BOLETÍN BIBLIOGRÁFICO de INMUNOTERAPIA

Marzo 2024

Actividad avalada por:

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Allergy Therapeutics

BBI BOLETÍN BIBLIOGRÁFICO de INMUNOTERAPIA

Sistema de alertas bibliográficas

para los profesionales sanitarios relacionados con el cuidado de pacientes que sufren enfermedades alérgicas y que podrían recibir inmunoterapia con alérgenos.

Los 10 artículos más novedosos o relevantes para la práctica clínica

son seleccionados mensualmente de forma independiente por dos especialistas en Alergología designados por el Comité de Inmunoterapia de la SEAIC.

Artículos relacionados con la inmunoterapia con alérgenos

publicados en revistas indexadas en la base de datos de la *U.S. National Library of Medicine* (motor de búsqueda PubMed).

Criterios de búsqueda

basados en las palabras clave *"Desensitization, Immunologic"[MeSH] OR (Immunotherapy[TIAB] AND allerg*[TIAB])* y los filtros establecidos por la McMaster University para recuperar de forma óptima ("Best balance of sensitivity and specificity") estudios clínicamente relevantes.

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Temática del artículo

A cada artículo se le deberá de asignar uno de los siguientes temas:

1. Biomarcadores en inmunoterapia
2. Cumplimiento, calidad de vida y coste-efectividad de la inmunoterapia
3. Inmunoterapia con péptidos y otros modelos experimentales
4. Inmunoterapia y prevención
5. Mejorando la selección de pacientes para inmunoterapia
6. Metodología de investigación en inmunoterapia
7. Otras rutas para inmunoterapia
8. Recomendaciones de calidad y acreditación en ITA
9. Seguridad y efectividad de la ITA
10. Síntesis critica de la literatura científica de ITA (metaanálisis y/o revisiones sistemáticas)
11. Crear, en caso que ninguna de las categorías anteriores sea oportuna

¿Anafilaxia por himenópteros? Sospecha enfermedad mastocitaria

1

Título del artículo original: High burden of clonal mast cell disorders and hereditary α-tryptasemia in patients who need Hymenoptera venom immunotherapy.

Autores: Korošec P, Sturm GJ, Lyons JJ, Marolt TP, Svetina M< et al

Referencia bibliográfica: Allergy. 2024 Mar 13. Epub ahead of print. PMID: 38477502.

Temática: Seguridad y efectividad de la ITA

Palabras Clave: anaphylaxis; hereditary α-tryptasemia; hypersensitivity; immunotherapy; mast cell; mastocytosis; venom.

ABSTRACT	**Background:** In patients who require venom immunotherapy (VIT), there is a need to identify underlying mast cell (MC) disorders since these may affect the risk and severity of future sting reactions and the long-term effectiveness of VIT. **Methods:** 1319 individuals with Hymenoptera venom allergy (HVA) who needed VIT from referral centers in Slovenia, Austria, Croatia, and Poland underwent examination for KIT p.D816V in peripheral blood leukocytes (PBL) using a highly sensitive PCR test and tryptase genotyping by digital droplet PCR. We also included 183 control individuals with large local reactions (LLRs) to Hymenoptera stings and with asymptomatic sensitization to Hymenoptera venoms. **Results:** 285 of 1319 individuals recommended for VIT (21.6%) were positive for KIT p.D816V in PBL, preferably those who present with severe reaction (33.9% [n = 207 of 610] with Ring-Messmer grade 3-4 vs. 11% [n = 78 of 709] with Grade 1-2; p < .0001), whereas only 1.3% (n = 2 of 152) of controls with LLR and none with asymptomatic sensitization (n = 31) had KIT p.D816V. KIT p.D816V allelic burden was higher in those with severe reaction (median 0.018% [n = 207] in Grade 3-4 vs. 0.001% [n = 78] in Grade 1-2; p < .0001), and the majority had normal baseline serum tryptase levels (69% [n = 196 of 285]). All KIT p.D816V-positive individuals (n = 41) who underwent bone marrow (BM) biopsy were found to have underlying clonal diseases, principally BM mastocytosis. HαT was also associated with severe HVA and symptoms (p < .01), and remarkably, 31.0% (n = 31 of 100) were found to have concomitant KIT p.D816V. Concomitant HαT and KIT p.D816V showed an additive effect, and having both was associated with the highest risk for severe HVA, even higher than having either HαT or KIT p.D816V alone (OR = 3.8; p < .01). **Conclusions:** By employing prospective universal tryptase genotyping and examination for KIT p.D816V in PBL in large HVA populations, we have demonstrated a high burden of clonal MC disorders and HαT in patients who require VIT.

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2 En la rinitis alérgica local crear anticuerpos bloqueantes predice la respuesta a ITA

Título del artículo original: Nasal allergen-neutralizing antibodies correlate closely with tolerated intranasal allergen challenge dose following grass pollen subcutaneous immunotherapy in patients with local allergic rhinitis.

Autores: Eguiluz-Gracia I, Parkin RV, Layhadi JA, Palmer E, Meng X, et al.

Referencia bibliográfica: Allergy. 2024 Mar 14. Epub ahead of print. PMID: 38483174.

Temática: Biomarcadores en inmunoterapia

Palabras Clave: IgA1; IgA2; IgE-FAB; IgG4; blocking antibodies; local allergic rhinitis; subcutaneous immunotherapy.

ABSTRACT

IBackground: Local allergic rhinitis (LAR) is defined by chronic nasal symptoms, absence of atopy, positive nasal allergen challenge (NAC) and a good response to subcutaneous allergen immunotherapy (SCIT). We sought to investigate SCIT capacity to induce local and systemic blocking antibodies in LAR patients.

Methods: A RDBPC study of grass SCIT was performed, with participants receiving either SCIT (Group A; n = 10) or placebo (Group B; n = 14) in the first 6 months. Both groups subsequently received SCIT for 12 months at Year 2. Nasal and serum antibodies (IgG_4 , IgA_1 and IgA_2) and their inhibitory capacity were measured at multiple timepoints.

Results: The allergen concentration tolerated increased significantly at 6 months (Group A; p = .047) and 24 months (Group B; p = .049) compared with baseline and persisted until the end of the study. Induction of serum $sIgA_1$ to Phl p was seen in Groups A and B, albeit the former being induced earlier (1.71-fold, p = .027). A significant induction in $sIgG_4$ to Phl p 1 and 5 was observed in serum of Group A (p = .047 and p = .0039) and $sIgA_2$ to Phl p in Group B (p = .032 and p = .0098) at 18 and 24 months, respectively. Both local and systemic blocking antibodies can inhibit allergen-IgE complexes binding to CD23 on B cells, and this correlated with level of allergen tolerated intra-nasally in Group A (serum; ρ = -.47, p = .0006, nasal; ρ = -.38, p = .0294).

Conclusions: Grass pollen SCIT induced functional systemic blocking antibodies that correlate with the concentration of allergen tolerated following NAC, highlighting their potential as a biomarker of SCIT in LAR.

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Ciclofilina, un panalergeno “desconocido”

Título del artículo original: IgE to cyclophilins in pollen allergic children: epidemiological, clinical and diagnostic relevance of a neglected panallergen.

Autores: Matricardi PM, Potapova E, Panetta V, Lidholm J, Mattsson L et al; Italian Pediatric Allergy Network.

Referencia bibliográfica: J Allergy Clin Immunol. 2024 Mar 19:S0091-6749(24)00235-5. Epub ahead of print. PMID: 38513837.

Temática: Mejorando la selección de pacientes para inmunoterapia

Palabras Clave: allergic rhinitis; allergy; asthma; component resolved diagnostics; cross-reactivity; cyclophilins; diagnosis; immunoglobulin E; oral allergy syndrome; panallergens; pollen; precision medicine.

ABSTRACT

Background: - Cyclophilins are ubiquitous panallergens whose epidemiological, diagnostic, and clinical relevance is largely unknown and whose sensitization is rarely examined in routine allergy practice. The aim of this study was to investigate the epidemiological, diagnostic, and clinical relevance of cyclophilin in seasonal allergic rhinitis and its comorbidities.
Methods: - We examined a random sample (25%, n 253) of 1263 Italian children affected by seasonal allergic rhinitis from the "Panallergen in Pediatrics" (PAN-PED) cohort. Patients' disease phenotype had been already fully characterized through questionnaires (ARIA), skin prick tests (ALK), IgE tests to extracts, major and cross-reactive allergenic molecules of a comprehensive variety of allergenic pollen (immunoCAP), and carbohydrate cross-reacting determinants (CCD) (NOVEOS). We also performed nested studies of sensitization prevalence, correlation and allergen extract inhibition in patients (A) sensitized to birch pollen extract but lacking IgE to Bet v 1, Bet v 2, and Bet v 4, (74/1263) or with the highest serum level of IgE to Bet v 1 (26 within 1263), and (B) in patients with sensitization to extracts of ragweed (18), mugwort (18), pellitory (20), Plantago (19), and plane tree (20), but not to their respective major allergenic molecule, profilins and polcalcins. IgE to cyclophilin was detected with recombinant Bet v 7 (ImmunoCAP) and extract inhibition tests were performed with the same rBet v 7.
Results: In the randomized population, IgE to rBet v 7 was detected in 43/253 (17%) patients. It was associated with asthma ($p<0.028$) and oral allergy syndrome ($p<0.017$) in univariate, but not in a multivariate analysis adjusted for IgE to profilins (Phl p 12), PR.10s (Bet v 1), and LTPs (Pru p 3). IgE to r Bet v 7 was also highly prevalent (47/74; 63%) among patients with unexplained sensitization to birch pollen extract. In patients with unexplained sensitization to ragweed, mugwort, pellitory, Plantago and plane tree pollen, the levels of IgE to those extracts correlated with the levels of IgE to rBet v 7, and they were also significantly inhibited by rBet v 7 (inhibition range 45%-74%).
Conclusions: - IgE sensitization to cyclophilin is very frequent in pollen-allergic patients living in temperate areas and can produce "false" positive outcomes in SPT and IgE tests to many different pollen extracts. The spectrum of pollen species containing allergenic cyclophilins is probably broader than previously known. Our results suggest that guidelines of molecular diagnostics should include this allergen family and that new tests based on plant cyclophilins should be produced and used with sera of pollen-allergic patients for a more precise

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Resultados en “vida real” sobre la efectividad a largo plazo de la ITA

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Título del artículo original: House dust mite SCIT reduces asthma risk and significantly improves long-term rhinitis and asthma control-A RWE study

Autores: Jutel M, Klimek L, Richter H, Brüggenjürgen B, Vogelberg C.

Referencia bibliográfica: Allergy. 2024 Apr;79(4):1042-1051. Epub 2024 Mar 2. PMID: 38429981.

Temática: Seguridad y efectividad de la ITA

Palabras Clave: allergen immunotherapy; house dust mite; long-term effect; real-world evidence; subcutaneous immunotherapy.

ABSTRACT	**Background:** The German Therapy Allergen Ordinance (TAO) triggered an ongoing upheaval in the market for house dust mite (HDM) allergen immunotherapy (AIT) products. Three HDM subcutaneous AIT (SCIT) products hold approval in Germany and therefore will be available after the scheduled completion of the TAO procedure in 2026. In general, data from clinical trials on the long-term effectiveness of HDM AIT are rare. We evaluated real-world data (RWD) in a retrospective, observational cohort study based on a longitudinal claims database including 60% of all German statutory healthcare prescriptions to show the long-term effectiveness of one of these products in daily life. Aim of this analysis was to provide a per product analysis on effectiveness of mite AIT as it is demanded by international guidelines on AIT. **Methods:** Subjects between 5 and 70 years receiving their first (index) prescription of SCIT with a native HDM product (SCIT group) between 2009 and 2013 were included. The exactly 3:1 matched control group received prescriptions for only symptomatic AR medication (non-AIT group); the evaluation period for up to 6 years of follow-up ended in February 2017. Study endpoints were the progression of allergic rhinitis (AR) and asthma, asthma occurrence and time to the onset of asthma after at least 2 treatment years. **Results:** In total, 892 subjects (608 adults and 284 children/adolescents) were included in the SCIT group and 2676 subjects (1824 adults and 852 children/adolescents) in the non-AIT group. During the follow-up period after at least 2 years of SCIT, the number of prescriptions in the SCIT group was reduced by 62.8% ($p < .0001$) for AR medication and by 42.4% for asthma medication ($p = .0003$). New-onset asthma risk was significantly reduced in the SCIT vs non-AIT group by 27.0% ($p = .0212$). The asthma-preventive effect of SCIT occurred 15 months after start of the treatment. In the SCIT group, the time to onset of asthma was prolonged compared to the non-AIT group ($p = .0010$). **Conclusion:** In this first product based RWD analysis on SCIT with a native HDM product, patients aged 5 to 70 years benefited from AIT in the long term in terms of reduced progression of AR and asthma after at least 2 years of treatment. The effects seemed to last for up to 6 years after treatment termination. A significantly reduced risk of asthma onset was observed, starting after 15 months of treatment.

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La IT epicutánea con cacahuete analizada con lupa

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Título del artículo original: From Skin to Solution: Exploring Epicutaneous Immunotherapy for Peanut Allergy-A Systematic Review and Meta-Analysis.

Autores: Banatwala UESS, Nasir MM, Javed R, Ahmed A, Farhan SA, Ajam A.

Referencia bibliográfica: Clin Rev Allergy Immunol. 2024 Mar 25. Epub ahead of print. PMID: 38526693.

Temática: Otras rutas para inmunoterapia

Palabras Clave: Allergen desensitization; Epicutaneous immunotherapy; Immunotherapy for allergy; Peanut allergy; Peanut protein.

ABSTRACT	Peanut allergy is a leading cause of severe food reactions. This meta-analysis evaluates the efficacy and safety of epicutaneous immunotherapy (EPIT) compared to placebo for peanut-allergic individuals. After prospectively registering on PROSPERO, we searched three databases (PubMed, Google Scholar, and Cochrane CENTRAL) and 2 trial registries till September 2023. Analysis was conducted via RevMan where data was computed using risk ratios (RR). The Cochrane Risk of Bias tool and GRADE criteria were used to appraise and evaluate the evidence. From 4927 records, six multicenter randomized placebo-controlled trials comprising 1453 participants were included. The 250 µg EPIT group had a significant increase in successful desensitization compared to placebo (RR: 2.13 (95% C.I: 1.72, 2.64), $P < 0.01$, $I^2 = 0\%$), while the 100 µg EPIT group did not (RR: 1.54 (95% C.I: 0.92, 2.58), $P = 0.10$, $I^2 = 0\%$) (moderate certainty evidence). Moreover, there was a significant increase in local (RR: 1.69 (95% C.I: 1.06, 2.68), $P = 0.03$, $I^2 = 89\%$) and systemic adverse events (RR: 1.75 (95% C.I: 1.14, 2.69), $P = 0.01$, $I^2 = 0\%$) with EPIT. Additionally, individuals administered EPIT have an increased probability of requiring rescue medications like epinephrine (RR: 1.91 (95% C.I: 1.12, 3.28), $P = 0.02$, $I^2 = 0\%$) and topical corticosteroids (RR: 1.49 (95% C.I: 1.29, 1.73), $P < 0.01$, $I^2 = 0\%$) to treat adverse events. The association of adverse events post-treatment including anaphylaxis (RR: 2.31 (95% C.I: 1.00, 5.33), $P = 0.05$, $I^2 = 36\%$), skin/subcutaneous disorders like erythema or vesicles (RR: 0.93 (95% C.I: 0.79, 1.08), $P = 0.33$, $I^2 = 0\%$), and respiratory disorders like dyspnea or wheezing (RR: 0.94 (95% C.I: 0.77, 1.15), $P = 0.55$, $I^2 = 0\%$) with EPIT is inconclusive. EPIT, although effective in desensitization, is linked to an increased risk of adverse events. PROSPERO registration: CRD42023466600.

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Enfoque por terciles para calcular mejor la efectividad de la ITA

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Título del artículo original: Efficacy of 300 IR house dust mite immunotherapy as a function of disease activity: Tertile analysis in clinical trials.

Autores: Devillier P, Demoly P, Gentil C, Bergmann KC, Casale TB, Okamoto Y, Pfaar O.

Referencia bibliográfica: Clin Exp Allergy. 2024 Mar 28. Epub ahead of print. PMID: 38545699.

Temática: Seguridad y efectividad de la ITA

Palabras Clave: allergic rhinitis; efficacy; house dust mite; sublingual immunotherapy; symptom and medication score.

ABSTRACT

Background: The symptoms of house dust mite (HDM)-induced allergic rhinitis (AR) vary with changes in exposure related to the weather or the domestic environment. In allergen immunotherapy (AIT) studies, a certain level of AR disease activity is necessary to demonstrate treatment efficacy; the latter can be underestimated if a substantial proportion of the patient population is weakly symptomatic.
Objective: To better estimate the real treatment effect of a HDM sublingual AIT (SLIT) tablet, we analysed the results of natural field studies in detail by applying a tertile approach.
Methods: We used data from three randomised, controlled trials (RCT) in a total of 2585 patients with AR treated with the 300 index of reactivity (IR) HDM SLIT-tablet or placebo. The study centres were grouped into tertiles according to the level of combined symptom and medication scores in patients in the placebo group. In each tertile, the difference between SLIT and placebo was assessed through an analysis of covariance.
Results: In the three RCTs, combined scores were found to be similar in the SLIT and placebo groups in the low tertiles. The treatment effect of the 300 IR HDM tablet increased in the medium and high tertiles, with notably significant differences versus placebo in the highest tertile and greater (ranging from -21% to -39%) than in the entire study population (-13% to -20%). The positive relationship between treatment efficacy and the combined score in each tertile was independent of the RCT and the score used.
Conclusion and clinical relevance: Application of the tertile approach to AIT studies in a field in which many variables interact strongly might provide more accurate and meaningful measurements of efficacy and benefit for patients, better reflecting their real-life condition.

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Efectividad de la ITO medido desde la transcriptómica

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Título del artículo original: Transcriptomic changes associated with oral immunotherapy for food allergy.

Autores: Ashley SE, Bosco A, Tang MLK.

Referencia bibliográfica: Pediatr Allergy Immunol. 2024 Mar;35(3):e14106. PMID: 38520061.

Temática: Biomarcadores en inmunoterapia

Palabras Clave: desensitization; food allergy; gene expression; oral immunotherapy; remission; systems biology; transcriptomics.

ABSTRACT	This review summarizes recent advances in characterizing the transcriptional pathways associated with outcomes following Oral Immunotherapy. Recent technological advances including single-cell sequencing are transforming the ways in which the transcriptional landscape is understood. The application of these technologies is still in its infancy in food allergy but here we summarize current understanding of gene expression changes following oral immunotherapy for food allergy and specific signatures underpinning the different clinical outcomes of desensitization and remission (sustained unresponsiveness). T helper 2A cells have been identified as a cell type which correlates with disease activity and is modified by treatment. Molecular features at study entry may differentiate individuals who achieve more positive outcomes during OIT. Recent findings point to T cell anergy and Type 1 interferon pathways as potential mechanisms supporting redirection of the allergen-specific immune response away from allergy towards remission. Despite these developments in our understanding of immune mechanisms following OIT, there are still significant gaps. Additional studies examining immune signatures associated with long term and well-defined clinical outcomes are required to gain a more complete understanding of the pathways leading to remission of allergy, in order to optimize treatments and gain improved outcomes for patients.

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Evidencia de la efectividad a largo plazo de los comprimidos en niños

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Título del artículo original: SQ sublingual immunotherapy tablets for children with allergic rhinitis: A review of phase three trials.

Autores: Csonka P, Hamelmann E, Turkalj M, Roberts G, Mack DP.

Referencia bibliográfica: Acta Paediatr. 2024 Mar 26. Epub ahead of print. PMID: 38529710.

Temática: Mejorando la selección de pacientes para inmunoterapia

Palabras Clave: allergic rhinitis; asthma; paediatric; randomised controlled trials; sublingual allergy immunotherapy tablets.

ABSTRACT

Aim: To provide paediatricians with a summary of efficacy and safety of SQ sublingual immunotherapy (SLIT) tablets from phase three, randomised, double-blind, placebo-controlled trials in children and adolescents with allergic rhinitis or rhinoconjunctivitis, with and without asthma.
Methods: PubMed searches were conducted and unpublished data were included if necessary.
Results: Of the 93 publications, 12 were identified reporting 10 trials. One trial was excluded as paediatric-specific efficacy data were unavailable. The nine eligible trials evaluated grass, house dust mite, ragweed and tree SLIT tablets. Consistent reductions in allergic rhinitis or rhinoconjunctivitis symptoms and medication use were observed with SQ SLIT tablets versus placebo. In a five-year trial, sustained reduction of allergic rhinoconjunctivitis symptoms, asthma symptoms and medication use were observed with SQ grass SLIT tablet versus placebo. The number-needed-to-treat to prevent asthma symptoms and medication use in one additional child during follow-up was lowest in younger children. SQ SLIT tablets were generally well tolerated across trials.
Conclusion: Evidence supports use of SQ SLIT tablets in children and adolescents with allergic rhinitis or rhinoconjunctivitis, with and without asthma. Long-term data demonstrate disease-modifying effects of SQ grass SLIT tablet and suggest the clinical relevance of initiating allergy immunotherapy earlier in the disease course.

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El uso de Apps durante la ITO mejora el cumplimiento y el manejo de incidencias

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Título del artículo original: Mobile App/Web Platform for Monitoring Food Oral Immunotherapy in Children: Longitudinal Clinical Validation Study.

Autores: Sánchez-Fernández S, Lasa EM, Terrados S, Sola-Martínez FJ, Martínez-Molina S, López de Calle M, Cabrera-Freitag P, Goikoetxea MJ.

Referencia bibliográfica: JMIR Pediatr Parent. 2024 Mar 13;7:e54163. PMID: 38477961; PMCID: PMC10973957.

Temática: Seguridad y efectividad de la ITA

Palabras Clave: adverse reactions; egg allergy; food oral immunotherapy; mHealth; milk allergy; monitoring.

ABSTRACT

Background: Milk and egg allergies significantly impact the quality of life, particularly in children. In this regard, food oral immunotherapy (OIT) has emerged as an effective treatment option; however, the occurrence of frequent adverse reactions poses a challenge, necessitating close monitoring during treatment.
Objective: This study aims to evaluate the ability of a new mobile/web app called OITcontrol to monitor milk and egg OIT.
Methods: Patients undergoing milk or egg OIT were recruited and divided into 2 groups: the active group used the OITcontrol app in conjunction with standard written monitoring methods, whereas the control group relied solely on written diaries. Investigators documented hospital doses, hospital reactions, and administered treatments on the website. Patients recorded their daily allergen home-dose intake, home reactions, and administered treatments using the app. The following variables were compared between both groups: number and severity of hospital and reported home reactions, patient's adhesion to the OITcontrol app or written diary or both in terms of daily home-dose intake and home reactions recording, and treatment and dose adjustment compliance at home in case of reaction.
Results: Sixteen patients were assigned to be monitored using the OITcontrol app along with additional written methods (active group), while 14 patients relied solely on a written paper diary (control group). A similar distribution was observed in terms of sex, age, basal characteristics, allergen treated in OIT, premedication, and sensitization profile. Active patients reported a comparable number of hospital and home reactions compared with the control group. In terms of recording system usage, 13/16 (81%) active patients used the OITcontrol app, while 10/14 (71%) control patients relied on the written diary. Among active patients, 6/16 (38%) used both methods, and 1 active patient used only written methods. However, control patients recorded home reactions more frequently than active patients (P=.009). Among active patients, the app was the preferred method for recording reactions (59/86, 69%), compared with the written diary (15/86, 17%) or both methods (12/86, 14%; P<.001). Treatment compliance in home-recorded reactions was similar between both groups (P=.15). However, treatment indications after an adverse reaction were more frequently followed (P=.04) in reactions recorded solely in the app (36/59, 61%) than in the written diary (29/71, 41%) or both systems (4/12, 33%). Moreover, compliance with dose adjustments after a moderate-severe reaction in home-recorded reactions was higher in the active group than in the control group

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La importancia de los adyuvantes en ITO.

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Título del artículo original: *Purified Free Mannan Promotes Tolerogenic Responses in Peanut-Stimulated Human Dendritic Cells*

Autores: *Sánchez-Herrero S, Benito-Villalvilla C, Palomares O*

Referencia bibliográfica: *Int Arch Allergy Immunol. 2024 Mar 21:1-7. doi: 10.1159/000537989. Epub ahead of print. PMID: 38513626.*

Temática: Biomarcadores en inmunoterapia

Palabras Clave: *Adjuvants; Dendritic cells; Food allergy; Peanut allergy; Regulatory T cells*.

ABSTRACT

Introduction: IgE-mediated peanut allergy is an important public health problem of increasing prevalence leading to anaphylactic reactions both in children and adults. Allergen-specific oral immunotherapy (OIT) is the single treatment with the potential capacity to modify the course of the disease, but it still faces some drawbacks in terms of efficacy, safety, patients' adherence, and cost. Alternative strategies, including the use of novel adjuvants, to overcome such limitations are highly demanded. The main aim of this study was to search for potential novel adjuvants for peanut OIT by assessing the capacity of free purified mannan and different toll-like receptor ligands (TLR-Ls) to immunomodulate the responses of human monocyte-derived dendritic cells (hmoDCs) to peanut allergens.
Methods: Monocytes were isolated from PBMCs of healthy donors and differentiated into hmoDCs. Flow cytometry, ELISA, coculture, and suppression assay were performed to assess the effects of TLR-Ls, mannan, and crude peanut extract (CPE) in hmoDCs.
Results: Purified free mannan increased the expression levels of HLA-DR, CD86, CD83, and PD-L1 and induced a higher IL-10/IL-6 cytokine ratio in hmoDCs compared to the stimulation with different TLR-Ls. Mannan significantly increased the expression of HLA-DR, the maturation marker CD83, the tolerogenic marker PD-L1, as well as the production of IL-10, IL-6, and TNF-α in CPE-stimulated hmoDCs. Supporting these tolerogenic properties, mannan also significantly increased the frequency of FOXP3+ regulatory T cells generated by CPE-treated hmoDCs with functional suppressive capacity.
Conclusions: We uncover that purified free mannan induces tolerogenic responses in human DCs stimulated with peanut allergens, suggesting mannan as a suitable potential novel adjuvant to be exploited in the context of OIT for peanut allergy.

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