Food Allergy in Infants With Atopic Dermatitis: Limitations of Food-Specific IgE Measurements

Jonathan M. Spergel, MD, PhD[a], Mark Boguniewicz, MD[b], Lynda Schneider, MD[c], Jon M. Hanifin, MD[d], Amy S. Paller, MD[e], Lawrence F. Eichenfield, MD[f]

abstract

BACKGROUND AND OBJECTIVES: Children with atopic dermatitis (AD) have a higher risk for development of food allergies. The objective of this study was to examine incidence of food allergy development in infants with AD and the predictive value of food-antigen–specific immunoglobulin E measurements.

METHODS: This trial examined the long-term safety and efficacy of pimecrolimus cream 1% in >1000 infants (3–18 months) with mild-to-severe AD without a history of food allergy. Food allergy development was followed throughout a 36-month randomized double-blind phase followed by an open-label (OL) phase up to 33 months. Additionally, sIgE for cow's milk, egg white, peanut, wheat, seafood mix, and soybean was measured by ImmunoCAP at baseline, end of the double-blind phase, and end of OL phase.

RESULTS: By the end of the OL phase, 15.9% of infants with AD developed at least 1 food allergy; allergy to peanut was most common (6.6%), followed by cow's milk (4.3%) and egg white (3.9%). Seafood, soybean, and wheat allergies were rare. Levels of sIgE for milk, egg, and peanut increased with severity of AD, as determined by Investigator's Global Assessment score. We assigned sIgE decision points for the 6 foods and tested their ability to predict definite food allergy in this population. Positive predictive values for published and newly developed sIgE decision points were low (<0.6 for all values tested).

CONCLUSIONS: In a large cohort of infants at risk for development of food allergy, sIgE levels were not clinically useful for predicting food allergy development.

WHAT'S KNOWN ON THIS SUBJECT: Food allergies are often thought to be a common trigger in atopic dermatitis (AD). Serum immunoglobulin E is frequently used to assess food sensitization and clinical allergy, but few studies have assessed it longitudinally in infants and children with AD.

WHAT THIS STUDY ADDS: In a large infant population with mild to moderate AD, 15.9% of patients developed food allergy during the study. Serum immunoglobulin E decision points had low positive predictive values, indicating that they are of limited use in this population.

[a]*The Children's Hospital of Philadelphia, Perelman School of Medicine at University of Pennsylvania, Philadelphia, Pennsylvania;* [b]*National Jewish Health and University of Colorado School of Medicine, Denver, Colorado;* [c]*Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts;* [d]*Oregon Health and Science University, Portland, Oregon;* [e]*Northwestern University Feinberg School of Medicine, Chicago, Illinois; and* [f]*Rady Children's Hospital, San Diego, University of California San Diego, San Diego, California*

This trial has been registered at www.clinicaltrials.gov (identifier NCT00124709).

www.pediatrics.org/cgi/doi/10.1542/peds.2015-1444

DOI: 10.1542/peds.2015-1444

Accepted for publication Aug 31, 2015

Address correspondence to Jonathan M. Spergel, MD, PhD, The Children's Hospital of Philadelphia, Perelman School of Medicine at University of Pennsylvania, 3550 Market St, Philadelphia, PA 19104–4399. E-mail: spergel@email.chop.edu

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

Atopic dermatitis (AD) is an inflammatory skin disorder that commonly presents in childhood. This disorder is associated with many comorbid conditions leading to impaired overall health and increased health care utilization.[1] Children with AD are more likely to develop other atopic conditions, including food allergy, than children who have no history of the disease.[2–4] Previous clinical studies have documented greatly varying estimates of the rate of IgE-mediated food allergy in AD patients, ranging from 15% to 40%. The most commonly cited range is 30% to 40%, all in tertiary care centers, reflecting more severely affected patients.[5–8] In a recent study of 4453 infants in the HealthNuts cohort from Australia, the authors found that by 12 months of age, infants with eczema were 11 times more likely to develop peanut allergy and 5.8 times more likely to develop egg allergy, compared with infants without eczema.[4] These estimates are also likely influenced by varying definitions of allergy, by study methodologies, and by subject demographics.

Because AD and food allergy often occur together, a persistent question has been whether allergic reactions to food contribute to AD signs and symptoms or clinical findings. Urticaria caused by food allergy has been implicated in exacerbating AD, as histamine release, pruritus, and resultant scratching can exacerbate existing skin lesions.[9,10] Removal of the allergenic food from the diet can lead to resolution of AD in selected cases.[9] However, formation of new eczematous lesions after a food challenge is uncommon,[9,11] and parental suspicions of food allergy have been shown to decrease when skin symptoms are controlled with proper medication.[12,13]

The sensitization pattern of IgE is influenced by maternal and environmental factors during the first year of life, which may contribute to the development of food allergies.[14] Screening for food allergy relies on measures of antigenic sensitization, such as skin prick tests and in vitro assays that measure food-antigen–specific immunoglobulin E (sIgE). However, >50% of patients who are sensitized to a particular food based on a positive screening test may not react to it in a food challenge, highlighting the fact that sensitization does not indicate the presence of a clinical food allergy.[5,8,15,16] Because food challenges are time-consuming and potentially dangerous, it could be advantageous to determine the serum sIgE concentration that predicts clinical food allergy. A number of sIgE decision points have been developed from subject cohorts of varying ages and with known or suspected food allergy (reviewed in Sicherer and Sampson[17]). Recent work by Fleischer and colleagues found that allergy testing has a high false-positive rate. In their study, negative food challenges occurred for 89% of 364 challenges in 125 children evaluated for AD at a referral center.[18] In the Australian HealthNuts cohort of 5276 infants, egg sIgE ≥1.7 kU_A/L and peanut sIgE ≥34 kU_A/L were associated with 95% positive predictive values for challenge-proven food allergy but this was not demonstrated for other foods.[19] However, the predictive value of specific IgE in patients with AD is unclear. Most recently, in the Learning Early About Peanut allergy study, Du Toit and colleagues used egg allergy and AD as risk factors for developing peanut allergy. In this study, they found that 3.4% of the total high-risk population developed peanut allergy. Interestingly, sIgE to peanut was not predictive of peanut allergy.[20]

In this prespecified analysis of patients enrolled in the Study of the Atopic March (SAM), we examined the ability of sIgE concentrations to predict clinical allergy not if a food was causing AD in a population of >1000 infants with AD but no history of food allergy.

METHODS

Patients

This analysis was performed by using data from SAM, a dual-phase study designed to explore the long-term safety and efficacy of 1% pimecrolimus cream in infants with AD. To be eligible for the study, patients had to be 3 to 18 months of age with a diagnosis of AD, as defined by the American Academy of Dermatology Consensus Conference criteria,[21] for no more than 3 months before enrollment. Patients also had to have at least mild disease activity, as defined by an Investigator's Global Assessment (IGA) score ≥2 at the start of the study. Study participants were required have a parent or sibling with a history of AD, allergic rhinitis, allergic conjunctivitis, or asthma but to have no atopic conditions other than AD. Patients who had received treatment within 7 days before the first application of study medication with topical or systemic agents known or suspected to affect AD were excluded from participation. Topical corticosteroid use was permitted before randomization.

Study Design

In total, 36 clinics in the United States participated in the SAM study, which was divided into 2 phases. The first phase was a 36-month, randomized, double-blind (DB), vehicle-controlled phase (randomized 1:1 placebo cream versus 1% pimecrolimus cream) and the second was an open-label (OL) phase in which qualified patients received 1% pimecrolimus cream (active drug) for up to 33 months or the patient's sixth birthday, whichever occurred sooner (see Supplemental Information for treatment plans).

Development of allergies, including food allergies, was monitored throughout the study as detailed in this article. Trial protocols were approved by the independent ethics committee or institutional review board of each study center and written informed consent was obtained from caregivers.

Assessment of AD Severity and IgE-Mediated Food Allergy

Enrolled patients were evaluated for AD severity at each visit. Investigators used the IGA scale, in which scores represented the following: 0, clear; 1, almost clear; 2, mild disease; 3, moderate disease; 4, severe disease; and 5, very severe disease. In addition, Total Body Surface Affected (scale of 0% to 100%) and Eczema Area and Severity Index (EASI)[22] were calculated at each visit.

Diagnosis of food allergy in enrolled patients used the criteria of Thompson and Hanifin,[13] in which clinical symptoms were assigned to a point system and the sum was used to assign definite (>25 points), probable (16–25 points), or possible (5–15 points) food allergy.[13] Major criteria (15 points each) included the presence of lip or face swelling, urticaria, nausea, vomiting, wheezing, or respiratory distress after food ingestion. Minor criteria (5 points each) were repeated reaction on exposure to the same food, reaction happening within 30 minutes of ingesting food, and reaction after ingestion of milk, egg, soybean, wheat, peanut, or fish/seafood. Possible, probable, or definite food allergies that occurred during the study were reported as adverse events and the suspected food as well as the grading category recorded. Definite food allergy diagnoses were also reported on a nonskin atopic symptom case report form, together with any exclusion diets prescribed by the treating physician.

Total IgE and sIgE for cow's milk, peanut, wheat, seafood mix (codfish, shrimp, tuna, salmon, and blue mussel), egg white, and soybean were determined for all patients from blood obtained by venipuncture during visits 2, 14, and 20 (at weeks 1, 158, and 303, respectively) using the ImmunoCAP assay (Phadia, Portage, MI).

Statistical Methods

The limit of detection was 0.1 kU/L and lower limit of quantification was 0.35 kU/L. sIgE decision points were selected by using published 90% positive predictive values in older children (14 kU/L, 15 kU/L, and 7 kU/L for peanut, cow's milk, and egg white, respectively),[23] and novel decision points selected by the investigators of 5 kU/L for peanut, 5 kU/L for cow's milk, and 2 kU/L for egg white for assessment based on optimal potential predictive values. For seafood, wheat, and soybean, a decision point of 0.35 kU/L, the lower limit of quantification for the ImmunoCAP test, was used for data analysis.

Statistical Analysis

The safety population included all randomized patients who were dispensed trial medication. The intent-to-treat (ITT) population included all randomized patients who were dispensed trial medication and from whom at least 1 postbaseline efficacy measurement was obtained. All statistical analyses were performed by using SAS, versions 8.2 and 9.1.3 (SAS Institute, Inc, Cary, NC). All statistical tests were conducted against a 2-sided alternative hypothesis, using a significance level of .05. The percentages of patients with food allergy were compared between the 2 treatment groups using the Cochran-Mantel-Haenszel test, adjusting for center and gender.[24] For each food allergy, the relationship between sIgE and food allergy was investigated by using logistic regression models.[25] Performance characteristics of investigational sIgE decision points were also calculated for each food allergy. The investigational sIgE points were determined for the ideal sensitivity and specificity by using logistic regression analysis. In addition, a receiver operating characteristic (ROC) analysis of definite food allergy for sIgE values was performed and the null hypothesis of whether the area under the ROC curve was 0.5 was tested.[26]

RESULTS

Patients and Development of Allergies

A total of 1091 patients were randomized; 1087 received at least 1 dose of study medication and were included in the safety population, and 1065 had at least 1 postbaseline efficacy measurement and were included in the ITT population. Patients were infants with a mean age of 7.3 months, were predominantly white, and most had mild to moderate AD (92% with an IGA score of 2 or 3; Table 1). By the end of the OL phase, 15.9% of patients had developed a food

TABLE 1 Demographic Characteristics of Subjects at Baseline

No. of subjects	1087
Gender, *n* (%)	
Boys	675 (62.1)
Girls	412 (37.9)
Age, mo, mean (SD)	7.3 (3.9)
Race, *n* (%)	
White	748 (68.8)
African-American	146 (13.4)
Other	193 (17.8)
Atopic Dermatitis Severity	
IGA score,[a] *n* (%)	
Mild	563 (51.8)
Moderate	440 (40.5)
Severe	78 (7.2)
Very Severe	6 (0.6)
TBSA, mean (SD)[b]	17.6 (15.7)
EASI score, mean (SD)[c]	6.5 (6.0)

Baseline demographics at enrollment (safety population).
TBSA, total body surface area affected.
[a] IGA, criteria for study participation, IGA ≥ 2.
[b] TBSA scale 0% to 100%.
[c] EASI scale 0–72.

allergy. The mean ± SD time to first diagnosis of food allergy was 439 ± 372 days and the median was 292 days. The most common food allergies among those enrolled, defined by definite adverse effects described previously,[13] were to peanut, cow's milk, and egg white, occurring in 6.6%, 4.3%, and 3.9% of the ITT population, respectively. In contrast, only 0.4% of patients developed allergy to seafood, 0.3% to wheat, and 0.4% to soybean by study visit 20, at the end of the OL phase. The percentage of food allergy decreased over time with the exception of fish consistent with the known natural history of food allergy (Supplemental Table 5). The magnitude of food allergy development was similar to that of other atopic conditions that occurred during the study: 10.7% of patients developed asthma, 14.1% developed allergic conjunctivitis, and 22.4% developed allergic rhinitis by the end of the OL phase.

Relationship Between Food Allergy, AD Severity, and AD Treatment

Patients' AD was classified at baseline according to IGA criteria. The percentage of patients who developed 1 or more food allergies by the end of the study increased with increasing IGA of AD severity at baseline (Fig 1A). The relative proportion of patients with 1, 2, and 3 or more food allergies within these IGA groups did not change with increasing severity; allergy to 1 food continued to be most common regardless of IGA score (n = 111 [81.6%] of 136 patients with allergy to any food), whereas allergy to 3 or 4 foods was found in only 5 (3.7%) of 136 patients with food allergy. Total serum IgE and sIgE for milk, egg, and peanut measured at the end of the OL phase (Fig 1B and C) were also increased in patients with increasing baseline IGA scores.

One secondary objective of the SAM was to assess the development of food allergy by patients in the

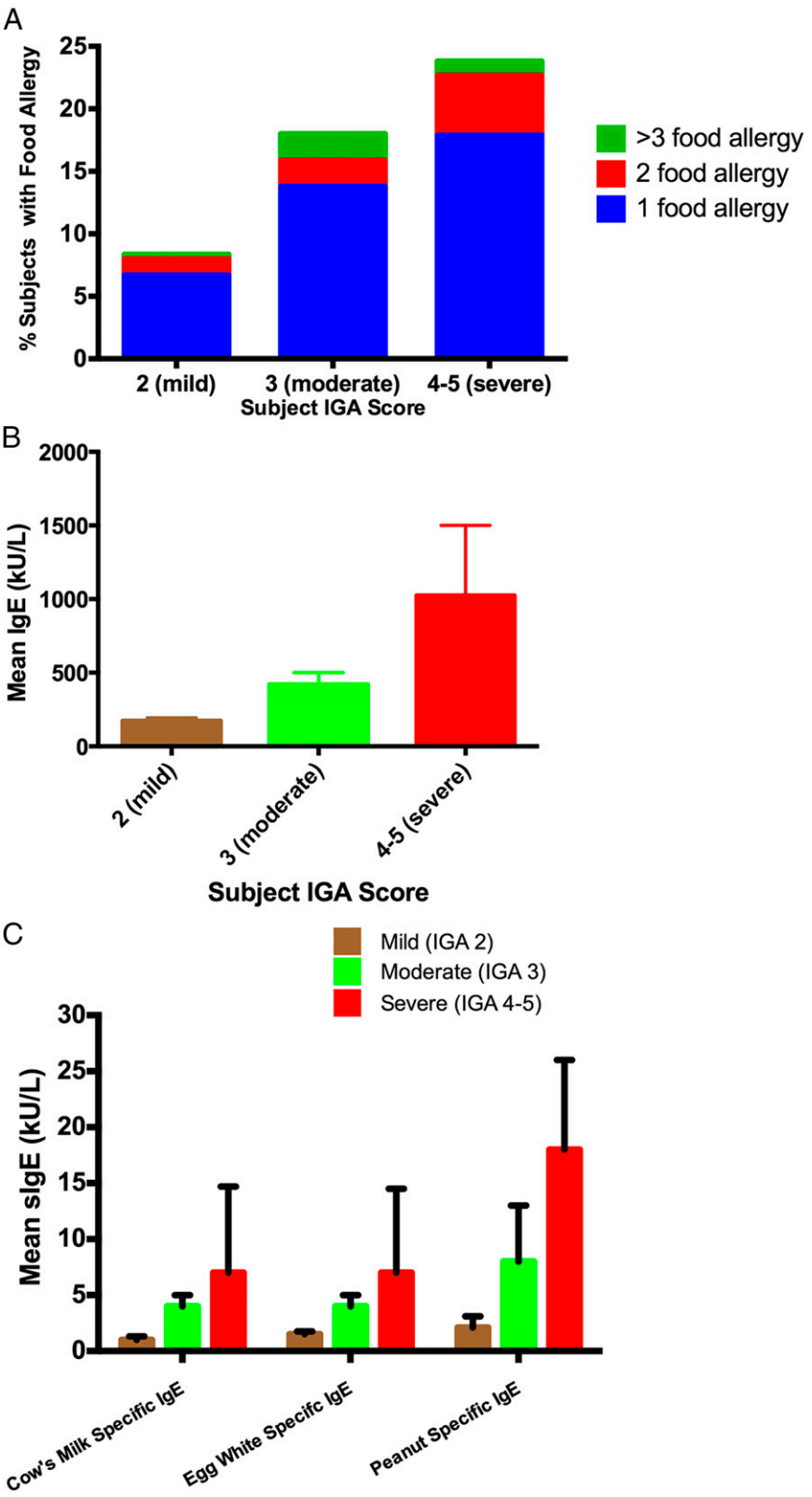

FIGURE 1

AD Severity (by baseline IGA score) and food hypersensitivity at the end of the OL phase (visit 20). A, Frequency of patients with 1 or more food allergies grouped by baseline IGA score; B, Mean total IgE; and C, selected allergen-specific IgE measurements by baseline IGA score. Error bars represent standard error of the mean.

pimecrolimus- and vehicle-treatment groups. There were no significant differences between treatment groups in the percentage of patients with food allergy at the end of the DB phase (16.1% in the pimecrolimus group and 13.7% in the vehicle group; $P = .1196$). Likewise, no significant difference in rates between groups was seen at the end of the OL phase (17.3% of patients derived from the pimecrolimus group and 14.5% from the vehicle group; $P = .0718$), during which time all patients received 1% pimecrolimus .

Relationship Between sIgE and Food Allergy

Analyses were performed to examine the relationship between measured sIgE and clinical food allergy. A logistic regression model for development of clinical allergy to each food (binary response) was fitted by using the natural logarithm of sIgE at baseline as the continuous explanatory variable. Baseline sIgE values for cow's milk, peanut, egg white, and seafood mix were associated with a statistically increased risk of developing allergies to these foods (Table 2). Higher levels of AD severity (by IGA) were also predictive for development of food allergy (Table 3).

In contrast, wheat and soybean baseline sIgE levels were not statistically significant predictors of clinical allergy to these foods, perhaps in part due to low numbers of patients with these allergies (Table 2). It has also been shown that soy and wheat allergens perform poorly in in vitro testing. Based on the logistic regression model, the estimated probabilities of developing definite food allergy by the end of the OL phase (visit 20) by sIgE decision level are shown for each of the 6 foods in Fig 2. Even if a sIgE cutoff at the upper limit of quantification for the ImmunoCAP test (100 kU/L) was selected, the estimated probability of patients developing clinical food allergy did not reach 0.90 for any food. In fact, this probability did not reach 0.50 for most foods (Fig 2) indicating that screening sIgE was not useful.

We examined the development of food allergy by exploring risk factors including baseline sIgE levels, IGA score (AD severity) at baseline, treatment group, and age group at baseline as explanatory variables (Table 3). Odds ratios for the development of milk, egg, and peanut allergy ranged from 2 to >11 for patients with sIgE at baseline above the cutoffs versus those with sIgE at baseline below cutoffs. In addition, baseline IGA score was a statistically significant risk factor for developing peanut and egg allergy. Comparison of pimecrolimus group versus the vehicle group was associated with milk allergy with an odds ratio of >2.

For the sIgE test to be clinically useful, it would need to have high predictive values. Therefore, performance characteristics were also determined for sIgE decision points by using sIgE measured at baseline or at the end of the DB phase (Table 4). Negative predictive values (NPVs) for baseline sIgE were high for all decision points tested (range of 0.94–1.00) and positive predictive

TABLE 2 Logistic Regression Analysis for Food Allergy

Food	Odds Ratio (95% CI)	P[a]
Cow's milk	1.876 (1.606–2.192)	<.001
Egg white	1.443 (1.258–1.655)	<.001
Peanut	1.584 (1.410–1.779)	<.001
Seafood mix	2.782 (1.493–5.195)	.0013
Wheat	1.332 (0.765–2.318)	.3109
Soybean	1.730 (0.995–3.006)	.0520

Food allergy as reported at study visits 3–20 (end of OL). Logistic regression analysis for reported food allergy with log sIgE at baseline as the explanatory variable (ITT population, $n = 1065$). CI, confidence interval.

[a] From a Wald test. The probability of having definite food allergy was estimated from a simple logistic model $P - 1/(\exp[-a - bx] + 1)$, where x is defined as the natural logarithmic sIgE value at baseline.

TABLE 3 Logistic Regression Analysis for Peanut, Cow's Milk, and Egg Allergy

Food	Explanatory Variable	Odds Ratio (95% CI)	P[a]
Peanut	IgE at baseline (< 5 and ≥ 5 kU/L)[b]	5.118 (2.8–9.354)	<.0001
	IGA group at baseline (2 and >2)[c]	1.699 (0.959–3.010)	.0694
	Treatment (control and pimecrolimus)[d]	1.491 (0.856–2.599)	.1582
	Age group at baseline (<12 mo and ≥ 12 mo)[e]	1.113 (0.523–2.366)	.7817
	IgE at baseline (< 14 and ≥ 14 kU/L)[b]	3.507 (1.665–7.387)	.0010
	IGA group at baseline (2 and >2)[c]	1.882 (1.071–3.308)	.0279
	Treatment (control and pimecrolimus)[d]	1.523 (0.880–2.635)	.1324
	Age group at baseline (<12 mo and ≥ 12 mo)[e]	1.036 (0.492–2.181)	.9265
Cow's milk	IgE at baseline (<5 and ≥ 5 kU/L)[b]	11.694 (5.426–25.202)	<.0001
	IGA group at baseline (2 and >2)[c]	1.525 (0.735–3.167)	.2573
	Treatment (control and pimecrolimus)[d]	2.410 (1.144–5.075)	.0206
	IgE at baseline (<15 and ≥ 15 kU/L)[b]	11.269 (4.587–27.687)	<.0001
	IGA group at baseline (2 and >2)[c]	1.718 (0.839–3.517)	.2573
	Treatment (control and pimecrolimus)[d]	2.344 (1.121–4.899)	.0206
Egg	IgE at baseline (<2 and ≥ 2 kU/L)[b]	5.514 (2.852–10.660)	<.0001
	IGA group at baseline (2 and >2)[c]	1.859 (0.927–3.730)	.0827
	Treatment (control and pimecrolimus)[d]	1.853 (0.943–3.643)	.0735
	Age group at baseline (<12 mo and ≥ 12 mo)[e]	0.728 (0.249–2.129)	.5626
	IgE at baseline (<7 and ≥ 7 kU/L)[b]	2.077 (0.910–4.745)	.0827
	IGA group at baseline (2 and >2)[c]	2.290 (1.158–4.528)	.0172
	Treatment (control and pimecrolimus)[d]	1.846 (0.950–3.588)	.0704
	Age group at baseline (<12 mo and ≥ 12 mo)[e]	0.601 (0.209–1.727)	.3445

Logistic regression analysis for peanut, cow's milk, and egg (ITT population, $n = 1065$). CI, confidence interval.

[a] From a Wald test.

[b] IgE value at baseline classified into 2 groups: <5 kU/L (reference category) and ≥5kU/L.

[c] IGA at baseline classified into 2 groups: IGA at baseline = 2 (reference category) and IGA at baseline ≥2.

[d] Treatment during DB phase with 2 groups: control (reference category) and pimecrolimus.

[e] Age group at baseline classified into 2 groups: <12 mo (reference category) and ≥12 mo of age. Age group is not included in the regression analysis for cow's milk because there were no patients with definite milk allergy ≥12 mo of age.

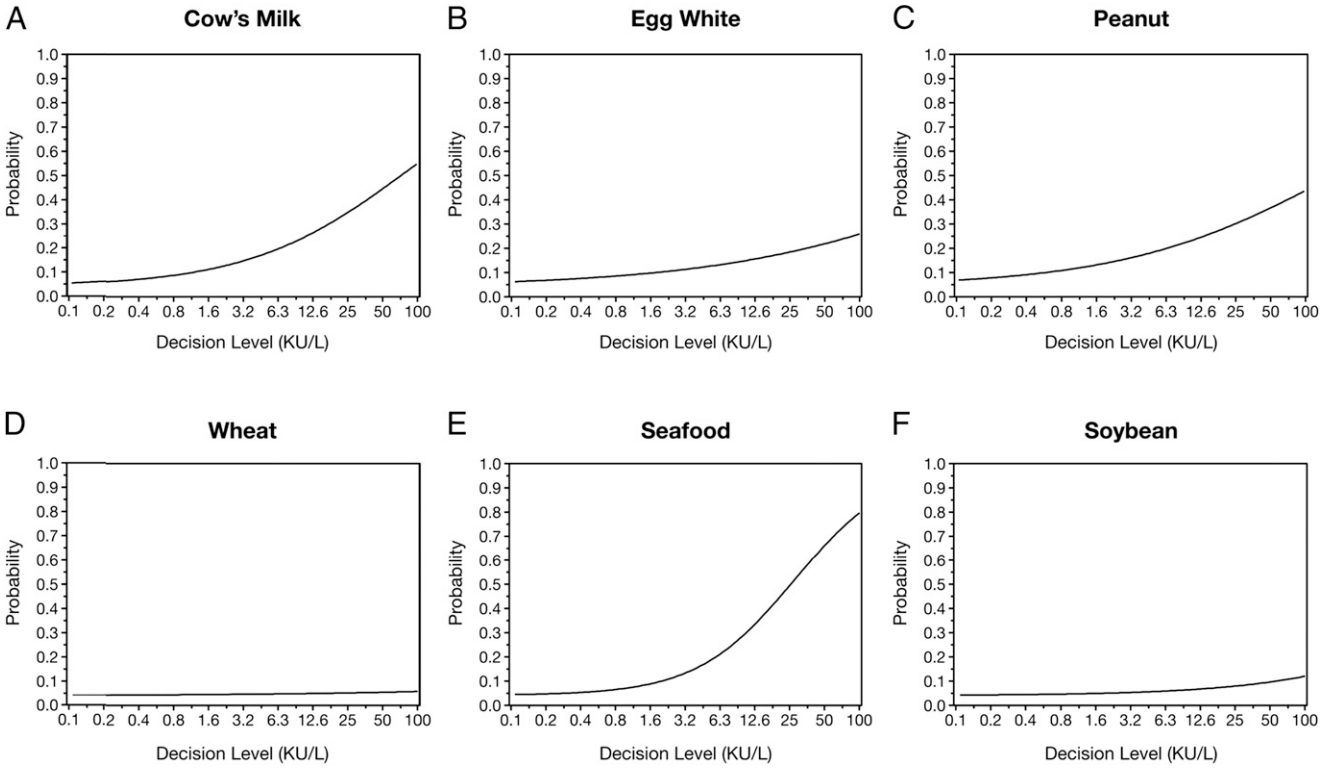

FIGURE 2

The probability of a patient with definite allergy to food is estimated by a simple logistic model P = 1/[exp(−a − bx) + 1], where x = ln (sigE at baseline) and the estimated values of a and b are as follows: (A) a = −2.7833, b = 0.6293; (B) a = −2.9095, b = 0.3666; (C) a = −2.4700, b = 0.4599; (D) a = −5.2812, b= 0.2866; (E) a = −3.3837, b = 1.0242; (F) a = −4.9241, b = 0.5479.

values (PPVs) were low, with all values ≤0.3. Using these same sIgE decision points at the end of the DB phase, when patients had aged 3 years, PPVs were increased relative to baseline, but values remained <0.6.

TABLE 4 Performance Characteristics of sIgE for Food Allergy

Food	IgE Cutoff, kU/L	Sensitivity	Specificity	PPV	NPV
Baseline					
Peanut	5	0.36	0.91	0.22	0.95
	14	0.19	0.95	0.20	0.94
Cow's milk	5	0.38	0.96	0.26	0.97
	15	0.24	0.98	0.30	0.97
Egg white	2	0.54	0.85	0.14	0.98
	7	0.20	0.92	0.10	0.96
Seafood mix	0.35	0.50	0.98	0.11	1.00
Wheat	0.35	0.33	0.86	0.01	1.00
Soybean	0.35	0.67	0.88	0.02	1.00
End of DB phase					
Peanut	5	0.62	0.89	0.43	0.95
	14	0.49	0.93	0.48	0.93
Cow's milk	5	0.42	0.97	0.41	0.97
	15	0.35	0.99	0.56	0.97
Egg white	2	0.45	0.86	0.16	0.96
	7	0.17	0.93	0.13	0.95
Seafood mix	0.35	1.00	0.90	0.06	1.00
Wheat	0.35	0.50	0.72	0.01	1.00
Soybean	0.35	0.67	0.77	0.02	1.00

Performance characteristics of sIgE for predicting definite food allergy (ITT population, n = 1065) as reported at study visits 3–20 (end of OL).

A range of sIgE cutoff values was also used to create ROC curves for each food and to calculate the area under the ROC (Supplemental Figure 3).

DISCUSSION

In the SAM study, 15.9% of a population of >1000 infants with AD developed 1 or more IgE-mediated food allergies. Unlike most studies of food allergy in children with AD, this study enrolled patients of all AD severities who had no history of food allergy at baseline and followed them prospectively for allergy development. The development of food allergy during the SAM study was lower than the range reported in many studies.[1,5–8,19,20] This is most likely because the study enrolled infants predominantly with mild to moderate AD (92%), in contrast to many previous studies

whose subjects mostly had moderate to severe disease.

The rate of food allergy in our cohort of children is similar to data derived from the 2007 National Survey of Children's Health, a prospective questionnaire-based study of 91 642 children aged 0–17 years. In this study, food allergy in the past 12 months was reported in 15.1% of children with AD, of whom 67% had mild and 26% moderate AD.[1,27]

One limitation in our study is that very young children (<4 months of age) were not enrolled, as this group might have higher risk factors for development of food allergy.[4] An IGA score ≥2 at baseline was predictive for development of food allergy and, as expected, the percentage of food allergies increased with patients' baseline AD severity. This ranged from 8% for those with mild AD at baseline to 24% for those with severe baseline AD. Food allergy in patients with AD may result from food protein absorption and sensitization through damaged skin.[28,29] This finding adds to the body of work that supports the "atopic march," the hypothesis that AD pathology predisposes individuals to the development of other atopic diseases and comorbid conditions associated with impaired overall health and increased health care utilization.[1,28,29]

As in other studies, allergies to peanut, cow's milk, and egg white were the most common, and were seen in a higher percentage of study participants than in the general population (3.9% to 6.6% of patients in this study had peanut allergy versus a reported 1.0% to 2.5% of all North American children).[2,30] Estimated rates of allergy to wheat and soybean vary widely; in clinical studies of children and adolescents with AD, rates as high as 30% have been reported.[6,20,31] The 0.3% to 0.4% prevalence found in this study is much lower but agrees closely with reported rates for the general population: 0.1% for fish or shellfish, 0.4% for wheat, and 0.4% for soybean.[30]

Although this study used careful determination of clinically relevant food allergy based on history, we did not confirm diagnoses with food challenges. sIgE testing was performed only for common food allergens, leaving the possibility that reactions to less common food allergens were missed. In addition, food challenges were not completed on all patients, suggesting possible false-positive testing leading to a higher rate. However, the criteria were similar to what has been used in studies sponsored by the National Institutes of Health.[32]

Although food challenges are time-consuming and potentially dangerous for patients, they represent the only definitive test for food allergy. In practice, sIgE testing is widely used to screen for potential food allergy in patients with AD. Maternal and environmental factors have been shown to influence the sensitization pattern of IgE during the first year of life. This early sensitization is suspected to contribute to the development of food allergies in at-risk infants.[4,18,33] Our assessment relied on strong historical indicators.[13] Used properly, sIgE tests then can be used to confirm or negate a diagnosis based on history.[2] sIgE values at which the probability of allergy reaches ≥90% have been developed based on various patient cohorts; most of these cohorts have a strong history of suspected food allergy, and it is unclear whether such decision points are useful for prophylactic use in high-risk populations.[6,19,32,34] The decision points have varied based on age and patient history, and some cohorts do not reach the 90% level.[34–37] sIgE decision points, both published values and the novel decision points used in this study, had high NPVs, in particular for peanut, egg white, and cow's milk. Thus, patients with mild AD with sIgE levels below these cutoffs would be unlikely to have or develop these specific allergies, and would not benefit from food challenges or elimination diets. Similarly, elevated sIgE, as defined by the decision points tested, had very low PPVs for food allergy, both for sIgE values at baseline and at the end of the DB phase. PPVs were particularly low for seafood, wheat, and soybean; other studies have found sIgE to be nonpredictive for these foods.[2,19,32,38] Thus, despite an increased likelihood of allergy development with increasing sIgE shown for cow's milk, egg, and peanut, our data do not support the use of sIgE testing for the diagnosis of food allergy in subjects without a history of reaction to that food. Consistent with our data, work from the National Jewish Hospital showed that 89% of challenges in patients with AD who were avoiding foods based on sIgE were negative, indicating a high false-positive rate for food allergy.[18] In addition, the recent examination of development of peanut allergy in the Learning Early About Peanut allergy study did not find that sIgE was predictive for development of peanut allergy.[20] Therefore, we recommend that children with persistent AD in spite of optimized management should be screened for food allergy, as suggested by the National Institutes of Health guidelines on food allergy.[2]

CONCLUSIONS

Among infants with AD and a family history of atopy, 15.9% developed a food allergy during a period of >3 years. Although peanut, cow's milk, and egg white allergies were common in this patient population,

allergies to seafood, soybean, and wheat were quite rare, even in this higher risk population. Current US guidelines recommend consideration of food allergy evaluation if there is persistent AD in spite of optimal management and/or if there is a reliable history of an immediate reaction after ingestion of a specific food.[2] The results of this study of food allergy development in >1000 infants with AD do not support the use of sIgE testing for these infants as a diagnostic substitute for food challenge and should discourage pediatricians from prescribing food-elimination diets on the basis of sIgE levels alone.

ACKNOWLEDGMENTS

The authors acknowledge the investigators who participated in the SAM (please see online Supplemental Information for full listing). In addition, they thank Shangbin Liu, PhD, of Premier Research Group Limited for statistical programming and analysis. Editorial assistance was provided by Amy Troy, PhD, of Oxford PharmaGenesis, Inc, and was funded by Novartis Pharmaceuticals Corporation.

ABBREVIATIONS

AD: atopic dermatitis
DB: double-blind
EASI: Eczema Area and Severity Index
IGA: Investigator's Global Assessment
IgE: immunoglobulin E
ITT: intent to treat
NPV: negative predictive value
OL: open label
PPV: positive predictive value
ROC: receiver operating characteristic
SAM: Study of the Atopic March
sIgE: specific immunoglobulin E

FINANCIAL DISCLOSURE: Dr Boguniewicz has consulted for Valeant. The other authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: Novartis Pharmaceutical Company funded the Study of Atopic March Trial.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

REFERENCES

1. Silverberg JI, Simpson EL. Association between severe eczema in children and multiple comorbid conditions and increased healthcare utilization. *Pediatr Allergy Immunol*. 2013;24(5):476–486
2. Boyce JA, Assa'ad A, Burks AW, et al; NIAID-Sponsored Expert Panel. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. *J Allergy Clin Immunol*. 2010;126(suppl 6): S1–S58
3. Eichenfield LF, Hanifin JM, Beck LA, et al. Atopic dermatitis and asthma: parallels in the evolution of treatment. *Pediatrics*. 2003;111(3):608–616
4. Martin PE, Eckert JK, Koplin JJ, et al; HealthNuts Study Investigators. Which infants with eczema are at risk of food allergy? Results from a population-based cohort. *Clin Exp Allergy*. 2015;45(1): 255–264
5. Burks AW, Mallory SB, Williams LW, Shirrell MA. Atopic dermatitis: clinical relevance of food hypersensitivity reactions. *J Pediatr*. 1988;113(3):447–451
6. Eigenmann PA, Sicherer SH, Borkowski TA, Cohen BA, Sampson HA. Prevalence of IgE-mediated food allergy among children with atopic dermatitis. *Pediatrics*. 1998;101(3). Available at: www.pediatrics.org/cgi/content/full/101/3/E8
7. Sampson HA. Role of immediate food hypersensitivity in the pathogenesis of atopic dermatitis. *J Allergy Clin Immunol*. 1983;71(5):473–480
8. Sampson HA, McCaskill CC. Food hypersensitivity and atopic dermatitis: evaluation of 113 patients. *J Pediatr*. 1985;107(5):669–675
9. Breuer K, Heratizadeh A, Wulf A, et al. Late eczematous reactions to food in children with atopic dermatitis. *Clin Exp Allergy*. 2004;34(5):817–824
10. Burks W. Skin manifestations of food allergy. *Pediatrics*. 2003;111(6 pt 3): 1617–1624
11. Niggemann B, Sielaff B, Beyer K, Binder C, Wahn U. Outcome of double-blind, placebo-controlled food challenge tests in 107 children with atopic dermatitis. *Clin Exp Allergy*. 1999;29(1):91–96
12. Rowlands D, Tofte SJ, Hanifin JM. Does food allergy cause atopic dermatitis? Food challenge testing to dissociate eczematous from immediate reactions. *Dermatol Ther (Heidelb)*. 2006;19(2): 97–103
13. Thompson MM, Hanifin JM. Effective therapy of childhood atopic dermatitis allays food allergy concerns. *J Am Acad Dermatol*. 2005;53(2 suppl 2):S214–S219
14. Depner M, Ege MJ, Genuneit J, et al; PASTURE Study Group. Atopic sensitization in the first year of life. *J Allergy Clin Immunol*. 2013;131(3): 781–788
15. Perry TT, Matsui EC, Kay Conover-Walker M, Wood RA. The relationship of allergen-specific IgE levels and oral food challenge outcome. *J Allergy Clin Immunol*. 2004;114(1):144–149
16. Noh G, Ahn HS, Cho NY, Lee S, Oh JW. The clinical significance of food specific IgE/IgG4 in food specific atopic dermatitis. *Pediatr Allergy Immunol*. 2007;18(1):63–70
17. Sicherer SH, Sampson HA. Food allergy: epidemiology, pathogenesis, diagnosis, and treatment. *J Allergy Clin Immunol*. 2014;133(2):291–307, quiz 308
18. Fleischer DM, Bock SA, Spears GC, Wilson CG, Miyazawa NK, Gleason MC, et al. Oral food challenges in children with a

diagnosis of food allergy. *J Pediatr*. 2011; 158(4):578–583.e1

19. Peters RL, Allen KJ, Dharmage SC, et al; HealthNuts Study. Skin prick test responses and allergen-specific IgE levels as predictors of peanut, egg, and sesame allergy in infants. *J Allergy Clin Immunol*. 2013;132(4): 874–880
20. Du Toit G, Roberts G, Sayre PH, et al; LEAP Study Team. Randomized trial of peanut consumption in infants at risk for peanut allergy. *N Engl J Med*. 2015;372(9): 803–813
21. Eichenfield LF, Hanifin JM, Luger TA, Stevens SR, Pride HB. Consensus conference on pediatric atopic dermatitis. *J Am Acad Dermatol*. 2003; 49(6):1088–1095
22. Hanifin JM, Thurston M, Omoto M, Cherill R, Tofte SJ, Graeber M; EASI Evaluator Group. The eczema area and severity index (EASI): assessment of reliability in atopic dermatitis. *Exp Dermatol*. 2001; 10(1):11–18
23. Sampson HA. Utility of food-specific IgE concentrations in predicting symptomatic food allergy. *J Allergy Clin Immunol*. 2001;107(5):891–896
24. Stokes M, Davis C, Koch G. *Categorical Data Analysis Using SAS System*. 2nd ed. Cary, NC: SAS Institute, Inc.; 2000
25. Bewick V, Cheek L, Ball J. Statistics review 14: Logistic regression. *Crit Care*. 2005;9(1):112–118
26. Bewick V, Cheek L, Ball J. Statistics review 13: receiver operating characteristic curves. *Crit Care*. 2004;8(6):508–512
27. Wahn U, Warner J, Simons FE, et al; EPAAC Study Group. IgE antibody responses in young children with atopic dermatitis. *Pediatr Allergy Immunol*. 2008;19(4):332–336
28. Ker J, Hartert TV. The atopic march: what's the evidence? *Ann Allergy Asthma Immunol*. 2009;103(4):282–289
29. Spergel JM. From atopic dermatitis to asthma: the atopic march. *Ann Allergy Asthma Immunol*. 2010;105(2):99–106; quiz 107–109, 117
30. Sicherer SH, Sampson HA. Food allergy. *J Allergy Clin Immunol*. 2010;125(2 suppl 2):S116–S125
31. Lo YC, Yang YH, Chiang BL. Food-specific immunoglobulin E among children with atopic dermatitis: a retrospective study. *J Microbiol Immunol Infect*. 2005;38(5): 338–342
32. Sicherer SH, Wood RA, Vickery BP, et al. The natural history of egg allergy in an observational cohort. *J Allergy Clin Immunol*. 2014;133(2):492–499
33. Wolkerstorfer A, Wahn U, Kjellman NI, Diepgen TL, De Longueville M, Oranje AP. Natural course of sensitization to cow's milk and hen's egg in childhood atopic dermatitis: ETAC study group. *Clin Exp Allergy*. 2002;32(1):70–73
34. Boyano Martínez T, García-Ara C, Díaz-Pena JM, Muñoz FM, García Sánchez G, Esteban MM. Validity of specific IgE antibodies in children with egg allergy. *Clin Exp Allergy*. 2001; 31(9):1464–1469
35. Celik-Bilgili S, Mehl A, Verstege A, et al. The predictive value of specific immunoglobulin E levels in serum for the outcome of oral food challenges. *Clin Exp Allergy*. 2005;35(3):268–273
36. García-Ara C, Boyano-Martínez T, Díaz-Pena JM, Martín-Muñoz F, Reche-Frutos M, Martín-Esteban M. Specific IgE levels in the diagnosis of immediate hypersensitivity to cows' milk protein in the infant. *J Allergy Clin Immunol*. 2001;107(1):185–190
37. Sicherer SH, Sampson HA. Cow's milk protein-specific IgE concentrations in two age groups of milk-allergic children and in children achieving clinical tolerance. *Clin Exp Allergy*. 1999;29(4):507–512
38. García BE, Gamboa PM, Asturias JA, et al; Clinical Immunology Committee; Spanish Society of Allergology and Clinical Immunology. Guidelines on the clinical usefulness of determination of specific immunoglobulin E to foods. *J Investig Allergol Clin Immunol*. 2009;19(6):423–432

Food Allergy in Infants With Atopic Dermatitis: Limitations of Food-Specific IgE Measurements

Jonathan M. Spergel, Mark Boguniewicz, Lynda Schneider, Jon M. Hanifin, Amy S. Paller and Lawrence F. Eichenfield

Pediatrics 2015;136;e1530
DOI: 10.1542/peds.2015-1444 originally published online November 23, 2015;

PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Food Allergy in Infants With Atopic Dermatitis: Limitations of Food-Specific IgE Measurements

Jonathan M. Spergel, Mark Boguniewicz, Lynda Schneider, Jon M. Hanifin, Amy S. Paller and Lawrence F. Eichenfield

Pediatrics 2015;136;e1530
DOI: 10.1542/peds.2015-1444 originally published online November 23, 2015;