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Long-Term Follow-up of Oral Immunotherapy for Cow's Milk Allergy

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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 18/21 (86%) subjects were initially partially or completely desensitized to cow's milk (CM) with OIT, this dropped to 14/20 (70%) after 4 ½ years(3). Other studies have generally reported limited or no follow-up data. Here, we report follow-up of two studies of CM OIT after up to five years in order to evaluate ongoing CM consumption, symptoms, and potential predictors of long-term outcomes.

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Both previously published studies enrolled CM allergic children 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 grams CM protein lasted approximately eight weeks, followed by three 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 (SLIT) in 30 children (6). Dose escalation, lasting approximately 30 weeks, started with a short course of SLIT, followed by OIT to a goal dose of 1 or 2 grams. After three months of maintenance, an OFC was administered and the dose was potentially adjusted to a maximum of 4 grams. Maintenance totaled 15 months and was followed by another OFC. For subjects who passed that challenge, tolerance challenges were done at one and six 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 standardized questionnaire and/or clinical follow-up for all 32 subjects treated with active OIT at Johns Hopkins, and 26/32 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 one occasion. In order to assess predictors of outcome, subjects were split into two groups: those who consumed at least one 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 Fischer's exact test for dichotomous variables or Wilcoxon rank sums 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 three who withdrew during active treatment). Subjects were followed-up after a median of 4.5 years (range 1.3-5.3) and 3.2 years (range 2.6-3.4) from 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 1 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 one subject reporting using epinephrine at least twice per month for reactions to CM. (**Supplemental Table 1** describes types of symptoms with CM consumption).

Baseline and follow-up characteristics and their relationship to long-term outcomes are shown in **Table 2**. Of note, several characteristics were associated with long-term outcome, including baseline CM-IgE, gastrointestinal and lower respiratory symptoms with OIT, food challenge threshold at three months of maintenance, amount of CM recommended for daily intake and SPT wheal size in follow-up. No subject with baseline CM IgE over 75 kU/L (n=8), respiratory symptoms with more than 2% of doses (n=8), or who had a post-treatment food-challenge threshold of less than 4 grams (n=7) was consuming at least one serving of milk in follow-up without symptoms. In addition, 7 (88%) of those with baseline CM IgE over 75 kU/L either had anaphylaxis or consumed no more than trace or baked milk in

follow-up. (**Supplemental Tables 2-3 and Figures 1-3**) 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 cut-offs would necessarily apply to other studies.

This report has several important limitations. First, we do not have follow-up serology or skin prick testing on most subjects with the worst outcome – those who were avoiding milk – which may 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 may 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, while we hope that newer OIT protocols that include higher doses and/or longer periods of maintenance will lead to better results, it is clear from these preliminary data that long-term outcomes following 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, where aversion among formerly allergic children is common(7), results may be far worse than we have found here. It is therefore 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Capsule Summary

Three to five years after oral immunotherapy for cow's milk allergy, less than a third of subjects in this study are consuming at least one serving of cow's milk per day without symptoms.

Table 1

Characteristics by long-term outcome category

	Characteristic	Total	Consumption/symptom group		
			>=1 serving and no more than oral/pharyngeal symptoms, n=9	Symptoms or less than one serving, n=23	P value
Baseline characteristics	Baseline Age, median (range) years	9 (6-16)	8 (6-16)	10 (6-16)	0.73
	Sex, n (%) male	21 (66%)	6 (67%)	15 (65%)	0.64
	Presence of Eczema, n(%)	18 (56%)	6 (67%)	12 (52%)	0.37
	Study assignment, n (%) study 1	16 (50%)	5 (56%)	11 (48%)	0.50
	Baseline CM IgE, median (range), kUa/L	31 (1-314)	25 (1-73)	41 (5-314)	0.04
	Baseline SPT wheal size, median (range) mm	9 (5-21.5)	8.5 (5-11.5)	9.5 (6-21.5)	0.14
	Baseline threshold, median (range) mg milk protein	40 (40-1350)	40 (40-1350)	40 (40-140)	0.79
Symptoms with initial treatment	Median percentage of doses with symptom (range)				
	Gastrointestinal	1.9% (0-44%)	0.6% (0-44%)	2.3% (0-16%)	0.03
	Lower respiratory	0.6% (0-7.7%)	0% (0-1.8%)	1.0% (0-7.7%)	0.04
	Skin	0.4% (0-47%)	0% (0-0.7%)	0.4% (0-47%)	0.06
	Median percentage of doses requiring treatment (range)				
	Anti-histamines	3.3% (0-59%)	2.2% (0-20%)	4.5% (0-59%)	0.13
	Beta-agonist	0.3% (0-8.3%)	0% (0-0.9%)	0.6% (0-8.3%)	0.03
Early outcomes	CM IgE at 3 months maintenance *, median (range) kUa/L	26 (1-398)	13 (1-67)	27 (2-398)	0.16
	SPT wheal size at 3 month maintenance, median (range) mm *	7 (0-15.5)	5 (0-15.5)	7.5 (2-14)	0.19
	Threshold at 3 months maintenance	6140 (0-8140)	8140 (4140-8140)	4140 (0-8140)	0.006
	No symptoms at full challenge at 3 months, n(%)	8 (25%)	4 (44%)	4 (17%)	0.68
	Amount of milk protein that subject went home on **, median (range) grams	2 (0-8)	4 (1-8)	1.5 (0-8)	0.04
Later outcomes	Passed tolerance challenge? (study 2), n (%) †	5 (31%)	3 (75%)	2 (17%)	0.12
	Milk IgE in follow-up, median (range) kUa/L ††	4 (0.4-55)	4 (0.4-20)	5 (0.7-55)	0.19
	SPT wheal size in follow-up median (range) mm ††	4 (0-15.5)	0 (0-4.5)	6 (0-15.5)	0.02

	Characteristic	Total	Consumption/symptom group		
			>=1 serving and no more than oral/pharyngeal symptoms, n=9	Symptoms or less than one serving, n=23	P value
	Milk IgG4 in follow-up, median (range) ug/ml ^{††}	19 (8-68)	18 (8-38)	19 (10-68)	0.25

Statistically significant differences are bolded.

*
n=30

**
Home milk protein recommendations based on food challenge threshold and symptoms

[†]
n=16

^{††}
n=26

Table 2

Milk consumption status and symptoms during follow-up.

	Milk Consumption Status					
Symptoms with milk consumption	Total	Unlimited	At least 1 serving/day	Less than one serving, but some uncooked	Trace or baked only	None
Total	32	6 (19%)	10 (31%)	9 (28%)	2 (6%)	5 (16%)
No Symptoms	8 (25%)	3 (50%)	4 (40%)	1 (11%)	0 (0%)	N/A
Frequent/predict able symptoms	12 (38%)	2 (33%)	2 (20%)	6 (67%)	2 (100%)	
Frequent/predict able, 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%)	N/A				
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%)	

N/A: Not Applicable.