Enquiring About Tolerance (EAT) study: Feasibility of an early allergenic food introduction regimen

Michael R. Perkin, PhD,[a,b]* Kirsty Logan, PhD,[b]* Tom Marrs, BM BS,[b] Suzana Radulovic, MD,[b] Joanna Craven, MPH,[b] Carsten Flohr, PhD,[b,c] and Gideon Lack, MD,[b] on behalf of the EAT Study Team *London, United Kingdom*

Background: The influence of early exposure to allergenic foods on the subsequent development of food allergy remains uncertain.

Objective: We sought to determine the feasibility of the early introduction of multiple allergenic foods to exclusively breast-fed infants from 3 months of age and the effect on breastfeeding performance.

Methods: We performed a randomized controlled trial. The early introduction group (EIG) continued breastfeeding with sequential introduction of 6 allergenic foods: cow's milk, peanut, hard-boiled hen's egg, sesame, whitefish (cod), and wheat; the standard introduction group followed the UK infant feeding recommendations of exclusive breastfeeding for around 6 months with no introduction of allergenic foods before 6 months of age.

Results: One thousand three hundred three infants were enrolled. By 5 months of age, the median frequency of consumption of all 6 foods was 2 to 3 times per week for every food in the EIG and no consumption for every food in the standard introduction group ($P < .001$ for every comparison). By 6 months of age, nonintroduction of the allergenic foods in the EIG was less than 5% for each of the 6 foods. Achievement of the stringent per-protocol consumption target for the EIG proved more difficult (42% of evaluable EIG participants). Breastfeeding rates in both groups significantly exceeded UK government data for equivalent mothers ($P < .001$ at 6 and at 9 months of age).

Conclusion: Early introduction, before 6 months of age, of at least some amount of multiple allergenic foods appears achievable and did not affect breastfeeding. This has important implications for the evaluation of food allergy prevention strategies. (J Allergy Clin Immunol 2016;■■■:■■■-■■■.)

Key words: *Food allergy, diet, allergens, infancy, breastfeeding*

The point prevalence of self-reported food allergy in a recent systematic review was around 6%,[1] and that for particular foods is increasing.[2] The role of allergen consumption in early infancy and its effect on the development of allergy or tolerance to food proteins remains uncertain.

The World Health Organization Global Strategy for Infant and Young Child Feeding,[3] which is endorsed by the United Kingdom (UK) Government,[4] recommends exclusive breastfeeding for the first 6 months with nutritious complementary foods introduced thereafter and continued breastfeeding up to the age of 2 years or beyond.[5] The UK Government infant feeding information leaflet for parents, "Weaning—starting solid food," adopts a more pragmatic target of *around* 6 months of exclusive breast-feeding.[6] It also states that if a mother decides to introduce complementary foods before 6 months of age, there are some foods that should be avoided because they can cause allergies, including "wheat-based foods...eggs, fish, shellfish, nuts (and) seeds." There is little evidence that this reduces allergic disease.[7] Interventions involving maternal diet during pregnancy alone[8] or pregnancy and lactation[9] and alterations to the timing and type of solid food introduction in infants[10] have thus far not halted the increase in food allergy. Furthermore, there is now observational evidence that early introduction of cow's milk,[11] peanut,[12] or egg[13] during infancy might prevent the development of food allergies.

In 2010, the UK government published the latest of its quinquennial reviews of infant feeding practice in the country (Infant Feeding Survey 2010 [IFS2010]).[14] Although the UK Government guidelines no longer stipulate delaying the introduction of allergenic foods beyond 6 months of age, the current feeding regimen of UK mothers clearly does delay introduction. At 8 to 10 months of age, only 8% of infants had been given peanuts or peanut products.[14]

The significant trend toward later introduction of solid foods and longer duration of exclusive breastfeeding in the UK has coincided with the prevalence of food allergy appearing to increase.[15] Although delayed introduction of allergenic foods prevents occurrence of an allergic reaction, there is no evidence to suggest it prevents the development of allergies and might simply delay the manifestation of a pre-existing allergy.

The Solids Timing for Allergy Research study suggested that induction of immune tolerance pathways is possible through early

From [a]the Population Health Research Institute, St George's, University of London; [b]the Department Paediatric Allergy, Division of Asthma, Allergy and Lung Biology, King's College London; and [c]the St John's Institute of Dermatology, Guy' and St Thomas' Hospital NHS Foundation Trust, London.

*These authors contributed equally to this work.

The main components of the EAT study are jointly funded by the UK Food Standards Agency (FSA) and the Medical Research Council (MRC). The skin-related aspects of the study are supported by the UK National Institute for Health Research (NIHR) through an NIHR Clinician Scientist Award (NIHRCS/01/2008/009) held by C.F. The views expressed in this publication are those of the authors and not necessarily those of the FSA, MRC, NHS, NIHR, Wellcome Trust, or UK Department of Health.

Disclosure of potential conflict of interest: M. R. Perkin, K. Logan, S. Radulovic, and J. Craven have received grants from the Food Standards Agency and the Medical Research Council. C. Flohr is a board member for and has consultant arrangements with Roche. G. Lack has received grants from the United Kingdom (UK) Food Standards Agency (T07051), the Medical Research Council, the National Institute for Health Research (NIHRCS/01/2008/009), and the National Peanut Board and has a board membership with and receives stock options from DBV Technologies. T. Marrs declares that he has no relevant conflict of interest.

Received for publication March 26, 2015; revised November 27, 2015; accepted for publication December 29, 2015.

Corresponding author: Gideon Lack, MD, Paediatric Allergy, King's College London, Clinical Academic Paediatric Allergy Service, Guy's & St Thomas' NHS Foundation Trust, Children's Allergies Department, St Thomas' Hospital, Westminster Bridge Rd, London SE1 7EH, United Kingdom. E-mail: gideon.lack@kcl.ac.uk.

0091-6749

http://dx.doi.org/10.1016/j.jaci.2015.12.1322

Abbreviations used
EAT: Enquiring About Tolerance
EIG: Early introduction group
IFS2010: Infant Feeding Survey 2010
LEAP: Learning Early About Peanut Allergy
SIG: Standard introduction group
SPT: Skin prick test
UK: United Kingdom

introduction of egg and resulted in a reduction, although a nonsignificant one, in egg allergy incidence.[16] The Learning Early About Peanut Allergy (LEAP) study found that early introduction of peanut into the diets of high-risk atopic infants protects against the development of peanut allergy.[17,18]

The Enquiring About Tolerance (EAT) study has a wider remit, namely to test the hypothesis that the early introduction of multiple allergenic foods from 3 months of age in an unselected population of exclusively breastfed infants will, as a primary outcome, reduce the prevalence of food allergy and, as a secondary outcome, influence asthma, eczema, allergic rhinitis, and the prevalence of combined allergic disease by 3 years of age.

The EAT study has completed enrollment with 1303 participants. All participants are now beyond 2 years of age, and this milestone affords the opportunity to present the study methodology and assess the feasibility and acceptability of the introduction regimen in this unique cohort.

METHODS

The EAT study is a population-based randomized controlled trial that enrolled exclusively breastfed infants from England and Wales regardless of atopic status or family history of allergy. Infants who had consumed anything other than breast milk or water since birth, were part of multiple births, were born prematurely, had any serious medical condition, or were participating in other medical research were not eligible for enrollment. A current household member with a food allergy was not an exclusion criterion.

Ethical approval for the EAT study was provided by St Thomas' Hospital REC (REC reference 08/H0802/93), and the study is registered with the International Standard Randomized Controlled Trial Number Register (14254740). Informed consent was obtained from the parents of all children enrolled in the study, and safety data were regularly reviewed by the EAT study's independent data monitoring committee.

Families were recruited to the study from those who responded to a flyer mailed to parents of young infants throughout England and Wales (Fig 1). The 6 allergenic foods selected to form the trial's intervention, cow's milk, peanut, hen's egg, sesame, whitefish (cod), and wheat, were chosen from the foods most commonly found to be responsible for IgE-mediated food reactions in children.[19,20] The trial's primary outcome is the prevalence of IgE-mediated food allergy, which we aimed to confirm using double-blind, placebo-controlled food challenge to 1 or more of the 6 intervention foods at between 1 and 3 years of age (see Table E1 in this article's Online Repository at www.jacionline.org). The trial is powered at 80% to detect a halving of food allergy prevalence between the study groups. At study commencement, the expected food allergy prevalence in the standard introduction group (SIG) was 6%. An analysis undertaken after 3 months of recruitment indicated that the EAT parental atopy rate was higher than that of a contemporary UK population-based study.[21] Data from the Early Prevention of Asthma in Atopic Children study was used to extrapolate the expected SIG food allergy rate based on the observed prevalence of 30% visible eczema among these initial participants.[22] Taken together, the revised estimate of expected food allergy prevalence in the SIG group was 8%. A principle intention-to-treat analysis will be undertaken for children evaluable for the primary outcome, with a secondary per-protocol analysis assessing the effect of degree of compliance on the primary outcome.

Trial design

Between 13 and 17 weeks of age, enrolled infants were randomly assigned to either the SIG or the early introduction group (EIG). Fig 2 shows the overall EAT study design.

SIG

Those randomized to the SIG were asked to comply completely with the current UK government infant feeding guidelines of exclusive breastfeeding until around 6 months of age and no consumption of allergenic foods before 6 months of age. After 6 months of age, introduction of allergenic foods was left to parental discretion.

EIG

Infants in the EIG were randomized to the sequential introduction of the 6 chosen allergenic foods alongside continued breastfeeding (see Fig E4 in this article's Online Repository at www.jacionline.org). Infants in this group underwent skin prick tests (SPTs) in duplicate to the 6 intervention foods and an open incremental food challenge if they showed any sensitization (SPT response >0 mm, no upper limit). Children who were not sensitized or who were sensitized but had a subsequent negative food challenge result were asked to follow the EIG introduction regimen. Those given a diagnosis of allergy based on results of a food challenge were advised to avoid that food and continue the introduction regimen for the other allergenic foods. Fundamental to the trial design was the intention that breast milk should remain an important source of nutrition until at least 6 months of age, regardless of study group. The EIG introduction regimen is described in more detail in the Methods section in this article's Online Repository at www.jacionline.org.

Online interim questionnaires

An online questionnaire completed monthly until 12 months of age and every 3 months between 12 and 36 months of age by the infants' parents was the main portal of communicating information about the health and diet of the participants to the study team. Parents reported any atopic symptoms in their children and any adverse events (serious and nonserious) through the online questionnaire.

Consumption monitoring

Within this online questionnaire, both groups completed a food frequency questionnaire section assessing how frequently foods containing the 6 study allergens were being consumed (see Fig E1 in this article's Online Repository at www.jacionline.org).

EIG families kept a weekly diary until 1 year of age and monthly thereafter to assess the degree to which they were meeting the consumption target of 4 g of each allergenic food protein per week. For each of the last 4 complete weeks preceding the child's monthly birthday and for each of the allergenic foods, parents recorded the percentage of the recommended amount of food their child was consuming (100%, 75%, 50%, ≤25%, or not tried yet), with guidance provided on the amount of each food constituting those percentages. These diary data were then entered into the online questionnaires.

Per-protocol compliance: Overall and food specific

The overall per-protocol compliance criteria for the SIG and EIG are listed in Table I. Further information about how the responses from the online questionnaires were used to determine whether per-protocol compliance was assessable for each participant and whether the criteria in Table I had been fulfilled in each group is explained in more detail in the Methods section in this article's Online Repository.

Holistic assessment

Participants in the study undergo a comprehensive series of investigations aimed at understanding what causes sensitization and food allergy to emerge in children (see the Methods section in this article's Online Repository).