IgE sensitisation predicts threshold but not anaphylaxis during oral food challenges to cow's milk

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Abstract

Predicting reaction threshold and severity are important to improve the management of food allergy, however the determinants of, and relationship between, these parameters are significant knowledge gaps. Identifying robust predictors could enable the reliable risk-stratification of food-allergic individuals. In this series of young people with CM-allergy undergoing DBPCFC – the largest reported in the literature – we did identify any baseline marker which predicted the occurrence of anaphylaxis at challenge, consistent with existing data. [1] There is one report of IgE-sensitisation being predictive of severity in CM-allergy, [5] however the authors included non-reactive patients in their analysis which significantly skewed the analyses, resulting in misleading conclusions. [6] IgE-sensitisation in our cohort, particularly to casein, was predictive of LOAEL. Including an assessment of casein IgE may therefore be of clinical utility when evaluating patients with CM-allergy in the clinical setting.

TITLE PAGE

LETTER TO THE EDITOR

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To the Editor:

There are increasing data relating to predicting the outcomes of oral food challenges (FC) to peanut, specifically severity of reaction and eliciting dose.[1] However, data are more limited for other allergens such as cow's milk (CM) protein, particularly in older children and teenagers with persisting allergy to CM. Given that CM is a major cause of severe and even fatal allergic reactions,[1] this is a significant knowledge gap. We therefore analysed predictors of severity and eliciting dose in young people undergoing double-blind placebo-controlled food challenges (DBPCFC) to CM in the SOCMA study (Clinicaltrials.gov NCT02216175).

We recruited children and young people aged 6-18 years with a clinical history of CM-allergy, presenting for clinical review in our hospitals. Exclusion criteria were: medically unfit for challenge (e.g. high fever or intercurrent illness); acute wheeze or poorly controlled asthma; oral corticosteroids within 14 days of FC; anaphylaxis in the 4 weeks prior to FC (to exclude patients in an anergic state); antihistamines within 5 days of FC. Subjects with a history of prior anaphylaxis were not excluded. The study was approved by the NHS Human Research Authority (reference 18/LO/1070) and the Hospital Infantil Universitario Niño Jesus Ethics Committee (reference R0003/17). Written informed consent was obtained for all participants.

98 participants (median age 10 years) were screened, of whom 93 underwent DBPCFC. The first challenge dose was 0.5mg CM protein (or tapioca starch as placebo, dissolved in rice "milk" with Nesquik® flavouring) followed by a 60 minute observation period. Subsequent doses were given every 20-30 minutes, according to the following schedule: 3mg, 10mg, 30mg, 100mg, 300mg, 1000mg and 3000mg of CM protein (or placebo), until stopping criteria (PRACTALL) were met. Eliciting dose was defined as the lowest observed adverse effect level (LOAEL) triggering objective symptoms.[2] 83 subjects (89%) reacted with objective symptoms at challenge, of whom 16 (19%) had anaphylaxis (WAO 2020 criteria) (Table S1). The median cumulative eliciting dose (cumED) was 143.5mg (IQR 43.5-443.5mg) CM protein.

Baseline markers of sensitisation and other relevant information are shown in Table 1. We did not identify any significant predictors for the occurrence of anaphylaxis at OFC. There was a moderate and significant correlation between specific IgE to CM protein/casein (both skin prick test (SPT) and serum IgE) and LOAEL ($p<0.0001$). At multivariate analysis, both SPT and serum IgE to casein were predictive of LOAEL ($p=0.007$ and $p=0.018$, respectively; Table S2). Population dose distributions were determined as previously described,[3] using an Interval-Censoring Survival Analysis (ICSA) approach in R (v4.1.2, survival package v3.2-13). The cumulative eliciting dose predicted to provoke reaction in 5% of the population (ED_{05}) was 2.5mg (95%CI 1.1-6.0) and 2.7mg (95%CI 1.2-6.1) CM protein, estimated using Log-Normal and Log-Logistic parametric models respectively. The dose-distributions are plotted in Figure 1, and are not dissimilar to existing data for LOAEL to CM protein in allergic individuals.[4]

Predicting reaction threshold and severity are important to improve the management of food allergy, however the determinants of, and relationship between, these parameters are significant knowledge gaps. Identifying robust predictors could enable the reliable risk-stratification of food-allergic individuals. In this series of young people with CM-allergy undergoing DBPCFC – the largest reported in the literature – we did identify any baseline marker which predicted the occurrence of anaphylaxis at challenge, consistent with existing data.[1] There is one report of IgE-sensitisation being predictive of severity in CM-allergy,[5] however the authors included non-reactive patients in their analysis which significantly skewed the analyses, resulting in misleading conclusions.[6] IgE-sensitisation in our cohort, particularly to casein, was predictive of LOAEL.

Including an assessment of casein IgE may therefore be of clinical utility when evaluating patients with CM-allergy in the clinical setting.

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The funders of the study had no role in study design, data collection, data analysis, data interpretation or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: grants from Jon Moulton Charity Trust, UK Medical Research Council, Spanish Society of Allergology and Clinical Immunology and Spanish Society of Paediatric Allergology, Asthma and Clinical Immunology. PJT reports additional grants from UK Medical Research Council, NIHR/Imperial BRC and UK Food Standards Agency during the conduct of the study; personal fees from UK Food Standards Agency, DBV Technologies, Aimmune Therapeutics, Allergenis, and ILSI Europe, outside the submitted work. RB reports funding from the Health Research Fund of Carlos III Health Institute (Spain), and honoraria for lectures from LETI Pharma. MVO reports additional research funding from the Health Research Fund of Carlos III Health Institute (Spain), and the FPIES Foundation. PRR reports funding from the Health Research Fund of Carlos III Health Institute, Foundation for Biomedical Research of the Niño Jesus University Children's

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FIGURE LEGENDS

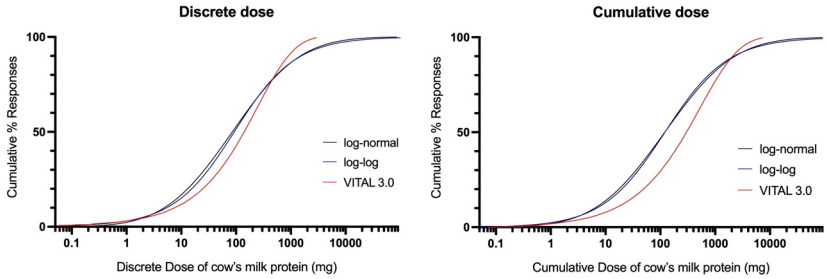

Figure 1. Eliciting dose curves from the model averaged population threshold dose distributions for cow's milk, based on discrete (**A**) and cumulative (**B**) dose datasets. Doses are expressed in mg cow's milk protein, and are compared to equivalent data reported by Houben et al used to inform VITAL 3.0 reference doses.[4]

Table 1: Characteristics of the study population and predictors of anaphylaxis or eliciting dose

	Overall cohort (n=98)	**Anaphylaxis Reaction at DBPCFC**	**Anaphylaxis Reaction at DBPCFC**	**Anaphylaxis Reaction at DBPCFC**	**Predictor of eliciting dose?**	**Predictor of eliciting dose?**
		Anaphylaxis (n=16)	Mild-moderate reaction (n=67)	p value	Correlation (Spearman's R)	Multivariate analysis
Age (years)	10 (7.8,13)	11 (8,13.5)	10 (7,13)	p=0.62	r_s=0.09 p=0.37	
Sex (Male)	56 (57%)	9 (56%)	38 (57%)	p=1.00		
Previous anaphylaxis to cow's milk (CM)	56 (57%)	11 (69%)	41 (61%)	p=0.77		

	Overall cohort (n=98)	**Anaphylaxis Reaction at DBPCFC**	**Anaphylaxis Reaction at DBPCFC**	**Anaphylaxis Reaction at DBPCFC**	**Predictor of eliciting dose?**	**Predictor of eliciting dose?**
Asthma	60 (61%)	9 (56%)	41 (61%)	p=0.78		
Eczema	60 (61%)	8 (50%)	43 (64%)	p=0.39		
Other food allergy	74 (76%)	12 (75%)	47 (70%)	p=0.77		
Total IgE (kUA/L)	576 (289, 1153)	447 (229, 991)	571 (246, 1202)	p=0.65	r_s=0.03 p=0.78	
Specific IgE (kUA/L) to:	18.7 (3.9, 59.6)	19.3 (9.7, 49.8)	23.6 (5.5, 83.1)	p=0.81	r_s=-0.63	p=0.052
CM protein	12.7 (2.3, 57.2)	15.9 (7.3, 62.9)	12.7 (2.9, 57.2)	p=0.78	p<0.001	p=0.018
Casein					r_s=-0.63 p<0.001	
SPT wheal (mm) to:	7 (5, 10)	7 (6, 9)	6.5 (5, 9)	p=0.42	r_s=-0.23	p=0.19
CM protein	6 (4, 9)	7.5 (6, 9)	14.26 (4.5, 69.8)	p=0.22	p=0.025	p=0.007
Casein					r_s=-0.43 p<0.001	
Eliciting dose (cumulative, mg protein)	143.5 (43.5, 443.5)	143.5 (68.5, 443.5)	143.5 (43.5, 1443.5)	p=0.80	N/A	N/A

Data are median (interquartile range). P values calculated in GraphPad Prism (vs 9.0) using Mann-Whitney test for continuous data and Fisher Exact test for categorical data.