life (or real-world) studies can provide information that cannot be derived from randomized controlled trials. This approach is currently becoming of relevance for many treatments. In recent years, the real-life method has been applied also to allergen immunotherapy, providing new insights on it. We reviewed herein the available literature on the argument.

RECENT FINDINGS

Several prospective and retrospective studies on allergen immunotherapy in the real-world setting have been published, mostly in the last 5 years. Most of them focused on adverse events, compliance, and the long term/preventive effects, and evidenced an overall favorable profile for different products and different allergens.

SUMMARY

Real life study provided novel information and evidenced those aspects of immunotherapy that worth a more detailed approach, without the strict limitations usually imposed by controlled randomized trials.

7

Lo último sobre rinitis alérgica

Advances and highlights in allergic rhinitis.

Zhang Y, Lan F, Zhang L

Allergy. 2021 Aug 11. doi: 10.1111/all.15044. Epub ahead of print.

ABSTRACT

Allergic rhinitis (AR) is a growing public health, medical and economic problem worldwide. The current review describes the major discoveries related to AR during the past 2 years, including risk factors for the prevalence of AR, the corresponding diagnostic strategy, precise underlying immunological mechanisms, and efficient therapies for AR during the ongoing global "coronavirus disease 2019 (COVID-19) pandemic. The review further attempts to highlight future research perspectives. Increasing evidence suggests that environmental exposures, climate changes, and lifestyle are important risk factors for AR. Consequently, detailed investigation of the exposome and the connection between environmental exposures and health in the future should provide better risk profiles instead of single predictors, and also help mitigate adverse health outcomes in allergic diseases. Although patients with dual AR, a newly defined AR phenotype, display perennial and seasonal allergens-related nasal symptoms, they are only allergic to seasonal allergens, indicating the importance of measuring inflammation at the local sites. Herein, we suggest that a combination of precise diagnosis in local sites and traditional diagnostic methods may enhance the precision medicine-based approach for management of AR; however, this awaits further investigations. Apart from traditional treatments, social distancing, washing hands, and disinfection are also required to better manage AR patients in the ongoing global COVID-19 pandemic. Despite recent advances in understanding the immune mechanisms underlying the effects of allergen immunotherapy (AIT), further understanding changes of cell profiles after AIT and accurately evaluate the efficacy of AIT are required.

8

La rinitis alérgica local va ganando aliados terapéuticos

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

Bozek A, Galuszka B, Gawlik R, Misiolek M, Ścierski W, Grzanka A, et al.

J Asthma. 2021 Aug 24:1-11. doi: 10.1080/02770903.2021.1971701. Epub ahead of print.

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

9

¿Tratamiento para la rinitis? Ninguna opción es mala

Meta-analyses of the efficacy of pharmacotherapies and sublingual allergy immunotherapy tablets for allergic rhinitis in adults and children.

Meltzer EO, Wallace D, Friedman HS, Navaratnam P, Scott EP, Nolte H

Rhinology. 2021 Aug 31. doi: 10.4193/Rhin21.054. Epub ahead of print.

Treatment options for seasonal and perennial allergic rhinitis (SAR/PAR) include pharmacotherapies and allergy immunotherapy. These meta analyses evaluated the efficacy of pharmacotherapies and sublingual immunotherapy tablets (SLIT-tablets) versus placebo on nasal symptoms associated with SAR and PAR.

METHODS

Randomized, double-blind, placebo-controlled trials were identified from systematic PubMED/EMBASE searches through 7/18/2019 (PROSPERO protocol CRD42018105632). The primary outcome was mean numerical difference in total nasal symptom score (TNSS; 0-12) between active treatment and placebo at the end of the assessment period. Random-effects meta-analyses estimated the mean difference for each medication group weighted by the inverse of the trial variance. Publication bias assessments and sensitivity analyses were conducted.

RESULTS

Rescue symptom-relieving pharmacotherapy was prohibited in most pharmacotherapy trials but was allowed in all SLIT-tablet trials. For adult/adolescent SAR, the mean numerical difference (95% CI) in TNSS versus placebo was: intranasal corticosteroids (INCS)=1.38 (1.18, 1.58; 39 trials); combination intranasal antihistamine/INCS=1.34 (1.15, 1.54; 4 trials); intranasal antihistamines=0.72 (0.56, 0.89; 13 trials); oral antihistamine=0.62 (0.35, 0.90; 18 trials); SLIT-tablets=0.57 (0.41, 0.73; 4 trials); and montelukast=0.48 (0.36, 0.60; 10 trials). For adult/adolescent PAR, mean difference in TNSS versus placebo (95% CI) was: INCS=0.82 (0.66, 0.97; 14 trials); SLIT-tablets=0.65 (0.42, 0.88; 3 trials); and oral antihistamine=0.27 (0.11, 0.42; 3 trials). The number of eligible trials limited meta-analyses for pediatric SAR/PAR.

CONCLUSIONS

All treatments significantly improved nasal symptoms versus placebo. SLIT-tablets provided improvement in TNSS despite access to rescue symptomrelieving pharmacotherapy. Extensive trial heterogeneity and strong indications of publication bias preclude the comparison of treatment effects among treatment classes.

10

ITA con mezclas en pacientes polialérgicos: ¿sí o no?

Safety and Effectiveness of a Single Multiallergen Subcutaneous Immunotherapy in Polyallergic Patients.

Nevot-Falcó S, Mancebo EG, Martorell A, Calatayud CM, Perotti SC, Rojas M, et al.

Int Arch Allergy Immunol. 2021 Aug 13:1-5. doi: 10.1159/000517473. Epub ahead of print

BACKGROUND

As the number of allergic sensitizations increases the severity of allergic respiratory diseases worsens. Multiple monoallergen immunotherapy can be accompanied by poor treatment adherence and high costs, single multiallergen immunotherapy needs to prove efficacy whilst maintaining a good safety profile.

METHODS

Observational, retrospective, multicenter study using a 2 pollen single undiluted multiallergen subcutaneous immunotherapy (SCIT) in routine clinical practice in Spain. Patients with rhinoconjunctivitis, with/without controlled asthma, sensitized to grass, olive, Parietaria, Cupressus, plane tree and/or Salsola pollen were included. Primary and secondary clinical efficacy endpoints were quality of life (mini Rhinitis Quality of Life Questionnaire (miniRQLQ)) and visual analogue scale (VAS) respectively. All adverse events were documented.

RESULTS

Ten centers included 97 patients, median age 32 years. SCIT treatment included combinations of grass mix with olive, Parietaria, Cupressus, plane tree or Salsola or olive with Parietaria, Cupressus or Salsola. The mean duration of SCIT was 1.8 years with a high treatment adherence (73%). Significant improvement in quality of life, nasal and ocular symptoms, activity limitations and practical problems ($p< 0.0001$) and other symptoms ($p= 0.024$) was observed. Most patients did not develop asthma-like symptoms and a significant improvement of all allergic symptom severity was perceived. VAS showed a significant improvement in rhinoconjunctivitis and asthma by patients and physicians. Twenty-nine patients experienced adverse reactions, 25 had local and 6 had systemic reactions.

CONCLUSIONS

Single undiluted multiallergen SCIT treatment of two different pollens is efficacious and safe in both children and adults, showing that it is a suitable option for the treatment of polyallergic patients.

1

Una vez más, los datos apoyan la dosis eficaz

How important is proper dosing for subcutaneous and sublingual allergy immunotherapy?

Nelson HS

Allergy Asthma Proc. 2021 Sep 1;42(5):368-377

ARTÍCULO DESTACADO

BACKGROUND

Results of surveys report that allergists use a wide range of doses for allergy immunotherapy; however, results of randomized, double-blind, placebo controlled studies suggest that the range of the optimum effective dosing is relatively narrow.

OBJECTIVE

To review studies that established effective or less than fully effective doses for allergy immunotherapy.

METHODS

Studies were reviewed that established effective and ineffective subcutaneous and sublingual immunotherapy doses. Only those studies that expressed dosing in terms of the content of a major allergen in the maintenance doses were included in defining effective and ineffective doses.

RESULTS

Studies were identified that showed effective doses for subcutaneous injection, established in randomized, double-blind, placebo controlled trials, for short ragweed, timothy grass, house-dust mites, cat and dog dander, birch, and Alternaria. For short ragweed, timothy grass, Dermatophagoides pteronyssinus, and cat and dog dander, less effective doses were determined, along with effective doses; the less effective doses were only one-fifth to one-tenth less in allergen content than were the effective doses. Effective doses of cockroach and all fungal extracts except Alternaria have not been established. Information is available on the mean major allergen content of U.S. standardized and a few nonstandardized extracts, which allows the information on effective and ineffective dosing to be used in prescribing subcutaneous allergy immunotherapy. With sublingual allergy immunotherapy, all the approved tablets had multidose studies that determined the optimal dose. For the U.S. liquid extracts, to my knowledge, there are no studies to define effective doses except for ragweed.

CONCLUSIONS

Although a wide range of doses are prescribed by U.S. allergists, analysis of available data suggests that effective doses fall within a narrow range and that use of doses one-fifth or one-tenth of the effective doses may sacrifice most or all of the potential efficacy of the treatment.

2

Biomarcadores de respuesta a la ITA: seguimos avanzando

Coordinated IgG2 and IgE responses as a marker of allergen immunotherapy efficacy

Bordas-Le Floch V, Berjont N, Batard T, Varese N, O'Hehir RE, et al.

Allergy. 2021 Sep 22. doi: 10.1111/all.15107. Epub ahead of print

BACKGROUND

IgG2 responses are associated with repeated antigen exposure and display highly mutated variable domains. A recent study highlighted a role of IgG2+ memory B cells and allergen-specific IgG2 levels after a 3rd consecutive pre-seasonal sublingual allergen immunotherapy (AIT) with grass pollen tablet. Herein, we aim to explore changes in allergen-specific IgG2 in individuals undergoing house dust mite immunotherapy (HDM-AIT) and explore whether the interrelationship with other humoral responses (i.e. IgG4 and IgE) may discriminate between high and low responders.

METHODS

Levels of serum D. pteronyssinus- and D. farinae-specific IgG2, IgG4 and IgE antibodies were measured by ELISA or ImmunoCap in a sub-group of individuals enrolled in a randomized, double-blind, placebo controlled, sublingual AIT study evaluating the safety and efficacy of a 300 IR HDM tablet.

RESULTS

After 1-year sublingual AIT, HDM-specific serum IgG2 responses increase mostly in high versus low responders and are distinctive according to the clinical benefit. Higher correlation between HDM specific IgG2, IgE and/or IgG4 responses are seen in subjects benefiting the most from HDM-AIT as indicated by changes in Average Total Combined Scores. More strikingly, statistically significant correlation between HDM-specific IgG2 and IgE responses are only observed in individuals stratified as high responders.

CONCLUSIONS

We provide evidence for coordinated serum immune responses upon AIT in HDM-allergic subjects exhibiting high clinical benefit when compared with low responders. Assessing HDM-specific IgE, IgG2 and IgG4 in serum could be used as follow-up combined markers to support decision as to AIT continuation and/or adaptation.

3

¿ITA sublingual para la rinitis alérgica local?

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

Bozek A, Galuszka B, Gawlik R, Misiolek M, Scierski W, et al.

J Asthma. 2021 Sep 6:1-9. doi: 10.1080/02770903.2021.1971701. Epub ahead of print

BACKGROUND

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.

4

Dos enfoques divergentes: mezclar o no mezclar

To mix or not to mix in allergy immunotherapy vaccines

Nelson HS

Curr Opin Allergy Clin Immunol. 2021 Sep 1. doi: 10.1097/ACI.0000000000000784. Epub ahead of print.

PURPOSE OF REVIEW

European and US allergists generally do not agree on the approach to subcutaneous allergy immunotherapy in patients with multiple allergies. The North American approach is to treat with a mixture that contains all the allergen extracts to which the patient has evident clinical sensitivity, whereas the European approach is to select for treatment the one or at the most two allergens that are clinically most important for the patient.

RECENT FINDINGS

Recent society guidelines continue to recommend these differing practices of treating the polyallergic patient and reviews of prescribing practices indicate these divergent recommendations are followed in Europe and the USA.

SUMMARY

The objections by European allergists to the practice by US allergists are that multiallergen immunotherapy leads to dilution of allergens to less than effective doses, that proteases in some extracts can degrade allergens in other extracts, that there is a problem of safety and inability to determine which component extract caused a systemic reaction, and finally that there is alack of convincing studies demonstrating efficacy of multiallergen mixtures. Each of these contentions is addressed.

5

¿Qué preocupa a los padres de niños con alergia alimentaria?

Caregiver perceptions and attitudes associated with oral immunotherapy on social media.

Kochis S, Keet C, Claus LE, Hairston T, Links AR, Boss EF

Allergy Asthma Proc. 2021 Sep 1;42(5):432-438. doi: 10.2500/aap.2021.42.210050.

BACKGROUND

Caregiver values and preferences with regard to oral immunotherapy (OIT) for treatment of food allergies are not widely reported. Understanding caregiver perspectives is integral to establishing shared decision-making in the treatment of food allergy.

OBJECTIVE

We aimed to understand caregiver opinions that may influence caregivers in their decisions about OIT through social media.

METHODS

We searched a popular parenting web site for posts related to OIT from December 2008 to September 2019. We applied a Preferred Reporting Items for Systematic Reviews and Meta-Analyses framework to review posts for inclusion, performed thematic content analysis to determine common themes, and calculated frequencies for each theme and subtheme. Posts and comments were included if they contained discussions about OIT for immunoglobulin E-mediated food allergy and were excluded if they were duplicates, comments from an original post from the original user, or comments on a nonrelevant original post.

RESULTS

Of 1300 posts and comments retrieved, 174 were included (13%). Most were excluded because they did not directly address OIT for food allergy. Relevant posts could fall into multiple themes and were categorized under three main themes: attitudes (n = 128, "I am scared to do OIT but scared not to!"), logistics (n = 168, "We will be doing this once LO [little one] is a little older"), and questions (n = 32, "How does it work?")

CONCLUSION

Caregivers communicate with each other through social media, expressing attitudes, logistics, and questions about OIT. Understanding these lay perspectives may help guide clinicians in counseling and engage caregivers in decision-making.

6

En busca de la medicina de precisión

Advances and highlights in biomarkers of allergic diseases

Ogulur I, Pat Y, Ardicli O, Barletta E, Cevhertas L, Fernandez-Santamaria R, et al

Allergy. 2021 Sep 14. doi: 10.1111/all.15089. Epub ahead of print

ABSTRACT

During the past years, there has been a global outbreak of allergic diseases, presenting a considerable medical and socioeconomical burden. A large fraction of allergic diseases is characterized by a type 2 immune response involving Th2 cells, type 2 innate lymphoid cells, eosinophils, mast cells, and M2 macrophages. Biomarkers are valuable parameters for precision medicine as they provide information on the disease endotypes, clusters, precision diagnoses, identification of therapeutic targets, and monitoring of treatment efficacies. The availability of powerful omics technologies, together with integrated data analysis and network based approaches can help the identification of clinically useful biomarkers. These biomarkers need to be accurately quantified using robust and reproducible methods, such as reliable and pointof-care systems. Ideally, samples should be collected using quick, cost-efficient and noninvasive methods. In recent years, a plethora of research has been directed toward finding novel biomarkers of allergic diseases. Promising biomarkers of type 2 allergic diseases include sputum eosinophils, serum periostin and exhaled nitric oxide. Several other biomarkers, such as pro-inflammatory mediators, miRNAs, eicosanoid molecules, epithelial barrier integrity, and microbiota changes are useful for diagnosis and monitoring of allergic diseases and can be quantified in serum, body fluids and exhaled air. Herein, we review recent studies on biomarkers for the diagnosis and treatment of asthma, chronic urticaria, atopic dermatitis, allergic rhinitis, chronic rhinosinusitis, food allergies, anaphylaxis, drug hypersensitivity and allergen immunotherapy. In addition, we discuss COVID-19 and allergic diseases within the perspective of biomarkers and recommendations on the management of allergic and asthmatic patients during the COVID-19 pandemic.

7

Cómo hacer que la ITO sea más segura

Combining Anti-IgE Monoclonal Antibodies and Oral Immunotherapy for the Treatment of Food Allergy

Guilleminault L, Michelet M, Reber LL

Clin Rev Allergy Immunol. 2021 Sep 22. doi: 10.1007/s12016-021-08902-0. Epub ahead of print.

ABSTRACT

Immunoglobulin E (IgE)-mediated food allergy is a real public health problem worldwide. The prevalence of food allergy is particularly high in children. Patients with food allergy experience high morbidity with a change in quality of life due to the risk of severe anaphylaxis. Current treatment options are poor. Allergen avoidance is widely recommended but exposes patients to accidental ingestion. Oral immunotherapy is also used in patients with food allergies to the most common allergens. Oral immunotherapy consists of a daily administration of small, gradually increasing amounts of allergens to induce desensitisation. This procedure aims at inducing immune tolerance to the ingested food allergens. However, some patients experience adverse reactions and discontinue oral immunotherapy.Given that IgE plays a crucial role in food allergy and anti-IgE are effective in allergic asthma, the use of anti-IgE therapeutic monoclonal antibodies (mAbs) such as omalizumab has been assessed in food allergy patients. The use of omalizumab as a monotherapy in food allergy has not been extensively studied but looks promising. There is more published evidence regarding the effect of omalizumab and oral immunotherapy in food allergy. Given the promising results of oral immunotherapy regarding sustained tolerance in clinical trials and the potential capacity of omalizumab to reduce symptoms in case of accidental exposure, a strategy combining oral immunotherapy with omalizumab pre-treatment has been suggested as a safer option in patients with severe food allergy compared to isolated therapy. Omalizumab seems useful in ensuring safer administration of oral immunotherapy with the oral immunotherapy maintenance dose being reached more rapidly. Quality-of-life improvement is greater with oral immunotherapy + omalizumab compared to oral immunotherapy alone. Moreover, sustained unresponsiveness is achieved more frequently with omalizumab. Considering that precision medicine and personalised therapy are major goals for allergic diseases, predictive biomarkers are crucial inorder to identify food allergy patients more likely to benefit from anti IgE therapies.

8

MicroRNAs: procesos epigenéticos en pacientes con alergia respiratoria

Sputum microRNA-screening reveals Prostaglandin EP3 receptor as selective target in allergen-specific immunotherapy.

Jakwerth CA, Chaker AM, Guerth F, Oelsner M, Pechtold L

Clin Exp Allergy. 2021 Sep 12. doi: 10.1111/cea.14013. Epub ahead of print.

BACKGROUND

Several microRNAs (miRs) have been described as potential biomarkers in liquid biopsies and in the context of allergic asthma, while therapeutic effects on the airway expression of miRs remain elusive. In this study, we investigated epigenetic miR-associated mechanisms in the sputum of grass pollen-allergic patients with and without allergen-specific immunotherapy (AIT).

METHODS

Induced sputum samples of healthy controls (HC), AIT-treated and -untreated grass pollen-allergic rhinitis patients with (AA) and without asthma (AR) were profiled using miR microarray and whole-transcriptome microarray analysis of the same samples. miR targets were predicted in silico and used to identify inverse regulation. Local PGE2 levels were measured using ELISA.

RESULTS

Two hundred and fifty-nine miRs were upregulated in the sputum of AA patients compared with HC, while only one was downregulated. The inverse picture was observed in induced sputum of AIT-treated patients: while 21 miRs were downregulated only 4 miRs were upregulated in asthmatics upon AIT. Of these 4 miRs, miR-3935 stood out, as its predicted target PTGER3, the prostaglandin EP3 receptor, was downregulated in treated AA patients compared with untreated. The levels of its ligand PGE2 in the sputum supernatants of these samples were increased in allergic patients, especially asthmatics, and downregulated after AIT. Finally, local PGE2 levels correlated with ILC2 frequencies, secreted sputum IL-13 levels, inflammatory cell load, sputum eosinophils and symptom burden.

CONCLUSIONS

While profiling the sputum of allergic patients for novel miR expression patterns, we uncovered an association between miR-3935 and its predicted target gene, the prostaglandin E3 receptor, which might mediate AIT effects through suppression of the PGE2 -PTGER3 axis.

9

ITO con huevo e inicio en domicilio: ¿parece razonable?

Home-Based Up-Dosing in Build-Up Phase of Oral Immunotherapy of Egg Allergy Is Safe and Feasible in Real-World Practice.

Jeong HI, Lee B, Kim S, Kyung Y, Jung M, Kim M, et al.

Asthma Immunol Res. 2021 Sep;13(5):791-798

ABSTRACT

Oral immunotherapy (OIT) has emerged to build sustained unresponsiveness or tolerance in patients with egg allergy. However, it is important to increase compliance and ensure safety because OIT requires an extended period of time and has a risk of side effects like anaphylaxis. We aimed to show the feasibility and safety of OIT during the build-up phase using a home-based, up-dosing method in children with egg allergy. Sixteen patients aged 4 to 12 years with egg allergy were enrolled. Patients increased the dose of boiled egg white (EW) by 5% per day at home and 25% per month at the hospital, with a target dose of 40 g of boiled EW (4.0 g of EW proteins). A historical control group (n = 16) was matched for age, sex, and clinical characteristics for comparisons with the OIT group. Oral food challenge (OFC) tests were performed after completing the build-up phase. In the OIT group, 93.8% (15/16) of patients achieved desensitization, with only 1 patient discontinuing OIT before the maintenance phase due to repeated allergic reactions. Mild allergic reactions and anaphylaxis occurred in 12 (75.0%) and 2 patients (12.5%), respectively. However, there were no significant adverse reactions such as serious anxiety or life-threatening events that required discontinuation of treatment. On the contrary, only 1 patient (6.3%) in the control group passed an OFC of 40 g of boiled EW during the same period ($P < 0.001$). Our results suggest that home based up-dosing protocols using boiled eggs may be safe and feasible for the build-up phase of OIT in children with egg allergy.

10

Historia de la eficacia, seguridad y calidad de una ITA con venenos

Venom Immunotherapy: From Proteins to Product to Patient Protectio

Martin Feindor, Matthew D. Heath, Simon J. Hewings et al.

Toxins (Basel) 2021 Sep 01;13(9)

ABSTRACT

In this review, we outline and reflect on the important differences between allergen-specific immunotherapy for inhalant allergies (i.e., aeroallergens) and venom-specific immunotherapy (VIT), with a special focus on Venomil® Bee and Wasp. Venomil® is provided as a freeze dried extract and a diluent to prepare a solution for injection for the treatment of patients with IgE-mediated allergies to bee and/or wasp venom and for evaluating the degree of sensitivity in a skin test. While the materials that make up the product have not changed, the suppliers of raw materials have changed over the years. Here, we consolidate relevant historical safety and efficacy studies that used products from shared manufacture supply profiles, i.e., products from Bayer or Hollister-Stier. We also consider the characterization and standardization of venom marker allergens, providing insights into manufacturing controls that have produced stable and consistent quality profiles over many years. Quality differences between products and their impacts on treatment outcomes have been a current topic of discussion and further research. Finally, we review the considerations surrounding the choice of depot adjuvant most suitable to augmenting VIT.

1

Las células T también son importantes en la alergia alimentaria

Allergen-specific T cells and clinical features of food allergy: Lessons from CoFAR immunotherapy cohorts.

Berin MC, Agashe C, Burks AW, Chiang D, Davidson WF, Dawson P, et al.
J Allergy Clin Immunol. 2021 Oct 12:S0091-6749(21)01518-9. doi: 10.1016/j.jaci.2021.09.029. Epub ahead of print.

ARTÍCULO DESTACADO

BACKGROUND
Allergen-specific IL-4+ and IL-13+ CD4+ cells (Type 2 cells) are essential for helping B cells class-switch to IgE and establishing an allergic milieu in the gastrointestinal tract. The role of T cells in established food allergy is less clear.
OBJECTIVE
We examined the food allergen-specific T cell response in participants of two food allergen immunotherapy (IT) trials to assess the relationship of the T cell response to clinical phenotypes including response to IT.
METHODS
Blood was obtained from 84 peanut-allergic and 142 egg-allergic participants who underwent double-blind placebo-controlled food challenges. Peanut and egg-responsive T cells were identified by CD154 upregulation after stimulation with the respective extract. Intracellular cytokines and chemokine receptors were also detected. The response to peanut epicutaneous immunotherapy (CoFAR6, 49 participants receiving EPIT) and egg oral immunotherapy or baked egg diet (CoFAR7, 92 participants) was monitored over time.
RESULTS
Peanut-specific Type 2 and CCR6+ T cells were negatively correlated with each other, and differently associated with immune parameters including specific IgE and basophil activation test. At baseline, Type 2 cells, but not CCR6+ cells, were predictive of clinical parameters including successfully consumed dose of peanut and baked egg tolerance. Exposure to peanut or egg immunotherapy was associated with a decrease in Type 2 cell frequency. At baseline, high egg-specific Type 2 cell frequency was the most predictive immune feature of oral immunotherapy failure.
CONCLUSIONS
Food-specific Type 2 T cells at baseline are informative of threshold of reactivity and response to immunotherapy.

2

Diseño en 3 fases en los ensayos de ITA

Allergen immunotherapy: A three-stage design for allergen immunotherapy trials.

Tang X, Rabin RL, Yan LK
Allergy. 2021 Oct 2. doi: 10.1111/all.15117. Epub ahead of print. PMID: 34599605.

BACKGROUND
Clinical trials of allergen immunotherapy (AIT) may require up to 5 years to complete. These lengthy trials may be complicated by high and potentially differential dropouts, especially among participants who perceive that they are receiving placebo. We propose a three-stage design in which the placebo group in Stage 1 crosses over to receive active treatment in Stage 2. In Stage 3, AIT is discontinued to determine whether benefit is maintained post treatment. We apply inferential statistics to support the three-stage design for clinical trials to determine clinical efficacy, treatment response over time, and sustained response to AIT.
METHODS
The proposed framework constitutes a series of hypothesis tests for comparing treatment responses at the end of each stage. A simulation study was performed to illustrate the statistical properties under varying statistical missing mechanisms and effect sizes.
RESULTS
The statistical properties in terms of bias and statistical power were consistent with what are expected from conventional analyses. Specifically, the extent of bias depended on the missing mechanism and magnitude. The statistical powers were largely driven by effect and sample sizes as well as prespecified success margins. As an illustration, assuming relative treatment differences of 25% and stagewise dropout rate of 15%, a sample size of 200 per group may achieve 93% power to demonstrate a treatment effect and 60% power to demonstrate a maintained response post-treatment.
CONCLUSIONS
Inferential statistics support our proposed study design for evaluating benefits of AIT over time and inform clinical understanding and decisions.

3

El impacto psicosocial de la alergia alimentaria

A systematic review of parent report measures assessing the psychosocial impact of food allergy on patients and families.

Proctor KB, Tison K, Estrem H, Park J, Scahill L, Vickery BP, et al.
Allergy. 2021 Oct 13. doi: 10.1111/all.15140. Epub ahead of print. PMID: 34647344.

BACKGROUND
Reducing the psychosocial impact of food allergy (FA) represents a top patient-centered research priority. This priority recognizes that psychosocial impact is an important outcome of current FA therapies (eg, oral immunotherapy), as well as interventions aimed at improving overall quality of life and illness adaptation. Reliable and valid measurement is a necessary prerequisite to developing and evaluating current and emerging FA therapies and potential changes in psychosocial impact.
METHODS
In this systematic review, we applied the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement to evaluate available parent report measures assessing the psychosocial impact of pediatric IgE mediated FA.
RESULTS
The systematic search yielded 64 articles involving 13 unique measures. Measures were evaluated through the lens of the Patient Reported Outcomes Measurement Information System (PROMIS) guidelines. Findings indicated that available measures show some evidence of reliability and validity; however, none completely adhere to PROMIS guidelines for measure development.
CONCLUSION
Results highlight a continued need to dedicate research to develop a measurement approach that assesses the full range of psychosocial impact that parents and families may experience as a result of FA, as well as serve as a research outcome as the field continues to develop effective treatments, including immunotherapy.

4

Coste/adhesión: un binomio a considerar en la ITA

Cost-effective Analysis of Subcutaneous vs Sublingual Immunotherapy From the Payor's Perspective.

Hardin FM, Eskander PN, Franzese C

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

OBJECTIVE

Compare the cost-effectiveness of subcutaneous immunotherapy (SCIT) and aqueous sublingual immunotherapy (SLIT) as treatment modalities for adult patients with allergic rhinitis and conjunctivitis who undergo testing and qualify for allergen immunotherapy (AIT).

METHODS

A systematic review was performed to identify key statistics for analysis, including the compliance and efficacy rates for each treatment. The body of literature on this topic is highly heterogeneous, so ranges were obtained and assumptions stated clearly where they were made. Charges were derived from average commercial payor charges from a single hospital institution. A hypothetical 100 patients are examined for the study.

RESULTS

A cost-effectiveness sensitivity analysis was then performed using a decision tree model to compare the modalities. A sensitivity and threshold analysis was then performed to assess the strength of recommendations after identifying results at baseline.

DISCUSSION

Assuming an 80% compliance rate with allergen immunotherapy and an estimated efficacy (assumed to be clinically significant improvement in symptoms) of 70% for SLIT and 80% for SCIT, at the 12-month mark, the baseline total cost to the payor of SLIT per successful treatment outcome is $1196 while the charge of SCIT per successful treatment outcome is $2691. Our analysis favors SLIT as the more cost-effective modality per successful outcome.

IMPLICATIONS FOR PRACTICE

When compared to SCIT, SLIT is economically favorable and should be considered the financially conscious option for patients with >40% adherence to therapy.

5

¿Qué ocurre tras 3 años de ITA sublingual de ácaros?

Effectiveness of Sublingual Immunotherapy in the Treatment of HDM-Induced Nasobronchial Allergies: A 3-Year Randomized CaseControl Study From Kashmir.

Baba SM, Rasool R, Gull A, Qureshi TA, Beigh AH, Qadri Q, et al.

Front Immunol. 2021 Oct 13;12:723814. doi: 10.3389/fimmu.2021.723814.

ABSTRACT

Allergen immunotherapy (AIT) is the only disease-modifying treatment for allergic disorders that induces immunological tolerance through administration of specific allergens. Studies on AIT for subcutaneous route are in abundance; however, the efficacy of AIT in tablet form through sublingual route has not been well elucidated. The present prospective, parallel-group, controlled study sought to compare the efficacy of sublingual immunotherapy (SLIT) tablets with pharmacotherapy (PT) in 332 house dust mite (HDM)-specific allergic asthma and/or rhinitis patients over a period of 3 years. Patients were followed up for a 6 month run-in period and then randomly stratified as those who would receive SLIT, SLIT in addition to PT (SLIT+PT), and PT alone. AIT was administered in the form of sublingual tablets. Symptom and medication scores were measured every 3 months. In vitro evaluation of serum total and HDM specific immunoglobulin E (HDM sIgE) levels was carried out every 3 months, whereas in vivo skin prick test was performed annually for 3 years. Our study demonstrated sustained clinical improvement, reduction in inhaled corticosteroid (ICS) dose and duration as well as prevention from development of neosensitization to other aero allergens in HDM-allergic asthmatics and/or rhinitis patients treated with 3 years SLIT. Despite a remarkable clinical improvement with AIT, we observed that SLIT did not significantly change the skin reactivity to HDM at 3 years and there was no significant change in the ratio of serum total and HDM sIgE. Given the immune and disease modifying effects of AIT in allergic diseases, the present study supports the notion of its sublingual mode being an effective long-term immunomodulator in HDM-sensitized nasobronchial allergies.

6

Rinitis alérgica local: ¿ITA subcutánea sí o no?

Efficacy and Safety of Subcutaneous Immunotherapy for Local Allergic Rhinitis: A Meta-Analysis of Randomized Controlled Trials.

Zhu W, Gao P, Zhang Q, Chen J

Am J Rhinol Allergy. 2021 Oct 19:19458924211050547. doi: 10.1177/19458924211050547. Epub ahead of print.

BACKGROUND

Subcutaneous immunotherapy (SCIT) has been used for treating local allergic rhinitis (LAR) patients. However, the clinical efficacy and safety were still questioned.

OBJECTIVE

This study was designed to estimate the efficacy and safety of SCIT for treating LAR patients through meta-analysis.

METHODS

We systemically searched MEDLINE, Cochrane Library, and Embase publications. Randomized, double-blind, clinical trials for the efficacy and safety of Allergen Immunotherapy (AIT) for LAR were included. A meta-analysis of 4 clinical endpoints (combined symptom and medication scores [CSMS], symptom scores [SS], medication scores [MS] and rhinoconjunctivitis quality of life questionnaire [RQLQ]) and adverse events (AEs)) was performed after bias and heterogeneity assessments. The immunologic response results were summarized.

RESULTS

Four RCTs with 134 patients were included. Four studies for analyzing primary outcomes (CSMS, SS, MS) and AEs, three for RQLQ results. The results indicated an important significant difference between SCIT and placebo groups, list as follows: CSMS (SMD = -2.42, 95% CI: -3.60 to -1.25, P < .0001), SS (SMD = -2.08, 95% CI -3.68 to -0.48, P = .01), MS (SMD = -1.43, 95% CI: -2.65 to -0.21, P = 0.02), RQLQ (SMD = -0.70, 95% CI -1.29 to -0.12, P = .02), Local AEs (RR = 4.13, 95% CI 1.08 to 15.77, P = .04). For immunologic response, significantly increased serum sIgG4 levels and improvements of allergen tolerance was observed after SCIT.

CONCLUSIONS

Our meta-analysis suggests that SCIT has a significant effect on improving symptoms and reducing medicine consumption for LAR patients. Larger and multicenter clinical trials are needed to clarify the safety and long-term efficacy.

7

¿Qué dice la evidencia sobre la ITA para la rinitis alérgica local?

Allergen-specific immunotherapy for local allergic rhinitis: a systematic review and meta-analysis.

Hoang MP, Samuthpongtorn J, Chitsuthipakorn W, Seresirikachorn K, Snidvongs K
Rhinology. 2021 Oct 5. doi: 10.4193/Rhin21.193. Epub ahead of print.

BACKGROUND

Local allergic rhinitis (LAR) is a phenotype of chronic rhinitis exhibiting a local Th2-driven inflammation without positive clinical markers of atopy. Immunomodulatory effects of allergen-specific immunotherapy (AIT) induce allergen-specific tolerance. However, AIT is not well-recognized as a treatment for LAR.

Methodology

Systematic search on six electronic databases and registries was performed. Experimental and observational studies of AIT for LAR patients were retrieved. The primary outcomes were symptom score, medication score, combined symptom medication score, and disease-specific quality of life. Secondary outcomes were serum specific(s) IgG4, sIgE, and adverse events.

RESULTS

Four double-blind randomized controlled trials (156 patients) from two research units assessed the effects of subcutaneous immunotherapy (SCIT). Compared with placebo, SCIT showed significant reductions in symptom score, medication score, combined symptom medication score, disease specific quality of life, and an increase in serum sIgG4. There was no significant change in serum sIgE. Likewise, two observational studies (one using SCIT and one using sublingual immunotherapy) improved post-therapeutic symptom score. No studies assessed the effects after discontinuation of treatment. AIT was safe without serious adverse events.

CONCLUSION

AIT has beneficial effects and safe for LAR. Its effects are restricted to studies with short-term follow-up. AIT may be considered in LAR patients.

8

“Estado del arte” de la ITO en niños

Oral immunotherapy in children with a food allergy - where do we stand?

Pulik K, Ruszczyński M, Krenke R
Clin Exp Pharmacol Physiol. 2021 Oct 30. doi: 10.1111/1440-1681.13607. Epub ahead of print.

ABSTRACT

The number of hospitalizations due to an anaphylactic reaction to food is continuously increasing. Therefore, there is an urgent need to seek effective therapy. Currently, the only way to treat food allergies is to avoid allergens and to administer intramuscular epinephrine if an accidental allergen intake occurs. The only causal therapeutic strategy is specific oral immunotherapy. An increasing amount of data confirms this therapy's effectiveness and safety, but the results remain inconclusive due to the lack of long-term follow-up. In this state-of-the art review, we briefly summarize the latest placebo-controlled randomized-controlled trials on oral immunotherapy to treat food allergy. During the paper's review, we asked the following questions: does the therapy permanently increase the amount of allergen consumed without symptoms? Does it significantly increase or decrease the occurrence of severe systemic reactions - requiring the administration of epinephrine or hospitalization? Many authors describe outcomes such as an increase in the amount of allergen that can be safely ingested; however, significant clinical benefits such as decreased hospitalizations or anaphylaxis incidence are rarely included in the results. To date, there is no unified protocol of therapy, which makes comparisons between studies difficult because of significant differences in types, doses, and routes of administration of the allergen, timeline for updosing and maintenance, duration of the therapy, and primary outcomes of OIT.

9

Alérgicos a la leche e ITO: cómo, cuándo y otras cuestiones

Oral Immunotherapy for Children with Cow's Milk Allergy.

Ogata M, Kido J, Nakamura K
Pathogens. 2021 Oct 15;10(10):1328. doi: 10.3390/pathogens10101328. PMID: 34684278.

ABSTRACT

Cow's milk allergy (CMA) is one of the most common IgE-dependent food allergies in children. Some children develop severe and persistent CMA, with near-fatal reactions after exposure to trace amounts of cow's milk (CM). Because milk and dairy products are included in various processed food products, it is difficult to completely remove milk, which negatively affects the quality of life of children with CMA. Oral immunotherapy (OIT) can alleviate food allergen-induced anaphylaxis under continuous ingestion of a little of the causative food. Children with severe CMA may benefit from OIT, but the treatment requires a long time and poses a risk of anaphylaxis. Moreover, in recent years, new therapies, including omalizumab, sublingual immunotherapy, and epicutaneous immunotherapy, have played the role of optional OIT. In this review, we present the current methods of and other attempts at OIT, and discuss OIT for safely treating CMA.

10

Perfilando el proteoma

Alteration of lung tissues proteins in birch pollen induced asthma mice before and after SCIT.

Xie Z, Sun H, Li X, Sun W, Yin J
PLoS One. 2021 Oct 7;16(10):e0258051.

ABSTRACT

Subcutaneous immunotherapy (SCIT) is a classic form of allergen specific immunotherapy that is used to treat birch pollen induced allergic asthma. To investigate the underlying molecular mechanisms of SCIT, we aimed to profile lung samples to explore changes in the differential proteome before and after SCIT in mice with allergic asthma. Fresh lungs were collected from three groups of female BALB/c mice: 1) control mice, 2) birch pollen-induced allergic mice, and 3) birch polleninduced allergic mice with SCIT. Tandem mass tag (TMT) labelling coupled with liquid chromatography-tandem mass spectrometry (LC-MS/MS) was used to analyze the lung proteome in the mice. Ingenuity pathway analysis (IPA) and Gene Ontology (GO) classification analysis were applied to identify differentially expressed proteins (DEPs) and crucial pathways. The screened DEPs were validated by immunohistochemistry analysis. A total of 317 proteins were upregulated and 184 proteins were downregulated in the asthma group compared to those of the control group. In contrast, 639 DEPs (163 upregulated and 456 downregulated proteins) were identified after SCIT in comparison with those of the asthma group. Among the 639 DEPs, 277 proteins returned to similar levels as those of the relative nonasthma condition. Bioinformatic analysis revealed that the 277 proteins played a significant role in the leukocyte extravasation signaling pathway. The leukocyte extravasation signaling pathway and related DEPs were of crucial importance in birch pollen SCIT.

1

ITA con ácaros en dermatitis atópica: ¿sí o no?

Efficacy of House Dust Mite Sublingual Immunotherapy in Patients with Atopic Dermatitis: A Randomized, Double-blind, Placebocontrolled Trial.

Langer SS, Cardili RN, Melo JML, Ferriani MPL, Moreno AS, Dias MM, et al

J Allergy Clin Immunol Pract. 2021 Nov 9:S2213-2198(21)01250-2. doi: 10.1016/j.jaip.2021.10.060. Epub ahead of print

ARTÍCULO DESTACADO

BACKGROUND

Sensitization to house dust mites (HDM) is frequent in patients with atopic dermatitis (AD).

OBJECTIVE

To investigate the efficacy of sublingual immunotherapy (SLIT) with Dermatophagoides pteronyssinus(Dpt) extract in patients with AD sensitized to HDM.

METHODS

In this randomized, double-blind, placebo-controlled trial, we enrolled 91 patients aged ≥3 years, with SCORing Atopic Dermatitis (SCORAD) ≥15 and positive skin test and/or IgE to Dpt. Patients were stratified according to age (<12 and ≥12 years) to receive HDM SLIT or placebo for 18 months. Primary outcome was a >15-point decrease in SCORAD. Secondary outcomes were decreases in SCORAD and objective SCORAD (O-SCORAD), Eczema Area and Severity Index (EASI), visual analog scale (VAS) for symptoms, pruritus scale; Investigator's Global Assessment (IGA) 0/1; and decrease ≥4 points in Dermatology Life Quality Index (DLQI). Background therapy was maintained.

RESULTS

A total of 66 patients completed the study (35 HDM SLIT, 31 placebo). After 18 months, 74.2% and 58% patients in HDM SLIT and placebo groups, respectively, showed >15-point decrease in SCORAD (relative risk[RR]1.28, 95% confidence interval[CI] 0.89-1.83). Significant SCORAD decreases from baseline of 55.6% and 34.5% in HDM SLIT and placebo groups (mean difference 20.4;95%CI 3.89-37.3); significant O-SCORAD decreases of 56.8% and 34.9% in HDM SLIT and placebo groups (mean difference 21.3;95%CI 0.66-41.81); and more patients with IGA 0/1 in HDM SLIT group as compared to placebo group (14/35 vs 5/31;RR 2.63, 95%CI 1.09-6.39), were observed at 18 months.

CONCLUSION

Our results suggest that HDM SLIT may be effective in HDM sensitized patients as an add-on treatment for AD.

2

La IT epicutánea con cacahuete se aproxima a la vida real

Safety of Epicutaneous Immunotherapy in Peanut-Allergic Children: REALISE Randomized Clinical Trial Results

Pongracic JA, Gagnon R, Sussman G, Siri D, Oriel RC, Brown-Whitehorn T, et al.

J Allergy Clin Immunol Pract. 2021 Nov 27:S2213-2198(21)01295-2. doi: 10.1016/j.jaip.2021.11.017. Epub ahead of print

BACKGROUND

Treatment options for peanut allergy are limited. In previous clinical trials, epicutaneous immunotherapy with a patch containing 250-μg peanut protein (Viaskin™ Peanut 250 μg [VP250]) was well tolerated and statistically superior to placebo in desensitizing peanut-allergic children.

OBJECTIVE

To examine the safety of VP250 in children, using a study design approximating potential real-world use.

METHODS

REALISE is a phase 3 multicenter study consisting of a 6 month, randomized, double-blind, placebo-controlled period followed by open-label active treatment. Children aged 4 to 11 years with physician diagnosis of peanut allergy received daily treatment with placebo (6 months) or VP250 (up to 36 months). Data from the 6-month, randomized, controlled phase of REALISE are reported.

RESULTS

Three hundred ninety-three children were randomized 3:1 to receive VP250 (n=294) or placebo (n=99) for 6 months; 284 (72.3%) children had a history of peanut anaphylaxis. According to parent diary, all participants receiving VP250 and 83.8% receiving placebo reported at least 1 episode of local skin reaction, with frequency decreasing over time. Only 4 participants (1.4%) receiving VP250 discontinued due to adverse events. Epinephrine was administered for allergic reactions attributed to VP250 in 7 children (2.4%), of whom 5 remained in the study; none involved severe anaphylaxis. Overall adverse event rates were similar among participants with and without history of peanut anaphylaxis.

CONCLUSIONS

In a study designed to mirror real-world use, VP250 was observed to be well tolerated in peanut-allergic children, consistent with previous phase 2b and 3 studies.

3

Un nuevo enfoque en el tratamiento de los alérgicos a la leche

Efficacy and Safety of Baked Milk Oral Immunotherapy in Children with Severe Milk Allergy: A Randomized, Double-blind, Placebocontrolled Phase 2 Trial

Dantzer J, Dunlop J, Psoter KJ, Keet C, Wood R

J Allergy Clin Immunol. 2021 Nov 2:S0091-6749(21)01681-X. doi: 10.1016/j.jaci.2021.10.023. Epub ahead of print

BACKGROUND

Cow's milk allergy is the most common food allergy in young children and has no current treatment. Oral immunotherapy studies to date have shown efficacy but high rates of adverse reactions.

OBJECTIVE

We sought to evaluate the safety and efficacy of baked milk oral immunotherapy (BMOIT) in baked milk allergic children.

METHODS

Participants (3-18 years) were randomized to receive BMOIT or placebo for 12 months. Efficacy was assessed by double-blind placebo-controlled food challenge after 12 months of treatment. Safety, quality of life, and mechanistic parameters were also evaluated.

RESULTS

11/15 (73%) of the BMOIT participants reached the primary endpoint, tolerating 4044 mg of baked milk protein after 12 months of OIT, compared to 0/15 (0%) on placebo. The median maximal tolerated dose (MTD) and median change from baseline was significantly higher in the BMOIT group compared to placebo (median MTD 4044mg vs 144mg; p=0.001; median change in MTD of 3900mg vs 0mg, p=0.0001). Dose-related reactions were common but >95% in both groups were mild. There was no significant change in CM- or beta lactoglobulin-IgE from baseline for either group. CM-sIgG4 did significantly increase and casein IgE decreased in the BMOIT group. For proxy-reported food allergy quality of life, there was a significant difference in the emotional impact domain only with more improving while on placebo compared BMOIT. The majority of children and adolescents in the BMOIT group directly reported improvement in at least one domain.

CONCLUSION

BMOIT was well tolerated and induced a substantial level of desensitization after 12 months of treatment.

4

¿En qué se basa el éxito de la ITO con leche?

Elevated cow's milk-specific IgE levels prior to oral immunotherapy decreases the likelihood of reaching the maintenance dose.

Cohen CG, Zhao WW, Ke D, Beaudette L, Lejtenyi D, McCusker C, et al.

J Allergy Clin Immunol Pract. 2021 Nov 15:S2213-2198(21)01267-8. doi: 10.1016/j.jaip.2021.11.005. Epub ahead of print.

BACKGROUND

Food desensitization via oral immunotherapy (OIT) is gaining higher acceptance in clinical practice. Due to adverse reactions, the duration of the buildup phase until a maintenance dose is achieved may be prolonged, and in a minority of cases, OIT is stopped.

OBJECTIVE

We aimed to assess factors associated with the probability of reaching the maintenance dose in cow's milk (CM) OIT.

METHODS

Data was collected from patients undergoing CM OIT at the Montreal Children's Hospital, BC Children's Hospital, and Hospital for Sick Children. We compared uni- and multivariable Cox regressions to evaluate sociodemographic factors, co-morbidities, clinical characteristics and biomarkers at study entry associated with the likelihood of reaching a maintenance dose of 200 mL of CM.

RESULTS

Among 69 children who reached 4 mL of milk, the median age was 12 years (Interquartile Range [IQR] 9-15) and 59% were male. The median duration of build-up phase from 4 mL to 200 mL was 24.0 weeks (IQR 17.7-33.4). After adjusting for age and sex, higher baseline levels of specific IgE (sIgE) antibodies for αlactalbumin (ALA, hazard ratio [HR] 0.80, 95% confidence interval [CI] 0.67-0.95), β-lactoglobulin (BLG, HR 0.86, 95% CI 0.76-0.98), casein (HR 0.82, 95% CI 0.72-0.94), and total CM (HR 0.79, 95% CI 0.65-0.97), were associated with a decreased probability of reaching maintenance. Additionally, for every increase of 10 mL CM tolerated at entry challenge, the probability of reaching maintenance increased by 10%.

CONCLUSION

The data suggest that higher levels of CM-sIgE decreased the likelihood of reaching maintenance, while an increased cumulative CM dose at entry challenge increased the likelihood. Assessing these factors prior to therapy may assist in predicting the success of CM OIT.

5

La ITO con trigo también es una opción

Oral Wheat Immunotherapy: Long-Term Follow-Up in Children with Wheat Anaphylaxis.

Babaie D, Ebisawa M, Soheili H, Ghasemi R, Zandieh F, Sahragard M, et al

Int Arch Allergy Immunol. 2021 Nov 16:1-9. doi: 10.1159/000519692. Epub ahead of print.

INTRODUCTION

There has been substantial increase in food allergies in recent decades. The management of severe food allergy often includes strict avoidance and medical therapies. However, oral immunotherapy (OIT) is a promising treatment option for these patients, which is still being investigated.

METHODS

The study recruited children from 2 years onward with a history of wheat anaphylaxis who had been referred to the Mofid Children Hospital. Wheat allergy was confirmed by a double-blind placebo-controlled food challenge. OIT was started to reach 5.28 g of wheat protein supplied in 60 g of bread. Besides immunologic measurements, a second and third oral food challenge (OFC) was performed after 3 months and 1 year of maintenance therapy to evaluate the long-term efficacy of wheat OIT (WOIT).

RESULTS

Seventeen patients completed the 3-month maintenance phase; 8 of them demonstrated negative OFCs. All of the 9 with positive OFCs were asked to continue the daily consumption of 60 g of bread for another year. Three patients with positive OFCs were followed for 1 more year and were asked to continue eating 60 g of bread every other day. The serum level of wheat sIgE was significantly increased at the end of the buildup phase ($p = 0.026$) and dramatically dropped at the end of the maintenance phase ($p = 0.022$).

CONCLUSION

To conclude, WOIT is an effective and safe modality of treatment if it is administered under strict supervision.

6

ITA con ácaros: ¿1 o 2 especies?

Efficacy of mite allergen immunotherapy in allergic rhinitis and the immune synergistic effect on cross-allergens.

Zheng P, Liu X, Lin L, Wu H, Zhao X, Sun B

Immunotherapy. 2021 Nov 30. doi: 10.2217/imt-2020-0326. Epub ahead of print.

AIM

To compare the efficacy of single- and double-species mite allergen immunotherapy.

MATERIALS AND METHODS

An open, pseudo-randomized, controlled study was conducted (n = 125 allergic rhinitis patients). The primary end point involved the visual analogue scale. Secondary end points included a basophil activation test and serum specific IgE and IgG4 assays.

RESULTS

Visual analogue scale analysis indicated considerable reductions in both groups. Both treatments improved quality of life and induced sIgG4 antibody production. Basophil activation and serum IgE inhibition were not evident in either treatment. Neither treatment displayed an early stage immune synergistic effect on cross-allergens.

CONCLUSIONS

Both treatments were effective against allergic rhinitis, and statistical differences were not observed. Future studies may require long-term, large-scale research.

7

Estrategias de efectividad en SLIT: adyuvantes y más

Current possibilities and future perspectives for improving efficacy of allergen-specific sublingual immunotherapy.

Sadeghi M, Keshavarz Shahbaz S, Dehnavi S, Koushki K, Sankian M

Int Immunopharmacol. 2021 Nov 12:108350. doi: 10.1016/j.intimp.2021.108350. Epub ahead of print.

ABSTRACT

Allergen-specific sublingual immunotherapy (SLIT), a safe and efficient route for treating type I hypersensitivity disorders, requires high doses of allergens. SLIT is generally performed without adjuvants and delivery systems. Therefore, allergen formulation with appropriate presentation platforms results in improved allergen availability, targeting the immune cells, inducing regulatory immune responses, and enhancing immunotherapy's efficacy while decreasing the dose of the allergen. In this review, we discuss the adjuvants and delivery systems that have been applied as allergen-presentation platforms for SLIT. These adjuvants include TLRs ligands, 1α, 25-dihydroxy vitamin D3, galectin-9, probiotic and bacterial components that provoke allergen-specific helper type-1 T lymphocytes (TH1), and regulatory T cells (Tregs). Another approach is encapsulation or adsorption of the allergens into a particulate vector system to facilitate allergen capture by tolerogenic dendritic cells. Also, we proposed strategies to increasing the efficacy of SLIT via new immunopotentiators and carrier systems in the future.

8

¿Qué ruta de ITA prefiere el paciente estadounidense?

Preference for Immunotherapy with Tablets by People with Allergic Rhinitis.

Tankersley M, Winders T, Aagren M, Brandi H, Hasse Pedersen M, Ledgaard Loftager AS, et al.

Patient Prefer Adherence. 2021 Nov 18;15:2539-2549. doi: 10.2147/PPA.S338337.

BACKGROUND

People with allergic rhinitis (AR) who are not controlled on conventional therapy can be treated using allergy immunotherapy (AIT) administered as tablets, injections or drops. In the US, the use of sublingual immunotherapy as tablets (SLIT-tablets) is limited in comparison to subcutaneous immunotherapy (SCIT).

OBJECTIVE

This study investigated patients' preference for SLIT-tablets vs monthly or weekly SCIT from a US patient perspective.

METHODS

We carried out a discrete choice experiment (DCE) consisting of two blocks with eight choice sets. Adults and caregivers of children with moderate tosevere AR were included if they had not previously or were not currently receiving AIT. Three attributes were included in the design: the mode and frequency of administration, the risk of systemic reactions and the co-payment.

RESULTS

A total of 724 adults with AR and 665 caregivers of children with AR were included in the study. Both adults and caregivers had a significant preference for SLIT-tablets compared with both weekly and monthly injections and for less risk of anaphylactic shock. Caregivers were more risk-averse than adults when choosing their treatment, and the younger the child, the more risk averse the caregiver. The preference for SLIT-tablets was found for both monoallergic and polyallergic adults and caregivers of monoallergic and polyallergic children. Respondents not wanting AIT for free were more risk-averse than those indicating that they wanted AIT for free.

CONCLUSION

Our findings suggest that SLIT-tablets is the preferred route of administration for AIT among adults and caregivers of children with AR.

9

Utilidad del cuestionario de calidad de vida en alergia alimentaria

Mapping the Food Allergy Quality of Life Questionnaire Parent Form onto the SF-6Dv2

Watts Y, Dufresne É, Samaan K, Graham F, Labrosse R, Paradis L, et al.

Allergy. 2021 Nov 25. doi: 10.1111/all.15190. Epub ahead of print.

BACKGROUND

The Food Allergy Quality of Life Questionnaire Parent Form (FAQLQ-PF) is the most widely used quality of life questionnaire in food allergy. The objective of this study was to develop a mapping algorithm to convert FAQLQ-PF scores into health state utilities.

METHODS

The Short-Form Six-Dimensions version 2 (SF-6Dv2) and FAQLQ-PF questionnaires were collected from an academic center oral immunotherapy referral cohort. Utility estimates were derived from the SF-6Dv2 using the food allergy preference set. Candidate mapping algorithm models were developed using seven regression methods starting from either the total average score, the average scores of each of the three domains or the individual item scores of FAQLQ-PF. The process was repeated twice, including only section A, common to all age groups, or including all age-applicable sections of the FAQLQ-PF. The mean absolute error (MAE) and root mean squared error (RMSE) were used to select the best fitting model. An independent cohort from a previous national online survey was used for external validation.

RESULTS

In the index cohort, 1000 of 1257 respondents had completed both questionnaires. The lowest MAE (0.0791) and RMSE (0.1020) were recorded when entering individual item scores in a categorical regression model. The model including only FAQLQ-PF section A was found to be most consistent when tested in the external validation cohort (n=248) (MAE of 0.0898).

CONCLUSION

The FAQLQ-PF was mapped onto SF-6Dv2 utilities with good predictive accuracy in two independent cohorts. This will enable calculation of health utility for cost-effectiveness analyses in food allergy.

10

El eje intestino-piel en la patogenia de las enfermedades alérgicas

Role of the gut-skin axis in IgE-mediated food allergy and atopic diseases.

Noor Hidayatul Aini Suaini, Kewin Tien Ho Siah, Elizabeth Huiwen Tham

Curr Opin Gastroenterol.2021 Nov 1;37(6):557-564. doi:10.1097/MOG.0000000000000780

PURPOSE OF REVIEW

In recent years, landmark clinical trials investigating the role of early oral exposure to food antigens for food allergy (FA) prevention have highlighted the importance of immunoregulatory pathways in the 'gut- skin axis'. This review highlights recent literature on the mechanisms of the immune system and microbiome involved in the gut-skin axis, contributing to the development of atopic dermatitis (AD), FA, allergic rhinitis (AR) and asthma. Therapeutic interventions harnessing the gut-skin axis are also discussed.

RECENT FINDINGS

Epicutaneous sensitization in the presence of AD is capable of inducing Th2 allergic inflammation in the intestinal tract and lower respiratory airways, predisposing one to the development of AR and asthma. Probiotics have demonstrated positive effects in preventing and treating AD, though there is no evident relationship of its beneficial effects on other allergic diseases. Prophylactic skin emollients use has not shown consistent protection against AD, whereas there is some evidence for the role of dietary changes in alleviating AD and airway inflammation. More randomized controlled trials are needed to clarify the potential of epicutaneous immunotherapy as a therapeutic strategy for patients with FA.

SUMMARY

The growing understanding of the gut-skin interactions on allergic disease pathogenesis presents novel avenues for therapeutic interventions which target modulation of the gut and/or skin.

1

Pérdida de la tolerancia conseguida tras la ITO con cacahuete

Maximum Dose Food Challenges Reveal Transient Sustained Unresponsiveness in Peanut Oral Immunotherapy (POIMD study)

Davis CM, Anagnostou A, Devaraj S, Vita DT, Rivera F, Pitts K, et al.
Allergy Clin Immunol Pract. 2021 Dec 7:S2213-2198(21)01363-5. doi: 10.1016/j.jaip.2021.10.074. Epub ahead of print

ARTÍCULO DESTACADO

BACKGROUND
The maximum tolerated dose (MTD) of peanut protein following peanut oral immunotherapy (POIT) is unknown because most research studies have not examined very high thresholds.
OBJECTIVE
To define the maximum dose tolerated by patients on POIT and severity of allergic reactions after a 1-month period of treatment discontinuation.
METHODS
In a Phase 2 three-year POIT open-label study, we enrolled participants age 5-13 years with a 1-year build-up period followed by a 2-year daily maintenance dose of 3,900 mg with assessment of the MTD utilizing double blind placebo-controlled food challenges (DBPCFCs) of 26,225 mg cumulative dose of peanut protein. DBPCFC was performed at baseline, after 12 month build-up, 2-year of maintenance and after a 1-month period of treatment discontinuation. Biomarkers were assessed every 6 weeks for the first 6 months of therapy. A general linear mixed model was used for analysis.
RESULTS
The mean maximum cumulative tolerated dose after 12 months increased by 12,063 mg ($p<0.001$) (n=12), slightly decreased during maintenance (n=11) and significantly decreased by 7,593 mg after avoidance for 1-month ($p=0.03$)(n=6). Biomarker analysis revealed decreases in cytokine expression within the first 6 weeks of initiation of POIT and decreased peanut-IgG4 and increased cytokine expression after 1-month of discontinuation. The DBPCFC reaction severity, examined through a symptom score with one point for each defined symptom, decreased after 12 months, but did not significantly change after 1-month of POIT discontinuation.
CONCLUSION
The evaluation of POIT and sustained unresponsiveness by MTD by DBPCFCs in this small phase 2 trial showed desensitization is diminished, with 100% loss of tolerated dose after 1-month of avoidance following 3 years of treatment.

2

Biomarcadores (nasales) de respuesta a la ITA sublingual

Nasal Nitric Oxide and Nasal Cytology as Predictive Markers of Short-Term Sublingual Allergen-Specific Immunotherapy Efficacy in Children with Allergic Rhinitis.

Parisi GF, Manti S, Papale M, Amato M, Licari A, Marseglia GL, et al.
Am J Rhinol Allergy. 2021 Dec 6:19458924211060592. doi: 10.1177/19458924211060592. Epub ahead of print

BACKGROUND
Few studies have been conducted on the short-term response to sublingual immunotherapy (SLIT).
OBJECTIVE
The purpose of our experimental trial was to evaluate if two markers such as nasal nitric oxide (nNO) and nasal cytology could be useful to identify a precocious clinical efficacy of SLIT treatment.
METHODS
We enrolled 34 children aged 6 to 14 years old with diagnosis of allergic rhinitis (AR) and documented sensitization towards house dust mites. We started allergoid-monomeric tablets immunotherapy along with any conventional therapy for AR and we evaluated at baseline (T0), after one (T1), two (T2), three (T3), and six months (T6) the effects of the treatment through the study of: i) a visual analogue scale (VAS 1-10); ii) measurement of nNO; iii) measurement of FeNO; iv) nasal cytology; v) spirometry; and vi) evaluation of any conventional therapy.
RESULTS
We observed an improvement in symptoms evaluated by global VAS (T0 vs. T6: 47.13 vs. 17.57; $p < .05$) and a statistically significant reduction of nNO (1035.2 ± 956.08 vs. 139.2 ± 59.01; $p < .05$). In this case, significance was reached when the patients completed the 6 months of treatment. Cytological evaluation revealed significant reduction in nasal eosinophils (T0 vs. T6: 87% vs. 16%; $p < .01$). Moreover, at T0, 56% of patients had also neutrophils that were reduced up to the 8% at T6 ($p < .05$).
CONCLUSIONS
Our data confirm the effectiveness of SLIT treatment from a clinical perspective and identifies two biomarkers, such as nNO and nasal cytology, as predictive of treatment efficacy in the short term.

3

¿Es la ITA coste-efectiva en los niños portugueses polínicos?

Cost-effectiveness analysis of grass pollen specific immunotherapy in children with allergic rhinitis compared to the standard of care symptomatic treatment in Portugal.

Farraia M, Paciência I, Castro Mendes F, Cavaleiro Rufo J, Delgado L, Moreira A
Eur Ann Allergy Clin Immunol. 2021 Dec 17. doi: 10.23822/EurAnnACI.1764-1489.240. Epub ahead of print.

BACKGROUND
Cost-effectiveness studies evaluating allergen immunotherapy (AIT) in children are scarce. We aim to compare the cost effectiveness of subcutaneous (SCIT) and sublingual immunotherapy (SLIT) against standard-of-care (SOC) treatment in children with grass pollen allergic rhinitis.
METHODS
We created a Markov model to compare the three strategies over a 10 year horizon. SOC was the reference to calculate the incremental cost effectiveness ratio (ICER). Deterministic and probabilistic sensitivity analysis were used to assess models' uncertainty.
RESULTS
We obtained an ICER of € 12,605 and € 6,318 for SLIT and SCIT, respectively. In sensitivity analysis, SCIT was more cost-effective than SLIT.
CONCLUSIONS
AIT is cost-effective in children with grass pollen allergic rhinitis, especially for the subcutaneous route.

4

Doble negatividad (Der p 1 y Der p 2) en alérgicos a ácaros

Cut-off value of D. pteronyssinus specific IgE in double negative patients Der p 1 and Der p 2 and its clinical repercussion.

Letrán A, García I, Espinazo-Romeu M, Moreno-Aguilar C, Moreno F

Sci Rep. 2021 Dec 8;11(1):23585. doi: 10.1038/s41598-021-03005-4.

ABSTRACT

Accessibility to more precise diagnostic techniques such as component resolved diagnostics (CRD), provides us with an important advance in diagnostic aspects as well as treatment. The subject of this study aims to better understand the profiles of sensitization to Der p 1, Der p 2 and Der p 23 and to know to what extent their use could help us in optimizing the decision-making for their treatment with Specific Immunotherapy. Cross-sectional study of subjects older than 5 years, diagnosed with allergy to HDM using skin prick test and sIgE, with symptoms of rhinitis and/or asthma. Total and specific IgE was determined to D. pteronyssinus, nDer p 1, rDer p 2 and rDer p 23 using ImmunoCAP. 240 patients were recruited (97.1% rhinitis and 46.25% rhinitis and asthma). Four different phenotypes were observed: positive or negative for sIgE nDer p 1 and/or IgE rDer p 2. 17% of these patients sIgE were double negative for Der p 1 and Der p 2 (increasing with age and with significantly lower sIgE levels than the rest of the groups). Using ROC curves, value less than 2.18 KUA/L for D. pteronyssinus sIgE gave us a sensitivity and specificity of 0.882 and 0.985, respectively, to double negative IgE nDer p 1 and IgE rDer p 2 group. Despite positive SPT and sIgE to D. pteronyssinus, 17% of the studied population is IgE nDer p 1 and IgE rDer p 2 double negative, with a cut-off value of 2.18 KU/L, which is very relevant for taking of decisions in prescription of AIT. The double positive population sIgE nDer p 1 and IgE rDer p 2 is associated with asthma compared to the other groups and this does not seem to be influenced by IgE rDer p 23.

5

Lo que ocurre a nivel “ómico” durante ITO con huevo

Integrative Transcriptomics Reveals Activation of Innate Immune Responses and Inhibition of Inflammation During Oral Immunotherapy for Egg Allergy in Children.

Karisola P, Palosuo K, Hinkkanen V, Wisgrill L, Savinko T, Fyhrquist N, et al

Front Immunol. 2021 Dec 15;12:704633.

ABSTRACT

We previously reported the results of a randomized, open-label trial of egg oral immunotherapy (OIT) in 50 children where 44% were desensitized and 46% were partially desensitized after 8 months of treatment. Here we focus on cell mediated molecular mechanisms driving desensitization during egg OIT. We sought to determine whether changes in genome-wide gene expression in blood cells during egg OIT correlate with humoral responses and the clinical outcome. The blood cell transcriptome of 50 children receiving egg OIT was profiled using peripheral blood mononuclear cell (PBMC) samples obtained at baseline and after 3 and 8 months of OIT. We identified 467 differentially expressed genes (DEGs) after 3 or 8 months of egg OIT. At 8 months, 86% of the DEGs were downregulated and played a role in the signaling of TREM1, IL-6, and IL-17. In correlation analyses, Gal d 1 4-specific IgG4 antibodies associated positively with DEGs playing a role in pathogen recognition and antigen presentation and negatively with DEGs playing a role in the signaling of IL-10, IL-6, and IL-17. Desensitized and partially desensitized patients had differences in their antibody responses, and although most of the transcriptomic changes were shared, both groups had also specific patterns, which suggest slower changes in partially desensitized and activation of NK cells in the desensitized group. OIT for egg allergy in children inhibits inflammation and activates innate immune responses regardless of the clinical outcome at 8 months. Changes in gene expression patterns first appear as posttranslational protein modifications, followed by more sustained epigenetic gene regulatory functions related to successful desensitization.

6

Nanopartículas como adyuvantes en la ITA: un futuro muy cercano

Nanoparticles in allergen immunotherapy.

Longo A, Longo V, Colombo P.

Curr Opin Allergy Clin Immunol. 2021 Dec 1;21(6):576-582.

PURPOSE OF REVIEW

Allergen immunotherapy is the only recognized causal treatment for allergic disease that modulates the immune system toward a tolerogenic or desensitized state. Allergens or their derivative preparations are formulated with adjuvants of different origin and having diverse immunological functions, such as prolonged tissue release and specific immunomodulatory properties. In the last 2 decades, thanks to developments in the field of nanotechnology, more biosafe nanoscale materials have become available for use as pharmaceutical adjuvants in medical research.

RECENT FINDINGS

Nanomaterials possess unique and versatile properties which can be employed to develop drug carriers with safer profiles, better stability in physiological conditions and immunomodulatory properties. Nanoparticles can have an adjuvant effect per se or also when they are packed in structures whose physicalchemical properties can be handled in a way that also influences its release dynamics. In particular, it has been suggested that nanoparticle preparations can be put in complexes or loaded with allergens or allergenic extracts, opening the way to innovative paradigms.

SUMMARY

In this review, we analyze allergen/nanoparticle properties in terms of cytotoxicity, stability and immunogenic reaction in in-vitro and animal systems.

7

ITO: todo lo que sabemos y más

Oral Immunotherapy in Children: Clinical Considerations and Practical Management.

Anderson B, Wong L, Adlou B, Long A, Chinthrajah RS

J Asthma Allergy. 2021 Dec 14;14:1497-1510

ABSTRACT

Oral immunotherapy (OIT) in pediatric patients provides an alternative option to the current standard of care in food allergy, which is allergen avoidance and reactive treatment. Because patients are exposed to one or more food allergens during treatment, OIT is associated with adverse events and can be a cumbersome process for children, their caregivers, and clinicians. However, there have been an overwhelming number of studies that show high efficacy in both single and multi-allergen OIT, and that quality of life is greatly improved for both patients and their families after undergoing immunotherapy. This review discusses clinical considerations for OIT in pediatrics, including efficacy and safety, practical management, and future directions of treatment.

8

Marcadores de eficiencia inmunológica de la ITA subcutánea

Allergen-Specific IgE and IgG4 as Biomarkers for Immunologic Changes during Subcutaneous Allergen Immunotherapy.
Nikolov G, Todordova Y, Emilova R, Hristova D, Nikolova M, Petrunov B
Antibodies (Basel). 2021 Dec 7;10(4):49.

BACKGROUND

Biomarkers of efficacy for subcutaneous immunotherapy (SCIT) on allergic rhinitis have not been evaluated in details. The present study aims to assess the relevance of measuring of sIgE, sIgG4 and IgE/IgG4 ratio during SCIT in patients with allergic rhinitis.

METHODS

20 patients, 13 men and 7 women aged 19 to 58 years, with clinically manifested seasonal and perennial allergic rhinitis were studied. At the initiation and in the end of the three-year course of SCIT serum allergen-specific IgE and IgG4 were measured with ImmunoCAP system. The sIgE/sIgG4 ratio was calculated as a biomarker for immunologic effectiveness.

RESULTS

There was a significant increase of sIgG4 antibodies ($p < 0.05$), while at the end of SCIT for the sIgE levels no significant changes were seen ($p > 0.05$). Moreover, 90% of patients showed a decrease of the IgE/IgG4 ratio.

CONCLUSIONS

In most of treated patients with AR, SCIT with Bulgarian allergen products leads to clear immunological changes. After a 3-year of SCIT there is a significant increase in allergen specific IgG4 levels and both decrease of sIgE and IgE/IgG4 ratio. sIgE, sIgG4 and IgE/IgG4 ratio can be used as a substantial biomarker for predicting immunological effectiveness of SCIT.

9

“Estado del arte” de la alergia alimentaria

Food allergy across the globe
Sampath V, Abrams EM, Adlou B, et al
J Allergy Clin Immunol 2021;148:1347-64.)

ABSTRACT

The prevalence of food allergy (FA) is increasing in some areas of the globe, highlighting the need for better strategies for prevention, diagnosis, and therapy. In the last few decades, we have made great strides in understanding the causes and mechanisms underlying FAs, prompting guideline updates. Earlier guidelines recommended avoidance of common food allergens during pregnancy and lactation and delaying the introduction of allergenic foods in children aged between 1 and 3 years. Recent guidelines for allergy prevention recommend consumption of a healthy and diverse diet without eliminating or increasing the consumption of allergenic foods during pregnancy or breast-feeding. Early introduction of allergenic foods is recommended by most guidelines for allergy prevention after a period of exclusive breast-feedng (6 months [World Health Organization] or 4 months [European Academy of Allergy and Clinical Immunology]). New diagnostics for FA have been developed with varied availability of these tests in different countries. Finally, the first oral immunotherapy drug for FA was approved by the US Food and Drug Administration and European Medicines Agency in 2020. In this review, we will address the global prevalence of FA, our current understanding of the causes of FA, and the latest guidelines for preventing, diagnosing, and treating FA. We will also discuss similarities and differences between FA guidelines.

10

De puntuación de síntomas a calidad de vida: algoritmo de conversión

Mapping naso-ocular symptom scores to EQ-5D-5L utility values in Japanese cedar pollinosis
Kumanomidou H, Kanai K, Oka A, et al
Allergol Int. 2021 Dec 3;S1323-8930(21)00141-6. doi: 10.1016/j.alit.2021.11.002. Online ahead of print.

BACKGROUND

The total naso-ocular symptom score (TSS) is widely used as an endpoint to evaluate the severity of seasonal allergic rhinitis. However, it is not a generic preference-based measure.We sought to develop an algorithm for mapping between the TSS and health utility in Japanese cedar pollinosis (JCP). We also performed a cost-utility analysis of sublingual immunotherapy (SLIT) for JCP by using this algorithm.

METHODS

Patients with JCP filled out the TSS questionnaire and EQ-5D 5L simultaneously during the pollen season in 2019 and in 2020. We estimated a direct utility mapping model by regressing responses to individual TSS questions directly onto utility. The incremental cost-effectiveness ratio (ICER) of active SLIT to a placebo was determined by examining the drug expense and the estimated quality-adjusted life year (QALY) using a dataset from a double-blind placebo-controlled clinical trial.

RESULTS

A total of 238 records were included for analysis. The estimated utility decreased with increasing severity of rhinitis. Patients with comorbid asthma showed lower utility. A negative and significant correlation was seen between the TSS and utility in both 2019 and 2020. The estimated equations were: Y(utility) . 0.0161*X(TSS) . 1.005 in non-asthmatic JCP patients. The ICER of active SLIT to the placebo was estimated to be 4,049,720 and 6,011,218 JPY/QALY in the first and second year, respectively.

CONCLUSIONS

It is possible to reasonably predict utility from the total nano-ocular symptom score by using regression models. In the estimated algorithm, pre-seasonal SLIT for JCP is cost-effective.