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POINT OF VIEW

New routes of allergen immunotherapy



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Carmen Moreno, asked Dr. Van Ree regarding to peanut immunotherapy with modified allergen, which could eventually be released as a registered product for all the states of EU. She wondered if the different phenotypes of peanut allergic patients had been considered. Most of patients of Southern countries in Europe are sensitized to Ara h 9. Safety concerns and lack of efficacy should be considered if only Ara h 2 and Ara h 6 are included in the final product.

Dr. Van Ree explained that, in general, there is very good evidence that the most severe reactions to peanut are associated with Ara h2 and Ara h 6. So it is important to at least, include this two allergens modified in the vaccine. There are actually diverse phenotypes. Ara h 3, an storage protein, is affected by reduction and alquilation, but not Ara h 1. Ara h 9, the LTP of peanut, which is important in Spain, is also affected by the reduction and alquilation. So, from a safety perspective, Spanish patients would not be in risk. LTP, Ara h 9, does not go in a solution easily because it only goes into solution in a lower pH. So the normal peanut extracts have a low quantity of Ara h 9. This has been shown in diagnostic extracts. In hazelnut extracts for diagnostics, there is enrichment with Cor a 9, the LTP of hazelnut, because normal extract has very low quantity. Moreover, LTP patients have no very severe reactions. In

conclusion, Dr. Van Ree considered that there are no safety concerns.

Background

Peanut allergy is a major cause of fatal food-allergic reactions. The prevalence has increased over the past decades, mostly in the Western world, where the disease is affecting 1–2% of children. Peanut avoidance and emergency medication to treat accidental reactions, form the routine management. Moreover, only one in five children are expected to outgrow their peanut allergy. These are the reasons to look for a good immunotherapy product to offer safe alternatives to patients.

Subcutaneous peanut immunotherapy was initially attempted, but unfortunately, there was a relevant rate of systemic. Lately, there has been a development in sublingual, epicutaneous, but mostly peanut oral immunotherapy (OIT) studies. OIT presents an interesting and promising novel form of desensitization for children with peanut allergy, with good safety profile, with most subjects experiencing mild or moderate reactions during treatment.

Currently, the WHO/International Union of Immunological Societies (IUIS) Allergen Nomenclature committee has documented 12 peanut allergens. Ara h 1 and Ara h 2 have been well-studied and are recognized as major allergens. Ara h 2 has a higher predictive value for diagnosis of clinical peanut allergy than Ara h 1, Ara h 3, Ara h 8 and Ara h 9. Ara h 2 is also more potent than Ara h 1 or Ara h 3 in histamine release assays and skin prick tests.

Abbreviations: EU, European Union; OIT, oral immunotherapy; LTP, lipid transfer protein; SLIT, sublingual immunotherapy; EPIT, epicutaneous immunotherapy; SCIT, subcutaneous immunotherapy.

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Another peanut allergen, Ara h 6, has recently emerged as an important allergen and has approximately the same seroprevalence as Ara h 2, so it is considered as a major peanut allergen.

Patients with peanut allergy recognize predominantly Ara h 2 and Ara h 6, which are storage proteins (Ara h1, Ara h 2, Ara h 3, Ara h 6 and Ara h 7). Together, they were able to predict peanut allergy with 98% sensitivity and 85% specificity at a predictive threshold of 0.1 kU/L.

Patterns of allergy have been described in order to allergy onset. Sensitization to rAra h 1 and 2 were exclusively observed in early onset peanut allergy.

Geographic differences were as well observed for rAra h 8 and rAra h 9, which were major allergens for central/western and southern Europeans, respectively. Peanut tolerant subjects were frequently sensitized to rAra h 8 or 9 but not to storage proteins.

In a study performed in children from the South of France, Ara h 6 and Ara h 2 were the best predictors of peanut allergy at diagnosis. Ara h 1, Ara h 8, and molecular complexity were associated persistence in these Mediterranean area.

A study conducted in several countries in Europe showed that all subjects with IgE to rAra h 8 were positive to birch pollen extract and all subjects with sIgE to rAra h 9 were positive to rPru p 3.

Luis Prieto asked to S. Scheurer what were the differences between sublingual immunotherapy (SLIT) and epicutaneous immunotherapy (EPIT) and whether the contact time affected the efficacy.

S. Scheurer commented that the time seems to be important issue. In study of Jones SM (2017), with a peanut EPIT for peanut allergy treatment in children, graduated dosing was performed with the same strength patch by increasing the time worn as follows: week 1, 3 h/d; week 2, 6 h/d; and week 3, 12 h/d. This was followed by patch application for 24 h/d beginning on day 22.

Background

EPIT is an emerging modality for the treatment of allergy. It is needle-free and painless immunotherapy, that represents an advantage over subcutaneous immunotherapy (SCIT). The epidermis has a high density of antigen-presenting Langerhans cells. Because the epidermis is not vascularized, epicutaneous immunotherapy should carry less risk of systemic reactions.

The first trial in patients with rhinoconjunctivitis was conducted in 2009 and showed benefits when used to treat grass pollen allergy in adults.

Murine models (peanut sensitized mice) indicate that epicutaneously applied antigen modulates TH2 immune responses through antigen driven activation of dendritic cells with later immune modulation through trafficking to

lymph nodes. This suggests that EPIT induces long-term tolerance in peanut-sensitized mice.

There are several unresolved questions of EPIT like the optimum dose into the patch or the duration of application with proper tolerability.

Finally, SLIT uses the tolerogenic environment of the oral mucosa and EPIT uses the immune cells of the epidermis to transport antigens to afferent lymph nodes to activate immune responses. More investigation is needed to define optimal doses, time of application and administration protocols.

References

1. Anagnostou K. Recent advances in immunotherapy and vaccine development for peanut allergy. *Therapeutic Adv Vaccines*. 2015;3:55–65.
2. Marsh J, Rigby N, Wellner K, Reese G, Knulst A, Akkerdaas J, et al. Purification and characterisation of a panel of peanut allergens suitable for use in allergy diagnosis. *Mol Nutr Food Res*. 2008;52 Suppl. 2:S272–85.
3. Koid AE, Chapman MD, Hamilton RG, et al. Ara h 6 complements Ara h 2 as an important marker for IgE reactivity to peanut. *J Agric Food Chem*. 2014;62:206–13.
4. Fernández-Rivas M, Barreales L, Mackie AR, Fritsche P, Vázquez-Cortés S, Jedrzejczak-Czechowicz M, et al. The EuroPrevall outpatient clinic study on food allergy: background and methodology. *Allergy*. 2015;70:576–84.
5. Ballmer-Weber BK, Lidholm J, Fernández-Rivas M, Seneviratne S, Hanschmann K-M, Vogel L, et al. IgE recognition patterns in peanut allergy are age dependent: perspectives of the EuroPrevall study. *Allergy*. 2015;70:391–407.
6. Jones SM, Sicherer SH, Burks AW, Leung DY, Lindblad RW, Dawson P, et al. Epicutaneous immunotherapy for the treatment of peanut allergy in children and young adults. *J Allergy Clin Immunol*. 2017;139:1242–52, e9.
7. Boulay A, Houghton J, Gancheva V, Sterk Y, Strada A, Schlegel-Zawadzka M, et al. A EuroPrevall review of factors affecting incidence of peanut allergy: priorities for research and policy. *Allergy*. 2008;63:797–809.
8. Kukkonen AK, Pelkonen AS, Mäkinen-Kiljunen S, Voutilainen H, Mäkelä MJ. Ara h 2 and Ara 6 are the best predictors of severe peanut allergy: a double-blind placebo-controlled study. *Allergy*. 2015;70:1239–45.
9. Agabriel C, Ghazouani O, Birnbaum J, Liabeuf V, Porri F, Gouitaa M, et al. Ara h 2 and Ara h 6 sensitization predicts peanut allergy in Mediterranean pediatric patients. *J Pediatr Allergy Immunol*. 2014;25:662–7.
10. Senti G, Graf N, Haug S, Ruedi N, von Moos S, Sonderegger T, et al. Epicutaneous allergen administration as a novel method of allergen-specific immunotherapy. *J Allergy Clin Immunol*. 2009;124:997–1002.
11. Dioszeghy V, Mondoulet L, Dhelft V, Ligouis M, Puteaux E, Benhamou P-H, et al. Epicutaneous immunotherapy results in rapid allergen uptake by dendritic cells through intact skin and down-regulates the allergen-specific response in sensitized mice. *J Immunol*. 2011;186:5629–37.