Long-term follow-up of oral immunotherapy for cow's milk allergy

To the Editor:

Oral immunotherapy (OIT) for food allergy is currently under active investigation, and its use in clinical practice is spreading despite important concerns.[1,2] Among the many reasons for caution is the paucity of data on long-term outcomes. One study in Italy found that although 18 (86%) of 21 subjects were initially partially or completely desensitized to cow's milk (CM) with OIT, this decreased to 14 (70%) of 20 after 4½ years.[3] Other studies have generally reported limited or no follow-up data. Here we report follow-up of 2 studies of CM OIT after up to 5 years to evaluate ongoing CM consumption, symptoms, and potential predictors of long-term outcomes.

Both previously published studies enrolled children with CM allergy at Johns Hopkins and Duke Universities after a double-blind, placebo-controlled oral food challenge (OFC).[4-6] The first study was a double-blind, placebo-controlled trial in 20 children.[4] Dose escalation to 0.5 g of CM protein lasted approximately 8 weeks, followed by 3-month maintenance. All placebo-treated children were offered active OIT after the final OFC. The second study was an open-label randomized trial of OIT versus sublingual immunotherapy in 30 children.[6] Dose escalation, lasting approximately 30 weeks, started with a short course of sublingual immunotherapy, followed by OIT to a goal dose of 1 or 2 g. After 3 months of maintenance, an OFC was administered, and the dose was potentially adjusted to a maximum of 4 g. Maintenance totaled 15 months and was followed by another OFC. For subjects who passed that challenge, tolerance challenges were done 1 and 6 weeks later. In both studies individualized recommendations regarding milk consumption after study completion were provided based on OFC results.

Follow-up data were collected by means of standardized questionnaire, clinical follow-up, or both for all 32 subjects treated with active OIT at Johns Hopkins and 26 of 32 participated in a follow-up visit, including phlebotomy and skin testing. Subjects were asked about CM consumption and symptoms with CM ingestion in the past year. Symptoms were classified as frequent or predictable if they typically occurred with CM consumption or sporadic if there were no frequent or predictable symptoms but definite reactions occurred on at least 1 occasion. To assess predictors of outcome, subjects were split into 2 groups: those who consumed at least 1 serving of CM daily with no more than oral/pharyngeal symptoms and those who either consumed less CM or reported symptoms. Differences were evaluated by using the Fischer exact test for dichotomous variables or Wilcoxon rank sum tests for continuous variables.

Sixteen subjects were eligible from each study, including 5 subjects who did not complete the questionnaire but for whom clinical data were available (including 3 who withdrew during active treatment). Subjects were followed up after a median of 4.5 years (range, 1.3-5.3 years) and 3.2 years (range, 2.6-3.4 years) from the end of dose escalation in study 1 and study 2, respectively. Because outcomes were similar between studies and between OIT randomization groups in the second study, data were combined for further analysis.

Table I shows current CM consumption status and symptoms with CM ingestion. Twenty-two percent reported limiting their consumption because of symptoms, 9% because of anxiety, and 13% because of taste. In addition, 25% limited CM with exercise and 6% with illness. Most reactions were not attributed to cofactors, but 13% reported increased symptoms with exercise, 9% with illness, and 6% after missing several days of CM. Notably, some subjects who initially did well and passed interim OFCs subsequently had increased symptoms and began to restrict CM. Disturbingly, some subjects had significant symptoms after study completion of which we were unaware, with 1 subject reporting using epinephrine at least twice per month for reactions to CM. See Table E1 in this article's Online Repository at www.jacionline.org for a description of the types of symptoms with CM consumption.

Baseline and follow-up characteristics and their relationships to long-term outcomes are shown in Table II. Of note, several characteristics were associated with long-term outcome, including baseline CM IgE levels, gastrointestinal and lower respiratory tract symptoms with OIT, food challenge threshold at 3 months of maintenance, amount of CM recommended for daily intake, and skin prick test wheal size in follow-up. No subject with baseline CM IgE levels of greater than 75 kU/L (n = 8), respiratory symptoms with more than 2% of doses (n = 8), or with a posttreatment food challenge threshold of less than 4 g (n = 7) was consuming at least 1 serving of milk in follow-up without symptoms. In addition, 7 (88%) of those with baseline CM IgE levels of greater than 75 kU/L either had anaphylaxis or consumed no more than trace or baked milk in follow-up (see Tables E2 and E3 and Figs E1-E3 in this article's Online Repository at www.jacionline.org). However, collectively, these predictors identified only 48% of subjects in the poorer outcome group, and given the relatively small sample size, we would be hesitant to suggest that these specific cutoffs would necessarily apply to other studies.

This report has several important limitations. First, we do not have follow-up serology or skin prick test results on most subjects with the worst outcome (ie, those who were avoiding milk), which might underestimate the discriminative capacity of these parameters. Second, we do not have a control group that was not treated to compare long-term outcomes. Third, these subjects might represent an especially severe phenotype of CM allergy. Most importantly, our data do not answer the question of whether subjects who continue to have symptoms are actually better off than they were before treatment.

However, although we hope that newer OIT protocols that include higher doses, longer periods of maintenance, or both will lead to better results, it is clear from these preliminary data that long-term outcomes after CM immunotherapy are decidedly mixed, with some subjects losing desensitization over time and no more than 31% of subjects tolerating at least full servings of CM with minimal or no symptoms.

These findings are particularly concerning for the future of OIT because, unlike most other allergenic foods, CM is typically consumed in diverse forms several times a day. Even young children are generally very motivated to incorporate CM into their diets. For foods like peanut, for which aversion among formerly allergic children is common,[7] results might be far worse than we

TABLE I. Characteristics by long-term outcome category

Characteristics	Total	Consumption/symptom group: ≥1 Serving and no more than oral/pharyngeal symptoms (n = 9)	Consumption/symptom group: Symptoms or <1 serving (n = 23)	*P* value
Baseline characteristics				
Baseline age (y), median (range)	9 (6-16)	8 (6-16)	10 (6-16)	.73
Male sex, no. (%)	21 (66)	6 (67)	15 (65)	.64
Presence of eczema, no. (%)	18 (56)	6 (67)	12 (52)	.37
Study assignment, study 1, no. (%)	16 (50)	5 (56)	11 (48%)	.50
Baseline CM IgE (kU_A/L), median (range)	**31 (1-314)**	**25 (1-73)**	**41 (5-314)**	**.04**
Baseline SPT wheal size (mm), median (range)	9 (5-21.5)	8.5 (5-11.5)	9.5 (6-21.5)	.14
Baseline threshold (mg milk protein), median (range)	40 (40-1350)	40 (40-1350)	40 (40-140)	.79
Symptoms with initial treatment				
Median percentage of doses with symptom (range)				
Gastrointestinal	**1.9% (0% to 44%)**	**0.6% (0% to 44%)**	**2.3% (0% to 16%)**	**.03**
Lower respiratory tract	**0.6% (0% to 7.7%)**	**0% (0% to 1.8%)**	**1.0% (0% to 7.7%)**	**.04**
Skin	0.4% (0% to 47%)	0% (0% to 0.7%)	0.4% (0% to 47%)	.06
Median percentage of doses requiring treatment (range)				
Antihistamines	3.3% (0% to 59%)	2.2% (0% to 20%)	4.5% (0% to 59%)	.13
β-Agonist	**0.3% (0% to 8.3%)**	**0% (0% to 0.9%)**	**0.6% (0% to 8.3%)**	**.03**
Early outcomes				
CM IgE (kU_A/L) at 3-mo maintenance*, median (range)	26 (1-398)	13 (1-67)	27 (2-398)	.16
SPT wheal size (mm) at 3-mo maintenance, median (range)*	7 (0-15.5)	5 (0-15.5)	7.5 (2-14)	.19
Threshold at 3-mo maintenance	**6140 (0-8140)**	**8140 (4140-8140)**	**4140 (0-8140)**	**.006**
No symptoms at full challenge at 3 mo, no. (%)	8 (25)	4 (44)	4 (17)	.68
Amount of milk protein (g) on which subject went home,† median (range)	2 (0-8)	4 (1-8)	1.5 (0-8)	.04
Later outcomes				
Passed tolerance challenge? (study 2), no. (%)‡	5 (31)	3 (75)	2 (17)	.12
Milk IgE (kU_A/L) in follow-up, median (range)§	4 (0.4-55)	4 (0.4-20)	5 (0.7-55)	.19
SPT wheal size (mm) in follow-up, median (range)§	**4 (0-15.5)**	**0 (0-4.5)**	**6 (0-15.5)**	**.02**
Milk IgG_4 (μg/mL) in follow-up, median (range)§	19 (8-68)	18 (8-38)	19 (10-68)	.25

Statistically significant differences are shown in boldface.
kU_A/L, Allergen-specific kilounits/liter, *SPT*, skin prick test.
*n = 30.
†Home milk protein recommendations based on food challenge threshold and symptoms.
‡n = 16.
§n = 26.

TABLE II. Milk consumption status and symptoms during follow-up

Symptoms with milk consumption	Total	Milk consumption status: Unlimited	≥1 Serving per day	<1 Serving but some uncooked	Trace or baked only	None
Totals	32	6 (19%)	10 (31%)	9 (28%)	2 (6%)	5 (16%)
No symptoms	8 (25%)	3 (50%)	4 (40%)	1 (11%)	0 (0%)	NA
Frequent/predictable symptoms	12 (38%)	2 (33%)	2 (20%)	6 (67%)	2 (100%)	
Frequent/predictable, more than oral/pharyngeal	9 (28%)	2 (33%)	1 (10%)	4 (44%)	2 (100%)	
Sporadic symptoms	7 (22%)	1 (17%)	4 (40%)	2 (22%)	0 (0%)	
Sporadic, more than oral/pharyngeal	5 (16%)	0 (0%)	3 (30%)	2 (22%)	0 (0%)	
Not consuming milk	5 (16%)			NA		
Anaphylaxis at least once	6 (19%)	0 (0%)	4 (40%)	1 (11%)	1 (50%)	
Used epinephrine at least once	3 (9%)	0 (0%)	0 (0%)	1 (11%)	2 (100%)	

NA, Not applicable.

have found here. Therefore it is clear that more research into the long-term outcomes of OIT for food allergy is necessary and, most importantly, that OIT for food allergy is far from ready for clinical practice.

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