Allergol Immunopathol (Madr). 2017;45(4):313–315

Allergologia et immunopathologia

Sociedad Española de Inmunología Clínica, Alergología y Asma Pediátrica

www.elsevier.es/ai

EDITORIAL

Food allergy in childhood: Are we close to having an effective treatment?

Food allergy (FA) has become a growing problem in recent years, particularly among the pediatric population.[1,2] A recent study has moreover emphasized that the ''epidemic'' has not yet peaked,[3] since the number of hospital admissions due to anaphylaxis continue to increase. Food allergy has a strong impact upon the quality of life of the affected patients and their families,[4,5] and can result in nutritional deficiencies secondary to the introduction of restrictive diets.[6]

Food allergy results from failure to develop oral tolerance or from failure of existing tolerance.[7] A proportion of children with FA will spontaneously overcome the disorder, particularly in the case of allergy to cow's milk and egg – thus indicating that oral tolerance can effectively develop.

At present, the only universally accepted therapeutic option is strict avoidance of the causal food and symptomatic management of the adverse reactions – with special emphasis on the administration of adrenalin in the case of anaphylaxis. However, this approach only reflects the fact that we lack effective etiological treatments, leaving patients vulnerable to the reactions caused by inadvertent ingestion of the causal foods.[8]

The adoption of primary prevention measures allowing the definition and induction of food tolerance mechanisms would be the ideal strategy for reducing the high prevalence of FA.[9,10] Once FA has become established, secondary prevention should ensure necessary avoidance of the allergen until spontaneous tolerance is reached or until tolerance is induced through oral immunotherapy (IOT). Due to the increasing frequency of FA in our pediatric population, we need treatments that are both effective and safe.

Food desensitization protocols or OIT have been used in the last few decades. These strategies involve administration of the causal food, starting with small doses and gradually increasing the dosage as the patient acquires tolerance, with two objectives in mind: (a) to protect the patient against adverse reactions resulting from accidental ingestion of the causal food; and (b) to normalize the diet by achieving specific desensitization to the allergen,[11] and ideally securing tolerance or ''sustained unresponsiveness''.[12]

The mechanisms of action underlying OIT in FA have not been clearly established, though studies on biomarkers[13–16] indicate that they are very similar to the mechanisms underlying immunotherapy for respiratory allergies.[17]

In Spain, as in other countries, a number of centers have been using this new treatment modality, with excellent results. The protocols must always be applied under close supervision by trained professionals, in hospitals where adequate treatment of any serious reactions can be guaranteed. The FA most commonly subjected to OIT is allergy to cow's milk and egg, though studies have also been made with peanut, fish, hazelnut, peach and other foods. The most widely used and documented route is the oral route, though the sublingual, subcutaneous and epicutaneous routes have also been used.

The literature on OIT reports high desensitization indices of between 60% to over 90%, depending on the food involved,[11,18–20] though the frequency of adverse reactions is also high.[21,22] The main problem in evaluating global OIT outcomes is the great variety of protocols used in different countries and centers. Because of this variability it is not possible to establish which are most effective and efficient procedures. Recent reviews and meta-analyses[23–25] have concluded that although OIT is effective, the quality of the evidence is low, due to the heterogeneity of the methods used. Furthermore, while effective, OIT is associated to a high incidence of adverse reactions. The latest review and meta-analysis[26] concludes that OIT can be effective in incrementing the reactivity threshold to several foods in patients with IgE-mediated FA, but is also associated to a risk of adverse effects.

This issue of *Allergologia et Immunopathologia* publishes a document that aims to serve as a clinical guide on the use of OIT in IgE-mediated allergy to cow's milk proteins and egg. It has been jointly developed by members of the *Sociedad Española de Inmunología Clínica, Asma y Alergia Pediátrica* (SEICAP) and the *Sociedad Española de Alergia y Inmunología Clínica* (SEAIC).

Based on a review of the literature, and contributing their own experiences, the authors propose a practical guide of

http://dx.doi.org/10.1016/j.aller.2017.06.001

use in implementing OIT in both the starting phase and in the maintenance phase. The document seeks to help professionals prescribe treatment schemes that are as homogeneous as possible, and to reduce the incidence of the adverse effects of such treatment. Likewise, models for intervention in cases of poor patient response to the conventional schemes are presented.

We believe that this guide constitutes a good basis for reaching these objectives.

A number of issues remain to be resolved, however:

1. Is OIT the most effective treatment for achieving food desensitization? Or is it preferable to use other procedures involving different routes and allergens, such as the sublingual route,[27–32] the epicutaneous route,[33–35] modified hypoallergenic molecules,[36–38] OIT with peptides,[39,40] or OIT with heat-modified (baked) foods?[41–48]
2. Is OIT cost-effective and efficient over the long term?

The ultimate aim of the guide is to improve clinical practice and allow the professionals in charge of such treatments to feel that their work is supported by this document.

References

1. Nwaru BI, Hickstein L, Panesar SS, Muraro A, Werfel T, Cardona V, et al. The epidemiology of food allergy in Europe: a systematic review and meta-analysis. Allergy. 2014;69:62–75.
2. Prescott S, Pawankar R, Allen KJ, Campbell DE, Sinn JKH, et al. A global survey of changing patterns of food allergy burden. World Allergy Org J. 2013;6:21.
3. Mullins RJ, Dear KB, Tang ML. Time trends in Australian hospital anaphylaxis admissions in 1998–1999 to 2011–2012. J Allergy Clin Immunol. 2015;136:367–75. PMID: 26187235.
4. DunnGalvin A, Dubois AE, Flokstra-de Blok BM, Hourihane JO. The effects of food allergy on quality of life. Chem Immunol Allergy. 2015;101:235–52.
5. Primeau MN, Kagan R, Joseph L, Lim H, Dufreshne C, Duffy C, et al. The psychological burden of peanut allergy as perceived by adults with peanut allergy and the parents of peanut allergic children. Clin Exp Allergy. 2000;30:1135–43.
6. Robbins KA, Wood RA, Keet CA. Milk allergy is associated with decreased growth in US children. J Allergy Clin Immunol. 2014;134, 1466–8.e6.
7. Peters RL, Dang TD, Allen KJ. Specific oral tolerance induction in childhood. Pediatr Allergy Immunol. 2016, http://dx.doi.org/10.1111/pai.12620.
8. Alvaro M, Muraro A. Oral immunotherapy in food allergy: present and future. An Pediatr (Barc). 2015;82:213–5.
9. Du Toit G, Roberts G, Sayre PH, et al. Randomized trial of peanut consumption in infants at risk for peanut allergy. N Engl J Med. 2015;372:803–13.
10. Perkin MR, Logan K, et al. Randomized trial of introduction of allergenic foods in breast-fed infants. N Engl J Med. 2016, http://dx.doi.org/10.1056/NEJMoa1514210.
11. Alvaro M, Giner MT, Vazquez M, Lozano J, Dominguez O, Piquer M, et al. Specific oral desensitization in children with IgE-mediated cow's milk allergy. Evolution in one year. Eur J Pediatr. 2012;171:1389–95.
12. Vickery BP, Scurlock AM, Kulis M, Steele PH, Kamilaris J, Berglund JP, et al. Sustained unresponsiveness to peanut in subjects who have completed peanut oral immunotherapy. J Allergy Clin Immunol. 2014;133, 468–75.e6.
13. Keet CA, Wood RA, et al. Emerging therapies for food allergy. J Clin Invest. 2014;124:1880–6.
14. Berin MC, Sicherer S, et al. Food allergy: mechanisms and therapeutics. Curr Opin Immunol. 2011;23:794–800.
15. Savilahti EM, Kuitunen M, Valori M, et al. Use of IgE and IgG4 epitope binding to predict the outcome of oral immunotherapy in cow's milk allergy. Pediatr Allergy Immunol. 2014;25:227–35.
16. Martínez-Botas J, Rodríguez M, Cerecedo I, Vlaicu C, Diéguez MªC, Gómez-Coronado D, et al. Identification of novel peptide biomarkers to predict safety and efficacy of Cow's Milk Oral Immunotherapy by peptide microarray. Clin Exp Allergy. 2015, http://dx.doi.org/10.1111/cea.12528.
17. Tortajada-Girbés M, Mesa del Castillo M, Larramona H, Lucas JM, Álvaro M, Tabar AI, et al. Evidence in immunotherapy for paediatric respiratory allergy: advances and recommendations. Document of the Immunotherapy Working Group of the Spanish Society of Pediatric Clinical Immunology and Allergology (SEICAP). Allergol Immunopathol (Madr). 2016;44(S1):1–32.
18. Keet CA, Frischmeyer-Guerrerio PA, Thyagarajan A, Schroeder JT, Hamilton RG, Boden S, et al. The safety and efficacy of sublingual and oral immunotherapy for milk allergy. J Allergy Clin Immunol. 2012;129:448–55, e1–5.
19. Burks AW, Jones SM, Wood RA, Fleischer DM, Sicherer SH, Lindblad RW, et al. Oral immunotherapy for treatment of egg allergy in children. N Engl J Med. 2012;367:233–43.
20. Martorell A, De la Hoz B, Ibanez MD, Bone J, Terrados MS, Michavila A, et al. Oral desensitization as a useful treatment in 2-year-old children with cow's milk allergy. Clin Exp Allergy. 2011;41:1297–304.
21. Vazquez M, Alvaro M, Alsina L, Garcia-Paba MB, Piquer M, Giner MT, et al. Safety and predictors of adverse events during oral immunotherapy for milk allergy: severity of reaction at oral challenge, specific IgE and prick test. Clin Exp Allergy. 2013;43:92–102.
22. Vazquez-Ortiz M, Álvaro-Lozano M, Piquer-Gibert M, Domínguez-Sánchez O, Machinena A, Martín-Mateos M, et al. Baseline specific IgE levels are useful to predict safety of oral immunotherapy in egg allergic children. Clin Exp Allergy. 2014;44:130–41.
23. Yeung JP, Kloda LA, McDevitt J, Ben-Shoshan M, Alizadehfar R. Oral immunotherapy for milk allergy. Cochrane Database Syst Rev. 2012;11:CD009542.
24. Brozek JL, Terracciano L, Hsu J, Kreis J, Compalati E, Santesso N, et al. Oral immunotherapy for IgE-mediated cow's milk allergy: a systematic review and meta-analysis. Clin Exp Allergy. 2012;42:363–74.
25. Nurmatov U, Devereux G, Worth A, Healy L, Sheikh A. Effectiveness and safety of orally administered immunotherapy for food allergies: a systematic review and meta-analysis. Br J Nutr. 2014;111:12–22.
26. Nurmatov U, Dhami S, Arasi S, Pajno GB, Fernandez-Rivas M, Muraro A, et al. Allergen immunotherapy for IgE-mediated food allergy: a systematic review and meta-analysis. Allergy. 2017, http://dx.doi.org/10.1111/all.13124.
27. Enrique E, Pineda F, Malek T, Bartra J, Basagana M, Tella R, et al. Sublingual immunotherapy for hazelnut food allergy: a randomized, double-blind, placebo- controlled study with a standardized hazelnut extract. J Allergy Clin Immunol. 2005;116:1073–9.
28. Kim EH, Bird JA, Kulis M, Laubach S, Pons L, Shreffler W, et al. Sublingual immunotherapy for peanut allergy: clinical and immunologic evidence of desensitization. J Allergy Clin Immunol. 2011;127, 640–6.e1.
29. Fleischer DM, Burks AW, Vickery BP, Scurlock AM, Wood RA, Jones SM, et al. Sublingual immunotherapy for peanut allergy:

a randomized, double-blind, placebo-controlled multicenter trial. J Allergy Clin Immunol. 2013;131:119–27, e1–7.
30. Burks AW, Wood RA, Jones SM, Sicherer SH, Fleischer DM, Scurlock AM, et al. Sublingual immunotherapy for peanut allergy: long-term follow-up of a randomized multicenter trial. J Allergy Clin Immunol. 2015;135:1240–8, e1–3.
31. Fernandez-Rivas M, Garrido-Fernandez S, Nadal JA, et al. Randomized double-blind, placebo-controlled trial of sublingual immunotherapy with a Pru p 3 quantified peach extract. Allergy. 2009;64:876–83.
32. Narisety SD, Frischmeyer-Guerrerio PA, Keet CA, Gorelik M, Schroeder J, Hamilton RG, et al. A randomized, double-blind, placebo-controlled pilot study of sublingual versus oral immunotherapy for the treatment of peanut allergy. J Allergy Clin Immunol. 2015;135:1275–82.
33. Mondoulet L, Dioszeghy V, Ligouis M, Dhelft V, Dupont C, Benhamou PH. Epicutaneous immunotherapy on intact skin using a new delivery system in a murine model of allergy. Clin Exp Allergy. 2010;40:659–67.
34. Dupont C, Kalach N, Soulaines P, Legoue-Morillon S, Piloquet H, Benhamou PH. Cow's milk epicutaneous immunotherapy in children: a pilot trial of safety, acceptability, and impact on allergic reactivity. J Allergy Clin Immunol. 2010;125:1165–7.
35. Dioszeghy V, Mondoulet L, Dhelft V, Ligouis M, Puteaux E, Benhamou PH, et al. Epicutaneous immunotherapy results in rapid allergen uptake by dendritic cells through intact skin and downregulates the allergen-specific response in sensitized mice. J Immunol. 2011;186:5629–37.
36. Yang M, Yang C, Mine Y. Multiple T cell epitope peptides suppress allergic responses in an egg allergy mouse model by the elicitation of forkhead box982 WOOD transcription factor 3 and transforming growth factor-beta-associated mechanisms. Clin Exp Allergy. 2010;40:668–78.
37. Swoboda I, Balic N, Klug C, Focke M, Weber M, Spitzauer S, et al. A general strategy for the generation of hypoallergenic molecules for the immunotherapy of fish allergy. J Allergy Clin Immunol. 2013;132:979–81.
38. Wood RA, Sicherer SH, Burks AW, Grishin A, Henning AK, Lindblad R, et al. A phase 1 study of heat/phenol-killed, *E. coli*-encapsulated, recombinant modified peanut proteins Ara h 1, Ara h 2, and Ara h 3 (EMP-123) for the treatment of peanut allergy. Allergy. 2013;68:803–8.
39. Li S, Li XM, Burks AW, Sampson HA. Modulation of peanut allergy by peptide-based immunotherapy. J Allergy Clin Immunol. 2001;107:S233 (Abstract).
40. Prickett SR, Voskamp AL, Dacumos-Hill A, et al. Ara h 2 peptides containing dominant CD4+ T-cell epitopes: candidates for a peanut allergy therapeutic. J Allergy Clin Immunol. 2011;127:608.
41. Bloom KA, Huang FR, Bencharitiwong R, et al. Effect of heat treatment on milk and egg proteins allergenicity. Pediatr Allergy Immunol. 2014;25:740–6.
42. Martos G, Lopez-Exposito I, Bencharitiwong R, Berin MC, Nowak-Wegrzyn A. Mechanisms underlying differential food allergy response to heated egg. J Allergy Clin Immunol. 2011;127, 990–7.e1–2.
43. Shin M, Lee J, Ahn K, Lee SI, Han Y. The influence of the presence of wheat flour on the antigenic activities of egg white proteins. Allergy Asthma Immunol Res. 2013;5:42–7.
44. Wood RA, Sicherer SH, Vickery BP, et al. The natural history of milk allergy in an observational cohort. J Allergy Clin Immunol. 2013;131:805–12.
45. Sicherer SH, Wood RA, Vickery BP, et al. The natural history of egg allergy in an observational cohort. J Allergy Clin Immunol. 2014;133:492–9.
46. Leonard SA. Debates in allergy medicine: baked milk and egg ingestion accelerates resolution of milk and egg allergy. World Allergy Organ J. 2016;9:1.
47. Nowak-Wegrzyn A, Bloom KA, Sicherer SH, et al. Tolerance to extensively heated milk in children with cow's milk allergy. J Allergy Clin Immunol. 2008;122:342–7, 347.e1–2.
48. Lemon-Mule H, Sampson HA, Sicherer SH, Shreffler WG, Noone S, Nowak-Wegrzyn A. Immunologic changes in children with egg allergy ingesting extensively heated egg. J Allergy Clin Immunol. 2008;122, 977–83.e1.

M. Alvaro[a,*], M. Escarrer[b]
[a] *Hospital Sant Joan de Déu, Esplugues, Universistat de Barcelona, Barcelona, Spain*
[b] *Clínica Juaneda, Palma de Mallorca, Spain*

[*] Corresponding author.
E-mail address: malvaro@sjdhospitalbarcelona.org (M. Alvaro).