EAACI Research Fellowship

FINAL REPORT

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Project title: Desensitization vs. sustained unresponsiveness: analyzing long term efficacy of oral food immunotherapy in cow's milk or egg allergic children

Host institution: Sant Joan de Déu Hospital, Barcelona, Spain

Type of fellowship: Research

Duration: Long term (12 months)

BACKGROUND:

Food allergy has been on the rise for the past 10 years in both developed and developing countries, becoming a growing global health concern. Food-induced anaphylaxis represents an economic liability on public health systems and measures should be taken by allergy specialists worldwide to anticipate and address this growing burden. (1)

Similarly, food allergy has profound repercussions in patients and their families. Highly restrictive diets can result in complications ranging from parental anxiety to children coping with social acceptance, resulting in a reduced quality of life. (2)

Present-day therapy in clinical practice relies solely on allergen avoidance and treatment of adverse reactions, but these strategies are not sufficient to address the current food allergy epidemic. International allergy societies, particularly EACCI, are moving rapidly forward in this area of research. (3)

Because of a growing understanding of food allergy mechanisms and pathways, new therapeutic strategies are currently under investigation. A shift towards induction of tolerance, through low-dose allergen exposure, has been a constant study subject. However, there are still important steps to take before food allergy oral immunotherapy (FA-OIT) is ready for an everyday clinical setting. (4)

There is great heterogeneity in FA-OIT protocols when it comes to induction and maintenance phases (5). Most FA-OIT protocols report frequent adverse reactions and even severe anaphylaxis, thus

the overall risk of OIT could, in some patients, out-weight the benefits. Further on, even if patients can undertake these obstacles, a complete clinical remission is not guaranteed. An effort should be made to find solid data that identifies these subjects early on. (6)

When addressing efficacy in FA-OIT there are two pathways: desensitization and sustained unresponsiveness. Desensitization addresses short-term efficacy and accounts for the change in dose threshold needed to cause an allergic reaction, resulting in the ability to safely consume a determined amount of food allergen, while on immunotherapy to this offender allergen. The concept of sustained unresponsiveness tackles long-term efficacy and is used in patients that have achieved tolerance to the allergen without being on active immunotherapy. (3,4)

Many studies report high rates of initial desensitization but neglect to report long term tolerance. Desensitization, ranges from 57% to 94% for egg-white oral immunotherapy (EW-OIT), and 36% to 91% for cow´s milk oral immunotherapy (CM-OIT). (4)

A EAACI meta-analysis, describes trials that measure efficacy of FA-OIT in regard to desensitization, revealing a benefit for patients undergoing OIT. However, there is incomplete data concerning sustained unresponsiveness. As well, an insufficient number of trials assess tolerance following a period of allergen avoidance after successful desensitization. (3)

To date it remains unclear if therapy needs to be continued permanently and patients sentenced to enduring life-long maintenance. There is limited evidence with regard to post-immunotherapy outcomes and likelihood of allergic relapse following cessation of treatment. All of these interrogations need to be well defined before FA-OIT is ready for routine clinical practice. (3,4)

OBJECTIVE:

The aim of this study is to investigate the long-term efficacy of CM and EW-OIT and determine useful clinical features and possible biomarkers that describe those patients more likely to achieve sustained unresponsiveness.

SIGNIFICANCE:

Since 2006, Hospital Sant Joan de Déu in Barcelona has an ongoing FA-OIT research program for cow's milk and egg allergic children, making it the ideal setting to study long-term efficacy. Earlier publications by this research team have addressed safety in FA-OIT (6,7), quality of life (8), and short-term desensitization (9), but none considered long-term tolerance.

Considering both clinical characteristics and immunological parameters, the study of children undergoing long-term FA-OIT can bring light to the many questions involving the differences in patients that achieve exclusively desensitization in comparison to those who have a complete sustained unresponsiveness.

ETHICS:

The protocol has been approved by Hospital Sant Joan de Déu Allergy department and by the hospitals ethics committee. Written material and informed consent will be given to both parents and patients.

ACTIVITIES:

A total of 207 patients were enrolled on CM-OIT or EW-OIT since 2006. The study subjects will be divided in two different groups, one for CM-OIT and one for EW-OIT. Evaluation of each one was done separately. All patients were aged 5-18 prior to the beginning of OIT. They were initially studied using skin prick test, specific IgE to cow's milk or egg proteins and a double-blind placebo control food challenge (DBPCFC). Descriptive data of the OIT evolution for the past decade was the first point analyzed.

New baseline parameters were recorded including clinical characteristics (age, gender, current comorbidities, multiple food allergies, rhinitis, atopic dermatitis, asthma and its severity), threshold dose of OIT, severity of reaction at baseline, months needed for induction phase and for maintenance of OIT, adverse reaction to FA-OIT throughout the years, adherence and current ingestion patterns of culprit allergen.

On a second instalment, the long-term tolerance and sustained unresponsiveness of patients who had successfully completed OIT was analyzed. Patients included in this second stage had more than 4 years since the start of FA-OIT protocol and experienced no moderate or severe adverse reactions in the last year of FA-OIT. Exclusion criteria was severe or uncontrolled asthma, severe atopic dermatitis according to SCORAD index above 40, cardiovascular diseases, neuropsychiatric impairment or treatment with an anti-IgE monoclonal antibody. A Spanish version of the food allergy quality of life questionnaire was be given to patients.

A strict avoidance diet of the culprit food was implemented for 8 weeks. After this exclusion period, the allergen will be reintroduced in a DBPCFC took place in the allergy day-hospital. This challenge followed hospital protocol and was based on PRACTALL parameters. The fellow was in charge of all interviews, as well as supervision of all OFC.

If the patient has no adverse reactions to the DBPCFC was considered to have achieved sustained unresponsiveness and was allowed a normal diet that included the formerly problematic food protein as often as preferred. In case the patient has an adverse reaction during the DBPCFC, a new FA-OIT induction phase was proposed for patients that want to continue lifelong maintenance. All patients who reacted during the OFC reinitiated the OIT without difficulties. The fellow was also in charge of follow-up and new OIT in these patients.

At baseline, immunological parameters were collected. Skin tests were performed on the forearm with commercial extracts (Alk-Abello, Spain). Wheals were measured by scanner using a Prick Film method (Inmunotek, Madrid). A wheal of ≥3 mm (major diameter) was considered positive according to the EAACI position paper guidelines. Specific IgE and IgG4 levels greater than 0.35 kU/L were also be considered positive.

In the case of CM-OIT, cow's milk-specific IgE and IgG4 levels for whole milk, α-lactalbumin, β-lactoglobulin and casein were compared to values before OIT (CAP-Phadia, Uppsala, Sweden). For EW-OIT, IgE and IgG4 to egg white, ovomucoid and ovoalbumin were compared to values before OIT. (CAP-Phadia, Uppsala, Sweden)

Basophile activation was performed at the beginning of avoidance diet and before the DBPCFC to see if changes are present. Basophil activation was assessed by flow cytometer, using fresh blood within 3 hours after blood withdrawal. The negative controls were obtained with only basophil stimulation buffer and the positive control with 20 ml of anti-IgE (0.5 mg/ml, Pharmingen). Activated basophils will undergo flow cytometer (BD Biosciences) following standards to cow’s milk or egg respectively.

IMPACT FOR FUTURE RESEARCH:

This project allowed us to find specific biomarkers and draw conclusions on the profile of patients that will be able to achieve long term remission of their food allergy after successful oral immunotherapy. Furthermore, we were able to identify characteristics for high risk patients that need to be monitored more closely during their OIT maintenance and who will probably need additional interventions such as biologics. This will allow for better selection of patients that can benefit from OIT.

ACKNOWLEDGEMENTS:

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CONCLUSION:

This project has been transcendental on a professionally and personal level. I have learned and shared knowledge with all co-workers in the Pediatric Allergy and Clinical Immunology Service at Hospital Sant Joan de Déu in Barcelona. On a clinical level, it has been rewarding to be in close contact with over 10 pediatric allergy specialists as well as dedicated nurses and allied health personnel. On a scientific level, I have gained solid bases for future projects and developed a thirst for continuing this line of research.

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