

## CORRESPONDENCE

## Predicting reactions severity at challenge in egg-allergic patients

M. Vazquez-Ortiz, M. Alvaro, M. Piquer, O. Dominguez, A. Machinena, M. A. Martín-Mateos and A. M. Plaza

Department of Paediatric Allergy and Clinical Immunology, Hospital Sant Joan de Déu, Universitat de Barcelona, Barcelona, Spain

We thank Dr Tosca et al. for their interest in our study about the usefulness of specific IgE (sIgE) to predict the safety of oral immunotherapy for egg allergy [1]. We value their work trying to identify biomarkers associated with anaphylaxis in egg-allergic children.

Our group has recently submitted for publication a study in 82 egg-allergic children (those enrolled in our above-mentioned oral immunotherapy study [1]) in which we aimed to evaluate the usefulness of clinical and molecular-based immunological parameters to predict anaphylaxis at double-blind placebo-controlled food challenge (DBPCFC) based on Sampson's anaphylaxis criteria [2,3]. The clinical data recorded were age, gender, asthma, rhinitis, atopic dermatitis and multiple food allergies. The immunological parameters determined were skin prick test (SPT) and sIgE to egg white, Gal d 1 (ovomucoid) and Gal d 2 (ovalbumin) by ImmunoCAP (ThermoFisher Scientific, Uppsala, Sweden). Further methodological details on inclusion criteria, parameters determination and DBPCFC protocol were described in our paper [1]. We observed that immunological parameters showed poor diagnostic performance to predict anaphylaxis at DBPCFC, with areas under ROC curves (AUC) ranging from 0.630 (for SPT to Gal d 1) to 0.680 (for sIgE to Gal d 1),  $P < 0.05$ . The most accurate cut-off was obtained by egg white-sIgE, although no differences were found in ROC curves or in the diagnostic properties of cut-offs of different parameters. Thus, the ability of SPT and sIgE to Gal d 1, Gal d 2 and egg white to accurately identify children at risk of anaphylaxis at DBPCFC seems poor.

Our results are similar to those reported by Tosca et al. (in terms of AUC), although they determined sIgE to Gal d 1 and Gal d 2 by ISAC microarray technique. Of note, the correlation between sIgE to Gal d 1 and Gal d 2 measured by ISAC and ImmunoCAP has not been evaluated yet. Due to methodological differences between these two techniques, their results are not equivalent. Importantly, ISAC assay is a semi-quantitative technique (as opposed to ImmunoCAP). Thus, ISAC may not be the most appropriate technique to provide

specific cut-offs as results ranges are more reliable than specific values [4].

As known, molecular-based diagnosis may improve egg allergy management, since sIgE and/or SPT to ovomucoid may help predict tolerance to baked and cooked egg [5–8]. However, its usefulness to predict egg allergy severity seems limited. In view of current evidence, ISAC technique should not generally replace ImmunoCAP when evaluating sIgE to egg allergens is the main purpose. Indeed, no clinical benefit has been proved by using ISAC in this context [9] and its cost is approximately twenty times higher than one sIgE determination by ImmunoCAP. Gal d 1 and Gal d 2 are the main allergens in egg white [10] and the determination of other (minor) egg allergens seems to be of very limited usefulness in most egg-allergic children, as shown by Tosca et al. In fact, we did not evaluate sIgE to Gal d 5 (the major allergen in egg yolk, mainly associated with egg-bird syndrome [11]) because all our 82 children were allergic to egg white, all tolerated chicken meat and none had experienced respiratory symptoms on exposure to birds. Likewise, we did not study sIgE to Gal d 3 and Gal d 4 as they had resulted not useful to predict clinical reactivity in a Spanish cohort of 157 egg-allergic children [12].

Finally, some other methodological differences between Tosca's work and our study should be highlighted. First, our patients' classification as 'anaphylaxis group' and 'no anaphylaxis group' is based on a consistent egg exposure in a controlled setting in all children (i.e. a DBPCFC), whereas in Tosca's study apparently is not. This fact might have biased their patients' classification, because reactions severity may depend on the dose ingested [13], the egg processing method (which modifies its allergenicity [10]) and potential co-factors associated to reactions (infections, emotions, exercise, specific drugs) [14]. In agreement with this, Hourihane et al. [15] found poor correlation between the severity of reported reactions to peanut in the community and the severity of reactions elicited during DBPCFC. Secondly, the criterion to select cut-offs should be described, as well as the diagnostic properties of these cut-offs. Lastly, ROC curves and diagnostic properties of cut-offs of the different test should be compared to determine whether any test provides better diagnostic performance than the others.

## Correspondence:

Marta Vazquez-Ortiz, Passeig de Sant Joan de Déu, 2. Esplugues de Llobregat 08950, Barcelona, Spain.

E-mail: marta.vazquez.ortiz@gmail.com

## References

- 1 Vazquez-Ortiz M, Alvaro M, Piquer 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.
- 2 Sampson HA. Anaphylaxis and emergency treatment. *Pediatrics* 2003; **111**:1601–8.
- 3 Sampson HA, Munoz-Furlong A, Bock SA *et al.* Symposium on the definition and management of anaphylaxis: summary report. *J Allergy Clin Immunol* 2005; **115**:584–91.
- 4 Goikoetxea MJ, Sanz ML, García BE, Mayorga C, Longo N, Gamboa PM. Recommendations for the use of in vitro methods to detect specific immunoglobulin E: are they comparable? *J Investig Allergol Clin Immunol* 2013; **23**:448–54.
- 5 Tan JW, Campbell DE, Turner PJ *et al.* Baked egg food challenges - clinical utility of skin test to baked egg and ovomucoid in children with egg allergy. *Clin Exp Allergy* 2013; **43**:1189–95.
- 6 Ando H, Movérare R, Kondo Y *et al.* Utility of ovomucoid-specific IgE concentrations in predicting symptomatic egg allergy. *J Allergy Clin Immunol* 2008; **122**:583–8.
- 7 Vazquez-Ortiz M, Pascal M, Jiménez-Feijoo R *et al.* Ovalbumin-specific IgE/IgG4 ratio might improve the prediction of cooked and uncooked egg tolerance development in egg-allergic children. *Clin Exp Allergy* 2014; **44**:579–88.
- 8 Alessandri C, Zennaro D, Scala E *et al.* Ovomucoid (Gal d1) specific IgE detected by microarray system predict tolerability to boiled hen's egg and an increased risk to progress to multiple environmental allergen sensitisation. *Clin Exp Allergy* 2012; **42**:441–50.
- 9 Ott H, Baron JM, Heise R, Ocklenburg C, Stanzel S, Merk HF *et al.* Clinical usefulness of microarray-based IgE detection in children with suspected food allergy. *Allergy* 2008; **63**(11): 1521–8.
- 10 Mine Y, Yang M. Recent advances in the understanding of egg allergens: basic, industrial, and clinical perspectives. *J Agric Food Chem* 2008; **56**:4874–900.
- 11 Quirce S, Marañón F, Umpiérrez A, de las Heras M, Fernández-Caldas E, Sastre J. Chicken serum albumin (Gal d 5\*) is a partially heat-labile inhalant and food allergen implicated in the bird-egg syndrome. *Allergy* 2001; **56**:754–62.
- 12 Diéguez MC, Cerecedo I, Muriel A *et al.* Utility of diagnostic tests in the follow-up of egg-allergic children. *Clin Exp Allergy* 2009; **39**:1575–84.
- 13 Wainstein BK, Studdert J, Ziegler M, Ziegler JB. Prediction of anaphylaxis during peanut food challenge: usefulness of the peanut skin prick test (SPT) and specific IgE level. *Pediatr Allergy Immunol* 2010; **21**(4 Pt 1):603–11.
- 14 Cardona V, Luengo O, Garriga T *et al.* Co-factor-enhanced food allergy. *Allergy* 2012; **67**:1316–18.
- 15 Hourihane JO, Grimshaw KE, Lewis SA *et al.* Does severity of low-dose, double-blind, placebo-controlled food challenges reflect severity of allergic reactions to peanut in the community? *Clin Exp Allergy* 2005; **35**:1227–33.