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Open Label Maintenance Following Milk Oral Immunotherapy (MOIT) for IgE Mediated Cow's Milk Allergy

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Capsule Summary

MOIT can be effective in desensitizing children with severe IgE-mediated CMA, with most tolerating markedly increased amounts of cow's milk protein over time and demonstrating changes in serologic markers.

Keywords

Cow's milk; food allergy; IgE; prognosis; desensitization; tolerance; oral immunotherapy

To the Editor

Cow's milk allergy (CMA) is a common disorder for which there is no effective treatment. Currently, the standard of care is strict food avoidance, although there have been several recent studies with encouraging results using oral and sublingual immunotherapy (OIT and SLIT) for the treatment of food allergy.^{1–8} One such study evaluated the safety and efficacy of OIT for CMA in a randomized, double-blind, placebo-controlled trial, and this report summarizes the subsequent, open label phase of this study.⁸

Participants who successfully completed the double-blind portion of the milk oral immunotherapy (MOIT) study were continued on measured dairy intake at home daily. The objectives of this phase were to determine, in children with severe IgE-mediated CMA: 1) the safety of continued milk intake after OIT, and 2) the efficacy in conferring tolerance to increasing amounts of cow's milk protein.

Only those who could tolerate > 2,540mg in their post-MOIT challenge were eligible for this institutional review board approved protocol. Initial home doses were based on the nature and frequency of symptoms experienced during MOIT, milk protein threshold determined in the

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post-MOIT oral food challenge (OFC), and severity of any reactions during that challenge. Gradual home dose escalations were determined by the investigators through ongoing reassessment. Daily home diaries documented the amount of milk protein taken, adverse symptoms, and treatment required. Participants then underwent follow-up OFC's with a cumulative dose of 16,000mg of milk protein, end point titration skin testing, and milk-specific serologic analyses.

Fifteen subjects aged 6–16 years were included with follow-up ranging from 3 to 17 months (see Table I). Initial milk doses ranged from 500 to 4,000mg (median 500). Fourteen participants were able to escalate daily doses by 2–32-fold (median 9-fold) with maximum doses ranging from 1,000 to 16,000mg (median 7,000).

After 13 to 75 weeks (median 17) of open label dosing, challenges were conducted on 13 participants, with the timing of challenges based on post-MOIT challenge outcome and success with home dosing. Six tolerated 16,000mg with no reaction and 7 reacted at 3,000 to 16,000mg. Of the 3 that reacted at 16,000mg, reactions included oral itch with abdominal pain, sneezing, and mild cough, respectively. One subject developed localized hives at 10,000mg and 2 experienced localized hives at 3,000mg. One required albuterol and diphenhydramine for cough, nausea and abdominal pain that developed at 6,000mg. Challenges were not conducted on two due to ongoing reactions with home dose escalations.

End point titration skin prick testing demonstrated decreasing reactivity over time ($p=0.0091$ from baseline). As previously reported, the baseline median end point was at the 1:50 dilution, while the post-MOIT median was 1:1. Ten subjects have had subsequent skin testing 8–15 months after MOIT. Seven had negative tests, 2 reacted at 1:5, and 1 at 1:1.

Median milk-specific IgE decreased as follows: baseline 29.9kUa/L (range 0.9–84.3), post-MOIT 26.7kUa/L (range 1–496), to 11.9kUa/L (range 0.6–58.5, $p=0.0355$ from baseline) over the 3 to 17 month follow-up period. Median milk-specific IgG4 increased as follows: baseline 3.9 μ g/ml (range 0.3–18.9), post-MOIT 23.1 μ g/ml (range 1.7–730); to 101.3 μ g/ml (range 1.3–908.3, $p=0.001$ from baseline) during the same period.

One subject's course deserves special note. This 8-year-old female had baseline studies as follows: milk-IgE 5.6kUa/L, IgG4 7.7 μ g/ml, skin test reactivity at 1:10, and reaction to 40mg during pre-MOIT OFC. She completed escalation and maintenance with minimal symptoms, tolerated the full 8,140mg post-MOIT OFC, successfully escalated home doses to 16,000mg, and had no reaction at the 16,000mg OFC after 4 months of home intake. During an acute gastroenteritis 3 months later, milk doses were withheld. Upon milk reintroduction, she developed intermittent oropharyngeal pruritis along with chronic nausea and abdominal pain suggestive of eosinophilic esophagitis that only resolved with strict milk avoidance. At that time her milk-IgE was 1.1kUa/L, IgG4 was 908.3 μ g/ml, and skin test was negative.

Three subjects who tolerated $\leq 2,540$ mg at the post-MOIT OFC were not eligible for this protocol but did maintain milk dosing and followed off protocol. The first developed itch, abdominal pain and wheezing to 1,340mg during the post-MOIT OFC and is currently tolerating 500 to 1,000mg daily. The second developed oral itch and sneeze at 2,540mg during the post-MOIT OFC and is currently tolerating 8,000 to 16,000mg daily with intermittent localized symptoms. The third developed localized hives and wheeze at 2,540mg during the post-MOIT OFC. She is taking 2,500 to 5,000mg daily and after 11 months of intake, developed localized hives and cough at 8,000mg during a subsequent OFC.

In the 2,465 total home doses recorded (median 157 per child, range 95–520), 419 local reactions were reported (17% of doses, median 30, range 2–109). Other reactions included 90 gastrointestinal (3.7%, median 1, range 0–40); 21 respiratory (0.9%, median 0, range 0–8); 20

cutaneous (0.8%, median 0, range 0–7); and 143 multi-system (5.8%, median 1.5, range 0–76). Treatment included diphenhydramine for 93 (3.8%) reactions, albuterol for 12 (0.5%), prednisone for 3 (0.1%), and epinephrine for 6 (0.2%; 4 subjects).

In the 12 subjects that kept complete home diaries, 49% of doses elicited some form of reaction (per subject range 2.4%–96.4%) in the first 3 months after MOIT compared to 23% (range 0%–79.8%) in the subsequent 3 months. Specifically, local reactions decreased from 31.5% (range 1.2–94%) to 11.2% (range 0–57.1%) and multi-system 11% (range 0–67.9%) to 4.8% (range 0–30.7%), while all other reactions remained relatively stable: respiratory 1.4% (range 0–10.8%) to 0.9% (range 0–6.4%), cutaneous 0.8% (range 0–7.1%) to 1.1% (range 0–4.8%) and gastrointestinal 4.2% (range 0–24.1%) to 5.1% (range 0–20.2%).

In summary, in highly milk allergic children, MOIT followed by careful introduction of measured cow's milk protein led to the ability to tolerate 1,000 to 16,000mg of milk daily with about 33% tolerating at least 16,000mg. Thresholds continued to improve over time; however, it is not clear whether this tolerance would be maintained without regular intake. Over the follow up period, milk-specific IgE decreased while IgG4 increased and skin test reactivity disappeared in most. The three off protocol subjects were still the most reactive after MOIT, but were able to substantially increase home doses over time.

Adverse reactions were common and largely unpredictable, with several systemic reactions occurring at previously tolerated doses, often in the setting of exercise or viral illness. However, the overall rate of reactions decreased over time, even as milk doses increased. In one subject, apparent clinical reactivity to milk recurred, primarily manifesting with gastrointestinal symptoms suggesting possible eosinophilic disease.

We conclude that MOIT can be effective in desensitizing children with severe IgE-mediated CMA. Nearly all participants developed markedly increased tolerance to cow's milk protein over time. However, before this treatment can be applied more widely, further studies are needed to understand the risks, mechanisms of desensitization, induction of tolerance, and markers of successful treatment.

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Milk threshold (mg)			End-point titration SPT (dilution)			CM IgE (kUa/L)			CM IgG4 (µg/mL)		
line	Post-MOIT	Follow up (mo)**	Baseline	Post-MOIT	Follow up (mo)**	Baseline	Post-MOIT	Follow up (mo)**	Baseline	Post-MOIT	Follow up (mo)**
8140*		16000 (5)*	1:100	Negative		9.8	11.4	6.5 (14)	4.8	68.1	601.5 (14)
4140		16000 (9)*	1:100	1:5	Negative (15)	31.4	496	58.5 (15)	5	24.2	618.2 (15)
4140		10000 (12)	1:100	1:100	1:1 (10)	42	27	7.7 (17)	3.9	24.4	61.4 (17)
8140		16000 (6)	1:5	Negative	Negative (12)	0.9	1	0.6 (12)	1.5	5.1	11.3 (12)
8140*		16000 (4)*	1:10	Negative	Negative (10)	5.6	2.3	1.1 (10)	7.7	730	908.3 (10)
8140*		16000 (3)*	1:50	1:1	Negative (12)	29.9	36.9	6.1 (12)	2.6	16.1	404.1 (12)
6140		16000 (4)	1:5	1:1		20.4	24.1	20.3 (4)	3	30.1	143.1 (4)
6140		16000 (17)*	1:100	1:1	Negative (14)	30.8	31.1	14.2 (15)	2.3	23.1	69.1 (15)
8140		16000 (3)	1:50	1:5	Negative (9)	13.5	10.3	10.4 (9)	1.6	4.8	80.6 (9)
4140			1:10	1:5		84.3	66.2	30.9 (5)	4.6	33.7	121.9 (5)
8140			1:50	1:100	1:5 (8)	28.4	26.3	13.4 (8)	0.3	1.7	1.3 (8)
8140*		16000 (3)*	1:100	1:1		8.2	7.5	5.6 (3)	2.4	7.4	13.7 (3)
3140		3000 (3)	1:100	1:5		34.8	40	43 (3)	5	17.2	66.5 (3)
4140		6000 (5)	1:10	Negative	Negative (14)	57.5	74.4	41.8 (5)	18.9	261	337.9 (5)
8140		3000 (9)	1:1	1:1	1:5 (9)	53.5	26.7		8.3	10.6	
6140		10000 (3)	1:50	1:1	Negative (11)	29.9	26.7	11.9 (9.5)	3.9	23.1	101.3 (9.5)
		0.001			0.0091			0.0355			0.001
		0.0034			0.0688			0.0035			0.0012
1340			1:100	1:1		119.6	59.7		22.8	133.5	
2540		8000 (11)	1:50	1:10		314	514		5.3	61.7	
2540			1:10	1:10		4.9	6.8	2.1 (13)	1.2	12	68.4 (13)
2540			1:50	1:10		119.6	59.7		5.3	61.7	

*** If multiple data points were recorded, the most recent value was used

*** Wilcoxon Sign Rank Test