

Baked egg oral immunotherapy desensitizes baked egg allergic children to lightly cooked egg

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Clinical Implications

- Baked egg oral immunotherapy may lead to desensitization to lightly cooked egg in baked egg-reactive children. This is the first study to describe baked egg oral immunotherapy in the baked egg-reactive population and to demonstrate significant immunomodulation consistent with desensitization.

TO THE EDITOR:

Hen's egg allergy affects 0.5% to 2.5% of children.¹ The majority of egg-allergic children tolerate baked egg (BE),²⁻⁴ and those able to safely ingest BE appear to acquire tolerance to all forms of egg (eg, raw [RE] and lightly cooked [LCE]) earlier than those reactive to BE.^{1,5,6} Interventions for patients who are specifically allergic to both RE and BE have not been studied closely. Our primary aim was to determine if BE-allergic children would become desensitized to 6 g of LCE (eg, scrambled) after undergoing BE oral immunotherapy (BE OIT) for approximately 2 years.

Subjects 1 to 18 years were recruited through the Food Allergy Center at Children's Medical Center and included if they experienced an objective reaction during an open BE oral food challenge (OFC) containing 3.8 g of egg protein (EP) or had a history of egg allergy and an ovomucoid (OVM) IgE ≥ 50 kU/L. Exclusion criteria included negative skin prick test (SPT) to egg white (EW), undetectable EW-specific IgE, eosinophilic esophagitis, eosinophilic gastroenteritis, uncontrolled asthma, pregnancy, or a chronic medical condition requiring the frequent use of oral steroids. The measurement of EW-specific IgE and IgG₄ levels was performed with ImmunoCAP (Thermo Fisher Scientific, Phadia US, Portage, Mich). SPTs were performed with EW extract (ALK Inc, Round Rock, Tex). Ethics approval was obtained through the Institutional Review Board at University of Texas (UT) Southwestern Medical School. Written informed consent was obtained in accordance with UT Southwestern's ethics guidelines for research in children. Outcomes were analyzed using the Wilcoxon signed-rank test (significance level at 0.05), and between-group comparisons were made using the unpaired *t* test, GraphPad Prism version 7.00 for Mac OS X, GraphPad Software (La Jolla, Calif; www.graphpad.com).

Eligible subjects were instructed to eat a serving of BE daily per protocol (Figure E1, available in this article's Online Repository at www.jaci-inpractice.org). Subject families were given a series of recipes containing progressively larger amounts of EP per serving with the final recipe containing 3.8 g of EP per serving. The maximum maintenance dose in the first year was 2.5 g of BE and increased to 3.8 g BE after the 1-year BE OFC.

Observed dosing was performed for the initial escalation day to 125 mg and the 12-month BE OFC. All other up-dosing occurred at home. Subjects were called after home up-dosing and at least monthly to ensure compliance, review adverse events (AEs), and address any concerns. Daily symptom diaries were recorded by families, reviewed monthly by study staff, and managed using REDCap electronic data capture tools hosted at UT Southwestern.⁷ After ingestion of 3.8 g of BE daily for approximately 1 year, subjects returned for an observed, open OFC to 6 g of LCE.

Thirteen subjects were enrolled (median age, 4.3 years [range, 1.5-11.7 years]) (Table E1, available in this article's Online Repository at www.jaci-inpractice.org). Nine subjects were male. Median EW IgE at entry was 21.2 kU/L (mean 38.2 kU/L, interquartile range [IQR] 12.7-47 kU/L), and median EW SPT wheal diameter was 6 mm (mean 6.7 mm, IQR 5-7 mm). Median cumulative reactive dose (CRD) at entry was 2.5 g BE protein (mean 2.2 g, IQR 0.76-3.8 g). Six subjects completed the trial. Baseline characteristics did not differentiate completers from those who discontinued early (Table E2, available in this article's Online Repository at www.jaci-inpractice.org). Five subjects withdrew because of difficulty ingesting the BE product daily. The parents of these subjects did not report objective or subjective AEs as the reason for discontinuation. One subject was diagnosed with leukemia and removed from the study. One subject began ingesting LCE at home before the LCE OFC and was removed from data analysis.

Eight subjects completed 12 months of BE OIT, and 7 subjects passed the 3.8 g BE OFC. After an additional year of daily 3.8 g BE ingestion, 6 subjects were challenged and 5 passed a 6 g LCE OFC. The ratios EW IgE:EW IgG₄, OVM IgE:OVM IgG₄, and ovalbumin (OVA) IgE:OVA IgG₄ decreased significantly ($P < .05$) by 6 months and remained suppressed through the end of the trial (Figure 1). EW, OVM, and OVA IgG₄ increased significantly ($P < .05$) by 6 months and remained significantly elevated through the end of the trial (Figure 2). OVA IgE decreased significantly ($P < .05$) at 12 and 24 months, and the EW SPT wheal diameter decreased significantly ($P < .05$) at 12 and 18 months (Figures E2 and E3, available in this article's Online Repository at www.jaci-inpractice.org). EW and OVM IgE did not change significantly.

Dosing was well tolerated with only 77 AEs reported of 5605 total recorded doses (1.37% of total doses). Of the 77 AEs, 12 were reported on the day of up-dosing, and 11 additional AEs occurred in the 2 weeks after up-dosing. The remainder did not correlate with timing of dose adjustment. All AEs were mild and none required epinephrine. Details of AEs are provided in Table E3 (available in this article's Online Repository at www.jaci-inpractice.org).

BE OIT may be effective at desensitizing children allergic to both LCE and BE. Our protocol demonstrates a safe approach in this small cohort that induces immunomodulatory changes consistent with desensitization comparable with those demonstrated with other forms of OIT. Importantly, all subjects tolerated the initial escalation to 125 mg and subjects compliant with daily therapy tolerated up-dosing, whether at home or in the clinic. Our approach suggests that the introduction of BE

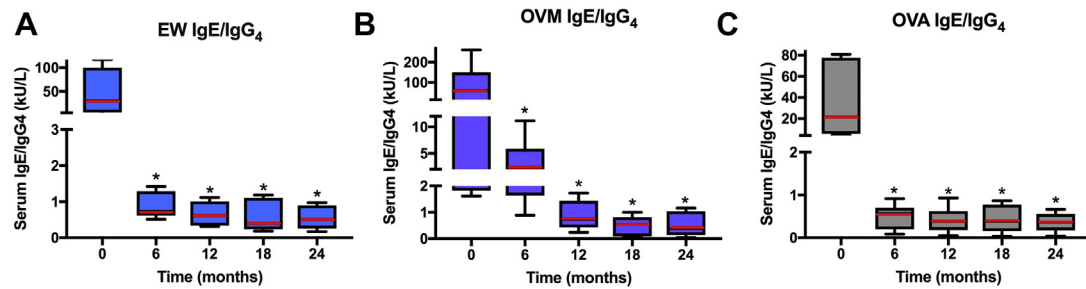


FIGURE 1. Serum levels of IgG4 during BE OIT. **A**, EW; **B**, OVM; and **C**, OVA IgG4 increases significantly at 6 months and remains significantly elevated through 24 months. The red horizontal bar indicates median value. * $P < .05$.

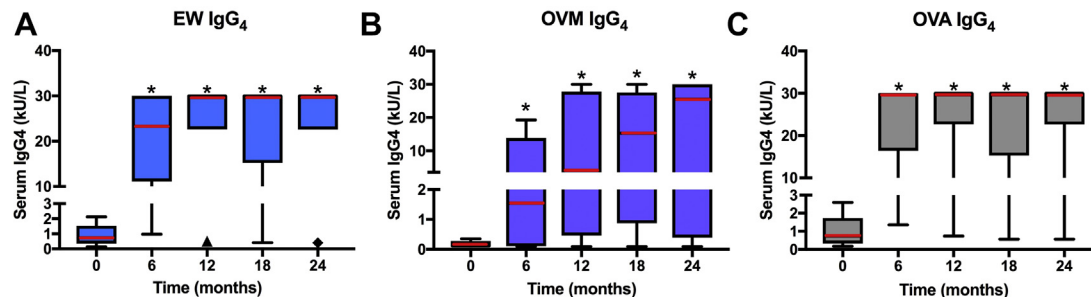


FIGURE 2. Serum levels of the ratio of IgE:IgG4 during BE OIT. The ratio of IgE:IgG4 decreases significantly at 6 months and remains suppressed for **A**, EW; **B**, OVM; and **C**, OVA. The red horizontal bar indicates medial value. * $P < .05$.

products with low protein content may be safe and, if taken daily, may induce desensitization to LCE.

Leonard et al⁸ examined the use of heated OVM for OIT in a murine model and showed that heated OVM induces desensitization similar to RE but without inducing anaphylaxis. Reports for BE OIT in BE-reactive subjects are lacking with the exception of Bravin's description of 8 of 15 patients desensitized to RE after a 60-day daily build-up protocol feeding a biscuit cooked by the authors, advancing from 125 μ g EP to a final dose of 6.25 g EP.⁹ Immunologic outcomes were not reported. Our protocol differed in OIT duration and dosing; however, desensitization outcomes are similar.

The small sample size, high dropout rate, lack of placebo-control, single-center design, lack of randomization, and open OFCs limit data interpretation. This was a proof of concept study with limitations in study rigor imposed by budgetary constraints. The high dropout rate was primarily related to compliance with daily ingestion of BE, especially in children less than 3 years. No participants withdrew from the study because of AEs. It is possible that AEs were generally mild because the median CRD at entry was 2.5 g, and a potential limitation to data interpretation is that the study group was biased toward higher tolerance at baseline. Parental fatigue related to product preparation may have also contributed to dropouts, though we believe that home preparation is advantageous in terms of the ability to adopt a similar approach in a community setting.

In summary, our data suggest that egg-allergic children reactive to BE may be able to undergo BE OIT to accelerate desensitization to LCE. An ongoing study is comparing BE

versus RE OIT in a multicenter egg-allergic population and will provide important data to inform the potential benefits of BE OIT in comparison with RE OIT (NCT01846208); however, NCT01846208 will not study the effects of BE OIT in BE-allergic subjects as demonstrated in our cohort. Our data in this pilot cohort suggest that this approach may be safe and potentially effective, deserving additional study for treatment of egg allergy.

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Conflicts of interest: J. A. Bird reports personal fees from Food Allergy Research and Education, Nutricia North America, Foresite Capital Management, Medscape, and Pharm-Olam International Ltd; grants, personal fees, and other from DBV Technologies; personal fees and nonfinancial support from American College of Allergy, Asthma and Immunology; personal fees and nonfinancial support from Food Allergy Research and Education; grants from Nestle Health Sciences; grants and personal fees from Aimmune Therapeutics, outside the submitted work. A. Clark reports personal fees from Nutricia North America, outside the submitted work. M. Crain reports personal fees from DBV Technologies, outside the submitted work. C. Parrish reports personal fees from Pharmacy Times Continuing Education; nonfinancial support from Aimmune Therapeutics; nonfinancial support from DBV Technologies, outside the submitted work. The rest of the authors declare that they have no relevant conflicts of interest.

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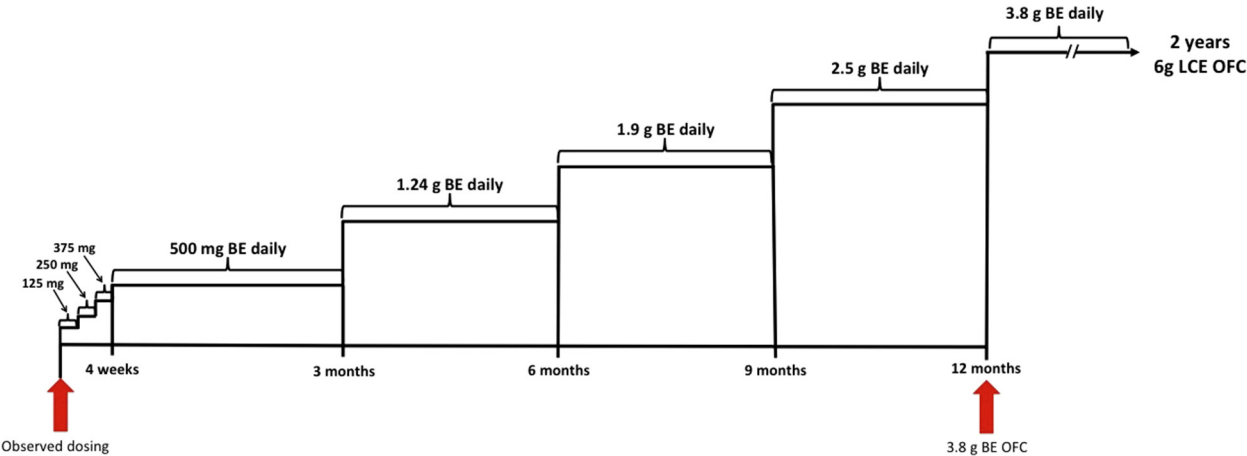


FIGURE E1. Study schematic. *BE*, Baked egg; *LCE*, lightly cooked egg; *OFC*, oral food challenge.

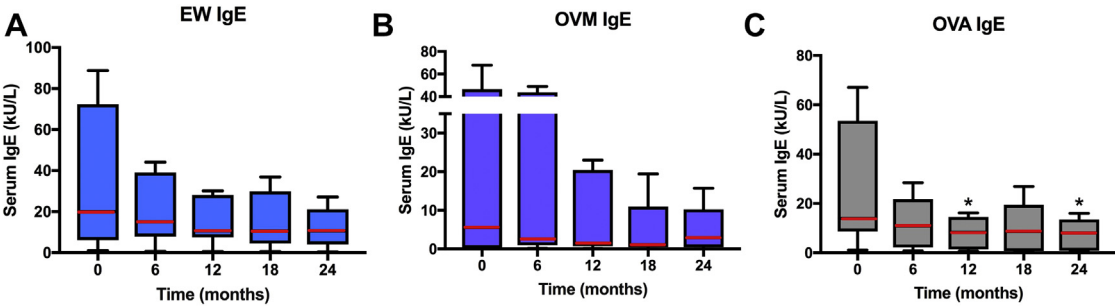


FIGURE E2. Serum levels of specific IgE during BE OIT. EW- (A) and OVM- (B) specific IgE do not change significantly during therapy. OVA-specific IgE (C) decreases significantly at 12 and 24 months. The median value is represented by a red horizontal bar (* $P < .05$). *BE*, Baked egg; *EW*, egg white; *OIT*, oral immunotherapy; *OVA*, ovalbumin; *OVM*, ovomucoid.

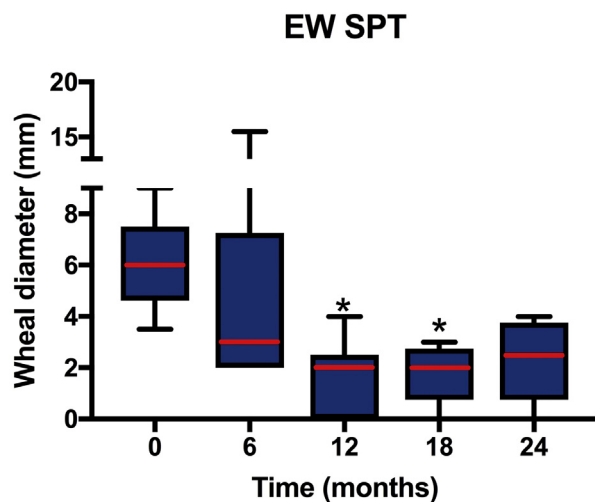


FIGURE E3. Egg white skin prick test wheal diameter during BE OIT. The EW SPT wheal diameter is significantly decreased from baseline at 12 and 18 months. The median value is represented by a red horizontal bar (* $P < .05$). *BE*, Baked egg; *EW*, egg white; *OIT*, oral immunotherapy; *SPT*, skin prick test.

TABLE E1. Participant demographics

	Subject	Age at entry (y)	Gender	Cumulative reactive dose at entry (grams of BE protein)	Symptoms at entry challenge	EW IgE (kU/L) at entry	OVm IgE (kU/L) at entry	EW SPT wheal diameter (mm) at entry	Outcome
Completer	2	2.2	M	3.8	C, E	1.22	0.17	5	Passed 12 mo BE OFC and end of study LCE OFC
	13	2.8	M	n/a*	n/a*	>100	68.5	3.5	Passed 12 mo BE OFC and end of study LCE OFC
	9	7.0	M	3.8	E, D	12.7	<0.10	9	Passed 12 mo BE OFC and end of study LCE OFC
	10	8.1	F	3.8	E	19.8	7.41	7	Passed 12 mo BE OFC and end of study LCE OFC
	11	8.9	M	n/a*	n/a*	>100	51.4	6	Passed 12 mo BE OFC and end of study LCE OFC
	12	11.7	M	0.04	R, T, CT	21.2	1.71	6	Failed end of study LCE OFC. Developed itchy mouth that resolved with cetirizine
Early discontinuation	6	1.5	F	1.33	E, S, R	0.8	<0.10	5	Difficulty complying with daily ingestion and withdrew after 1.5 mo in study
	4	1.8	M	0.19	U, S, R, A	35.4	0.22	7	Difficulty complying with daily ingestion and withdrew after 3 mo in study
	8	2.7	M	3.8	E, S, U	24.3	0.83	4	Difficulty complying with daily ingestion and withdrew after 3.5 mo in study
	5	3.1	M	1.33	U, P, C, W	42.4	7.4	16	Difficulty complying with daily ingestion and withdrew after 3.5 mo in study
	3	4.3	M	2.5	NP, S, C, F, AbdP	3.02	1.24	7	Diagnosed with leukemia and withdrew after 3 mo in study
	1	4.8	M	0.04	C, G, EP	73.5	25.6	7	Removed from data analysis because he began ingesting LCE at home before the final OFC
	7	6.0	F	3.8	P, S, C	60.8	68.4	5	Difficulty complying with daily ingestion. Failed 12 mo BE OFC with sneezing, rhinorrhea, pruritis, and coughing. Improved with 1 dose of epinephrine and diphenhydramine. Encouraged to eat 2.5 g BE daily. Voluntarily withdrew after 20 mo in study
	Median	4.3		2.5		21.2	7.4	6	
	Mean	5		2.2		38.2	21.2	6.7	
	Range	(1.5-11.7)		(0.04-3.8)		(0.8->100)	(<0.10-68.5)	(3.5-16)	
	IQR	(2.7-7.3)		(0.76-3.8)		(12.7-47)	(1.0-21.1)	(5-7)	

A, Angioedema; *AbdP*, abdominal pain; *BE*, baked egg; *C*, coughing; *CT*, chest tightness; *D*, diarrhea; *E*, emesis; *EP*, ear pruritus/pulling at ears; *EW*, egg white; *F*, flushing; *G*, gagging; *IQR*, interquartile range; *LCE*, lightly cooked egg; *NP*, nasal pruritus; *OFC*, oral food challenge; *OVm*, ovomucoid; *P*, pruritus; *R*, rhinorrhea; *S*, sneezing; *SPT*, skin prick test; *T*, throat pain; *U*, urticaria.

*Subjects qualified for study based on OM IgE $\geq$ 50 kU/L and did not have entry OFC.

TABLE E2. Comparison of baseline characteristics of completers versus all subjects removed from data analysis because of early discontinuation and versus those who discontinued secondary to difficulty ingesting the product

	Completer (mean ± SEM)	Early discontinuation (mean ± SEM)	Discontinuation due to difficulty ingesting product (mean ± SEM)*	P value (completer vs early discontinuation)	P value (completer vs discontinuation due to difficulty ingesting product)
Age	6.8 ± 1.5 y	3.5 ± 0.6 y	3.0 ± 0.8 y	.0529	.0669
Reactive dose	2.86 ± 0.94 g	1.7 ± 0.52 g	1.87 ± 0.63 g	.2659	.3932
EW IgE	42.49 ± 18.42 kU/L	34.32 ± 10.36 kU/L	32.73 ± 9.95 kU/L	.6954	.6717
OVm IgE	21.55 ± 12.39 kU/L	14.83 ± 9.58 kU/L	15.39 ± 13.32 kU/L	.6715	.7432
EW SPT	6.0 ± 0.8 mm	7.3 ± 1.5 mm	7.4 ± 2.2 mm	.5170	.5570

Unpaired *t* test used to compare groups.

EW, Egg white; OVm, ovomucoid; SEM, standard error of the mean; SPT, skin prick test.

*Subjects 4, 5, 6, 7, and 8 were included in this analysis.

TABLE E3. Summary of home-dosing treatment-related AEs reported in patient diaries

System/organ	No. of individuals with AE (percent of total participants) (n = 13)	No. of reported AEs (percent of total doses) (n = 5605)	Medication* administration for AEs (percent of total doses)
Any hypersensitivity event	8 (62%)	77 (1.4%)	25 (0.45%)
Gastrointestinal	8 (62%)	58 (1.0%)	22 (0.39%)
Abdominal pain	8 (62%)	58 (1.0%) [†]	21 (0.37%)
Vomiting	3 (23%)	8 (0.14%)	1 (0.018%)
Skin			
Urticaria	5 (38%)	16 (0.29%)	1 (0.018%)
Respiratory	3 (23%)	17 (0.30%)	2 (0.036%)
Cough	2 (15%)	4 (0.071%)	0
Wheezing	1 (7.7%)	2 (0.036%)	2 (0.036%) [‡]
Sneezing	3 (23%)	6 (0.11%)	0
Rhinorrhea/congestion	3 (23%)	8 (0.14%)	0
Other			
Oral pruritus	1 (7.7%)	7 (0.12%)	0

AE, Adverse event.

*Only medication given was diphenhydramine except as noted below.

[†]Half (29) of abdominal pain events occurred in a single patient who successfully completed the trial. These reactions accounted for 84% (21 of 25) of reactions treated with medications.

[‡]Albuterol.