COVID-19 patients: implications for assessment of post-acute COVID-19 syndrome. *J Proteome Res*. 2021;20(6):3315-3329. 10.1021/acs.jproteome.1c00224
6. Wallukat G, Hohberger B, Wenzel K, et al. Functional autoantibodies against G-protein coupled receptors in patients with persistent Long-COVID-19 symptoms. *J Transl Autoimmun*. 2021;4:100100. 10.1016/j.jtauto.2021.100100
7. Gebremeskel S, Schanin J, Coyle KM, et al. Mast cell and eosinophil activation are associated with COVID-19 and TLR-mediated viral inflammation: implications for an anti-Siglec-8 antibody. *Front Immunol*. 2021;12:650331. 10.3389/fimmu.2021.650331
8. Yang L, Xie X, Tu Z, Fu J, Xu D, Zhou Y. The signal pathways and treatment of cytokine storm in COVID-19. *Signal Transduct Target Ther*. 2021;6(1):255. 10.1038/s41392-021-00679-0
9. Desai A, Jung MY, Olivera A, et al. IL-6 promotes an increase in human mast cell numbers and reactivity through suppression of suppressor of cytokine signaling 3. *J Allergy Clin Immunol*. 2016;137(6):1863–1871 e6. 10.1016/j.jaci.2015.09.059
10. Aigner L, Pietrantonio F, Bessa de Sousa DM, et al. The leukotriene receptor antagonist montelukast as a potential COVID-19 therapeutic. *Front Mol Biosci*. 2020;7:610132. 10.3389/fmolb.2020.610132
11. Schanin J, Gebremeskel S, Korver W, et al. A monoclonal antibody to Siglec-8 suppresses non-allergic airway inflammation and inhibits IgE-independent mast cell activation. *Mucosal Immunol*. 2020;14:366–376. 10.1038/s41385-020-00336-9
12. Peter AE, Sandeep BV, Rao BG, Kalpana VL. Calming the storm: natural immunosuppressants as adjuvants to target the cytokine storm in COVID-19. *Front Pharmacol*. 2020;11:583777. 10.3389/fphar.2020.583777

SUPPORTING INFORMATION

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

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 the 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 hospital. Skin prick testing (SPT) of CM and casein was performed according to international guidelines using ALK lancets and commercial extracts (ALK-Abello) with 1% histamine as a positive control, and the mean wheal diameter was noted. Blood samples were collected from participants prior to FC, and specific IgE to CM and casein was measured by ImmunoCAP (ThermoFisher Scientific). The exclusion criteria were medically unfit for challenge (eg high fever or intercurrent illness), acute wheeze or poorly controlled asthma, oral corticosteroids within 14 days of FC, anaphylaxis in 4 weeks prior to FC (to exclude patients in an anergic state) and 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 from all participants.

98 participants (median age 10 years) were screened, of whom 93 underwent DBPCFC. The first challenge dose was 0.5 mg CM protein (or tapioca starch as placebo, dissolved in rice "milk" with Nesquik® flavouring) followed by a 60-min observation period. Subsequent doses were given every 20–30 min, according to the following schedule: 3 mg, 10 mg, 30 mg, 100 mg, 300 mg, 1000 mg and 3000 mg of CM protein (or placebo), until stopping criteria (PRACTALL) were met. Eliciting dose was defined as the lowest observed adverse effect level (LOAEL) triggering 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 143.5 mg (IQR 43.5–443.5 mg) CM protein.

Baseline markers of sensitization 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 SPT and serum IgE) and LOAEL ($p < .0001$). At multivariate analysis, both SPT and serum IgE to casein were predictive of LOAEL ($p = .007$ and $p = .018$, respectively; Table S2). Population dose-distributions were determined as previously described[3] using 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 2.5 mg (95% CI 1.1–6.0) and 2.7 mg (95% CI 1.2–6.1) CM protein, estimated using

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

		Clinical reaction at DBPCFC			Predictor of eliciting dose?	
	Overall cohort ($n = 98$)	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)	$p = .62$	$r_s = .09$, $p = .37$	
Sex (Male)	56 (57%)	9 (56%)	38 (57%)	$p = 1.00$		
Previous anaphylaxis to cow's milk (CM)	56 (57%)	11 (69%)	41 (61%)	$p = .77$		
Asthma	60 (61%)	9 (56%)	41 (61%)	$p = .78$		
Eczema	60 (61%)	8 (50%)	43 (64%)	$p = .39$		
Other food allergy	74 (76%)	12 (75%)	47 (70%)	$p = .77$		
Total IgE (kUA/L)	576 (289, 1153)	447 (229, 991)	571 (246, 1202)	$p = .65$	$r_s = .03$, $p = .78$	
Specific IgE (kUA/L) to						
CM protein	18.7 (3.9, 59.6)	19.3 (9.7, 49.8)	23.6 (5.5, 83.1)	$p = .81$	$r_s = -.63$, $p < .001$	$p = .052$
Casein	12.7 (2.3, 57.2)	15.9 (7.3, 62.9)	12.7 (2.9, 57.2)	$p = .78$	$r_s = -.63$, $p < .001$	$p = .018$
SPT wheal (mm) to						
CM protein	7 (5, 10)	7 (6, 9)	6.5 (5, 9)	$p = .42$	$r_s = -.23$, $p = .025$	$p = .19$
Casein	6 (4, 9)	7.5 (6, 9)	14.26 (4.5, 69.8)	$p = .22$	$r_s = -.43$, $p < .001$	$p = .007$
Eliciting dose (cumulative, mg protein)	N/A	143.5 (68.5, 443.5)	143.5 (43.5, 1443.5)	$p = .80$	N/A	N/A

Note: Data are median (interquartile range). p values were calculated in GraphPad Prism (vs 9.0) using Mann-Whitney test for continuous data and Fisher Exact test was used for categorical data. Eliciting dose was not stated for overall cohort as only 83 participants had a clinical reaction at FC.

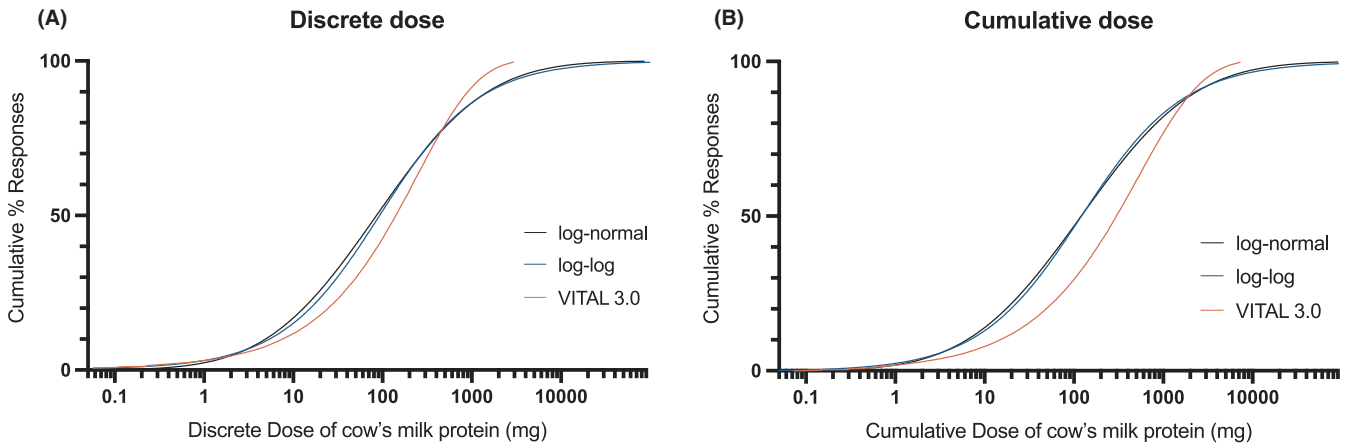

FIGURE 1 Eliciting dose curves from the model averaged population threshold dose distributions for cow's milk, based on discrete (A) and cumulative (B) dose datasets. Doses are expressed in mg cow's milk protein, and are compared to equivalent data reported by Houben et al[4] used to inform VITAL 3.0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

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.[1] 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 that predicted the occurrence of anaphylaxis at challenge, consistent with existing data.[1] There is one report of IgE-sensitization being predictive of severity in CM-allergy[5]; however, the authors included non-reactive patients in their analysis that significantly skewed the analyses, resulting in misleading conclusions.[6] IgE-sensitization in our cohort, particularly to casein, was predictive of LOAEL. Including an assessment of IgE-sensitisation to casein may therefore be of clinical utility when evaluating patients with CM-allergy in the clinical setting.

KEYWORDS

allergy, anaphylaxis, cow's milk, eliciting dose, food challenge, lowest observed adverse effect level, thresholds

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CONFLICT OF INTERESTS

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AUTHOR CONTRIBUTIONS

PJT and MVO conceived the study, and drafted the study protocol together with PRR. PJT and PRR are the lead investigators for the study. PJT, BD, OA, RB and PRR were responsible for recruitment and clinical assessments. PJT, BD, RB and SAC were responsible for data analysis and SAC and PJT undertook statistical analyses. PJT drafted this manuscript which was then reviewed and approved by all authors.

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REFERENCES

1. Turner PJ, Baumert JL, Beyer K, et al. Can we identify patients at risk of life-threatening allergic reactions to food? *Allergy*. 2016;71(9):1241-1255.
2. Westerhout J, Baumert JL, Blom WM, et al. Deriving individual threshold doses from clinical food challenge data for population risk assessment of food allergens. *J Allergy Clin Immunol*. 2019;144(5):1290-1309.
3. Dano D, Remington BC, Astier C, et al. Sesame allergy threshold dose distribution. *Food Chem Toxicol*. 2015;83:48-53.
4. Houben GF, Baumert JL, Blom WM, et al. Full range of population Eliciting Dose values for 14 priority allergenic foods and recommendations for use in risk characterization. *Food Chem Toxicol*. 2020;146:111831.
5. Petersen TH, Mortz CG, Bindslev-Jensen C, Eller E. Cow's milk allergic children - can component-resolved diagnostics predict duration and severity? *Pediatr Allergy Immunol*. 2018;29(2):194-199.
6. Turner PJ, Custovic A. Life-threatening anaphylaxis to peanut – impossible to predict? *J Allergy Clin Immunol*. 2021. (in press).

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