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Rapid oral desensitization in combination with omalizumab therapy in patients with cow's milk allergy

Kari C. Nadeau, MD, PhD[b], **Lynda C. Schneider, MD**[a], **Lisa Hoyte, NP**[b], **Irene Borras, NP**[a], and **Dale T. Umetsu, MD, PhD**[a]

[a]Division of Immunology, Children's Hospital, Harvard Medical School, Boston, Mass

[b]the Division of Immunology and Allergy, Department of Pediatrics, Stanford University, Calif.

To the Editor:

We conducted a pilot phase I study in 11 children (age, 7-17 years) with cow's milk allergy by using omalizumab (anti-IgE mAb; Xolair; Genentech, South San Francisco, Calif) in combination with relatively rapid oral milk desensitization. We hypothesized that oral desensitization might occur rapidly and with few side effects when performed with omalizumab. Our primary objectives were to examine the safety of this approach and to determine whether subjects could be dosed up to 2000 mg milk within 7 to 11 weeks of initiating the desensitization.

Eleven patients with a history of IgE-mediated milk allergy were enrolled in the study at 2 sites—Children's Hospital Boston and Stanford University—under institutional review board and US Food and Drug Administration approval. All subjects had histories of acute clinical reactions to milk, including immediate reactions (urticaria, vomiting, and/or anaphylaxis) after ingestion of milk, as well as elevated milk-specific IgE (median, 50 kilounits of antibody (kUA)/L; range, 41.6-342 kUA/L; Table I). At entry, the median wheal/flare skin prick test to milk was 20/50 mm (wheal/erythema diameter; range, 11-45/20-52 mm), and the median total serum IgE was 349 kU/L (range, 148-2593 kU/L). The median age was 8 years (range, 7-17 years). Seven subjects had a diagnosis of asthma and/or eczema. For children with IgE levels <700 kU/L, omalizumab was dosed according to the package insert, and for the 3 children with serum IgE levels >700 kU/L, the dose was 225 to 300 mg (approximately 0.016 mg/kg/IgE [U/ mL]) every 2 to 4 weeks. During the course of the study, subjects were asked to exclude all dairy products from their diets except what was given as the study milk dose.

Nine weeks after the start of omalizumab treatment, oral cow's milk desensitization was performed in 2 phases. Rush oral desensitization occurred on the first day of desensitization, starting with 0.1 mg of milk powder (dried nonfat powdered cow's milk, Carnation Instant Milk; Nestlé, San Francisco, Calif), with doses every 30 minutes to a maximum dose of 1000 mg (cumulative dose, 1992 mg). One subject (subject 7; Table I) voluntarily discontinued the study because of abdominal migraines; eosinophilic esophagitis and other allergic disorders were ruled out. Nine of the 10 remaining subjects reached the 1000-mg dose on the first day of desensitization. However, 1 subject, subject 5 (Table I), after

knadeau@stanford.edu, dale.umetsu@childrens.harvard.edu.

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administration of the 1000-mg dose, received epinephrine for nasal obstruction and generalized urticaria refractory to diphenhydramine and cetirizine. Subject 8 reacted at the 7-mg dose on the first day. Desensitization with daily doses of milk continued in the 10 subjects, with weekly increases in the dose of milk over the next 7 to 11 weeks (all dose increases were given in the clinical research unit, and if the dose was tolerated, the dose was then given daily at home). During the study, subjects were asked to take the study milk dose on a full stomach and to half the study milk dose during a viral infection. Nine of the 10 patients reached the maximum daily dose of 2000 mg milk (the primary end point of the study); the subject who received epinephrine during the rush phase of desensitization achieved a daily dose of 1200 mg when the omalizumab was stopped (end of the weekly dose escalation phase, week 16).

Omalizumab treatment was then discontinued at week 16, whereas daily oral milk was continued at home. A double-blind, placebo-controlled food challenge (DBPCFC) was performed 8 weeks later (week 24 of the study). The DBPCFC consisted of 5 doses (milk or placebo, eg, rice or soy beverage) administered orally every 15 minutes: 500 mg, 750 mg, 1000 mg, 2000 mg, and 3000 mg (cumulative dose, 7250 mg, equivalent to 220 mL milk). Allergic reactions occurring during the protocol were scored by using the system developed by Bock et al.[1] All 9 patients who had reached a daily dose of 2000 mg passed the DBPCFC and an open challenge (for subjects taking their oral food challenge on the same day of the DBPCFC [n = 4], 4000 mg was given as the open challenge; for subjects taking their open challenge on the day after the DBPCFC [n = 5], 8000 mg was given). All 9 patients continued with daily milk ingestion >8000 mg/d, which included different types of milk products.

In terms of overall safety, the mean frequency for total reactions reported by week 24 was 1.6% (32 reactions of 2199 doses total for all 11 subjects; Table II). All patients experienced some adverse events, though most reactions were defined as mild[1] (1%) and needed no treatment. There were moderate reactions (0.3%), and these included abdominal pain and vomiting, which responded within 1 hour to oral antihistamine dosing. Severe reactions (0.1%) included swelling of the tongue in 1 subject during the initial rush desensitization day, which responded to oral antihistamines. Another subject developed rhinitis and urticaria after the 1000-mg dose during the rush desensitization and responded to epinephrine. The most common types of reactions were local (mostly pruritus or urticaria) and/ or gastrointestinal (eg, abdominal pain), occurring with a frequency of 1%. No reactions occurred that involved the cardiovascular system or that failed to respond rapidly to treatment. There were 2 other subjects who were given epinephrine at home by their guardians during the maintenance phase of dosing. One received epinephrine for a moderate reaction that was manifested by upper lip swelling and urticaria (7.5 cm × 5cm) on the left upper leg; the second received epinephrine for urticaria (2.5 cm × 5 cm) on the right upper arm. In addition, this subject had wheezing, which began before the milk ingestion that day, and which most likely was a result of a viral infection. Overall, the reaction rate in our study was relatively low given the rapidity of the desensitization, although the rate of epinephrine use was similar to that in previous desensitization studies. All subjects tolerated omalizumab treatment with no signs of allergic reactions.

Previous studies of slow, deliberate oral milk desensitization in patients with cow's milk allergy showed that desensitization can increase the amount of milk tolerated by many of the treated subjects.[2-6] We now show that milk desensitization can be performed relatively rapidly with minimal hospitalization time when combined with omalizumab treatment. The limitations of our study include the small sample size, the lack of a placebo group, and lack of a baseline oral food challenge. In addition, it is possible that our desensitization protocol with omalizumab might be further optimized by limiting the number of milk doses during

the rush phase; by extending the dose escalation phase over a longer period, beyond the 7 to 11 weeks used in our current protocol; and by performing the DBPCFC 12 or more weeks after discontinuation of omalizumab.

In summary, we demonstrated that omalizumab treatment combined with oral milk desensitization in children with clinical reactions to cow's milk permitted rapid milk dose escalation in the majority of subjects. This study is the first to use omalizumab in combination with oral desensitization and demonstrates a potential value of this approach for the treatment of food allergy, a major public health problem,[7-9] although it must be first confirmed by future phase II and III trials. Nine of the 11 patients achieved the primary objective, tolerating desensitization to a dose of 2000 mg/d within a period of 7 to 11 weeks. Moreover, 9 of the 10 patients who completed the study passed a DBPCFC and an open challenge of milk without symptoms. Importantly, the 9 patients, after passing the DBPCFC, began tolerating almost normal amounts of milk in their diet (≥240 mL, equivalent to ≥8000 mg/d). The tenth patient is tolerating 4000 mg/d.

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REFERENCES

1. Bock SA, Sampson HA, Atkins FM, Zeiger RS, Lehrer S, Sachs M, et al. Double-blind, placebo-controlled food challenge (DBPCFC) as an office procedure: a manual. J Allergy Clin Immunol. 1988; 82:986–97. [PubMed: 3060514]
2. Skripak JM, Nash SD, Rowley H, Brereton NH, Oh S, Hamilton RG, et al. A randomized, double-blind, placebo-controlled study of milk oral immunotherapy for cow's milk allergy. J Allergy Clin Immunol. 2008; 122:1154–60. [PubMed: 18951617]
3. Meglio P, Bartone E, Plantamura M, Arabito E, Giampietro PG. A protocol for oral desensitization in children with IgE-mediated cow's milk allergy. Allergy. 2004; 59:980–7. [PubMed: 15291907]
4. Longo G, Barbi E, Berti I, Meneghetti R, Pittalis A, Ronfani L, et al. Specific oral tolerance induction in children with very severe cow's milk-induced reactions. J Allergy Clin Immunol. 2008; 121:343–7. [PubMed: 18158176]
5. Staden U, Blumchen K, Blankenstein N, Dannenberg N, Ulbricht H, Dobberstein K, et al. Rush oral immunotherapy in children with persistent cow's milk allergy. J Allergy Clin Immunol. 2008; 122:418–9. [PubMed: 18602681]
6. Pajno GB, Caminiti L, Ruggeri P, De Luca R, Vita D, La Rosa M, et al. Oral immunotherapy for cow's milk allergy with a weekly up-dosing regimen: a randomized single-blind controlled study. Ann Allergy Asthma Immunol. 2010; 105:376–81. [PubMed: 21055664]
7. Boyce JA, Assa'ad A, Burks AW, Jones SM, Sampson HA, Wood RA, et al. Guidelines for the diagnosis and management of food allergy in the United States: summary of the NIAID-sponsored Expert Panel report. J Allergy Clin Immunol. 2010; 126:1105–18. [PubMed: 21134568]
8. Branum AM, Lukacs SL. Food allergy among children in the United States. Pediatrics. 2009; 124:1549–55. [PubMed: 19917585]
9. Sicherer SH, Sampson HA. Food allergy. J Allergy Clin Immunol. 2010; 125:S116–25. [PubMed: 20042231]

TABLE I

Characteristics of enrolled subjects

Subject no.	Age (y)	Sex	Total IgE (kU/L)	Milk-specific IgE (kUA/L)	Milk skin test wheal (mm)/ erythema (mm)	Organ systems involved simultaneously in last historical reaction to milk (subjects had clinical reactivity to both cooked and uncooked milk products)*	Omalizumab dose and frequency	Total doses of omalizumab
1	11	M	500	42	25/50	Urticaria, angioedema, vomiting	225 mg every 2 wk	9
2	8	M	342	50	45/50	Wheezing, urticaria	225 mg every 4 wk	5
3	8	M	148	73	20/45	Urticaria, wheezing	150 mg every 4 wk	5
4	10	F	900	42	11/30	Vomiting, congestion	225 mg every 4 wk	5
5	8	M	239	50	46/52	Vomiting, generalized urticaria	225 every 2 wk	9
6	7	F	297	44	16/49	Wheezing, vomiting, urticaria	150 mg every 4 wk	5
7	12	M	199	68	15/50	Wheezing, urticaria, allergic rhinitis	150 mg every 4 wk	4
8	16	M	349	56	20/20	Wheezing, urticaria, abdominal complaints	225 mg every 2 wk	12
9	17	M	364	43	16/58	Wheezing, urticaria, conjunctivitis	300 mg every 2 wk	9
10	8	F	2016	268	24/46	Wheezing, vomiting, urticaria, conjunctivitis	300 mg every 2 wk	8
11	7	F	2593	342	16/22	Wheezing, urticaria, conjunctivitis	300mg every 2 wk	9
Median	8		349	50	20/50	Not applicable	Not applicable	8

Entry criteria: children 4 to 18 years of age with cow's milk–specific IgE >25 kUA/L, total IgE <2500 kU/L; with significant clinical history of IgE mediated cow's milk allergy, but without history of intubation, severe asthma, or previous immunotherapy or biologic therapy, and without a medical diagnosis of non–IgE-mediated eosinophilic disease.

F, Female; *M*, male.

*None of the subjects had a diagnosis of eosinophilic esophagitis at screening and during the course of the study.

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TABLE II

Overall safety data

Milk doses per child, mean (range)		**209 (36-334)**
Total doses		**2301**
Symptom/treatment	**No. (%) of total doses**	**No. of reactions per child, mean (range)**
Total reactions	41 (1.8)	3.7 (1-7)
Grade 1 (mild) symptoms	29 (1.3)	2.6 (1-5)
On rush desensitization day	14	
During weekly dose escalation phase	10	
During maintenance dosing	5	
Grade 2 (moderate) symptoms	8 (0.3)	0.7 (0-2)
On rush desensitization day	5	
During weekly dose escalation phase	1	
During maintenance dosing	2	
Grade 3 (severe) symptoms	4 (0.1)	0.3 (0-1)
On rush desensitization day	2	
During weekly dose escalation phase	1	
During maintenance dosing	1	

Total number of subjects = 11.

Grading of reactions was defined by Bock et al.[1] Grade 1 (mild) reactions did not require medications, whereas for any grade 2 (moderate) reaction, antihistamine was administered, and, in 2 cases, epinephrine was administered (by parent). Grade 3 (severe) reactions included 1 reaction during rush desensitization with severe rhinitis and moderate urticaria, treated with epinephrine (by physician); 1 reaction of generalized urticaria and severe rhinitis during the DBPCFC treated with antihistamines; 1 reaction of tongue swelling during the rush desensitization responding to oral antihistamines; and a reaction of severe abdominal pain during the home maintenance dosing, resolving with antihistamines. Reactions occurring at home were self-reported in diaries up to 24 to 28 weeks and were reported by phone or electronic mail throughout the study. Ten subjects have completed all 52 weeks of the study; reporting is complete for all subjects up to 36 weeks of the study.