Safety, Tolerability, and Feasibility of the Milk Ladder for Reintroduction of Cow's Milk in Infants With IgE-Mediated Cow's Milk Allergy

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J Investig Allergol Clin Immunol 2024; Vol. 34(6)
doi: 10.18176/jiaci.1017

Key words: Milk Ladder. Cow's milk allergy. Food allergy. Early intervention. Safety.

Palabras clave: Escalera de la Leche. Alergia a la leche de vaca. Alergia a los alimentos. Intervención temprana. Seguridad.

Immunoglobulin E (IgE)–mediated cow's milk protein allergy (CMPA) is a common condition that progresses favorably [1]. However, CMPA can continue into adulthood. Reports on anaphylaxis have shown milk to be the culprit allergen in severe anaphylaxis [2-3]. Interestingly, data from death registries show that milk-related near fatalities and fatalities have increased compared to those caused by peanuts and tree nuts [4,5].

Although the elimination diet is the cornerstone of CMPA management, oral immunotherapy is now offered in some centers [6]. Other forms of dietary advancement therapy include the milk ladder. The milk ladder is a stepwise process consisting of the systematic titration of milk-containing meals. The initial steps of the ladder involve foods that have been more extensively cooked in a cereal matrix. The ladder serves as a protocol for reintroducing food and progresses by introducing meals requiring shorter cooking times and terminates with liquid milk consumption [7,8].

Our study was conducted to evaluate the feasibility of the milk ladder in IgE-mediated CMPA (NCT03466931). The methods and the recipes used have been described elsewhere [9]. In this publication, we report the safety results. Exhaustive safety monitoring was carried out throughout the study by an ad hoc external safety committee. Reactions were graded using the ordinal Food Allergy Severity Score [10].

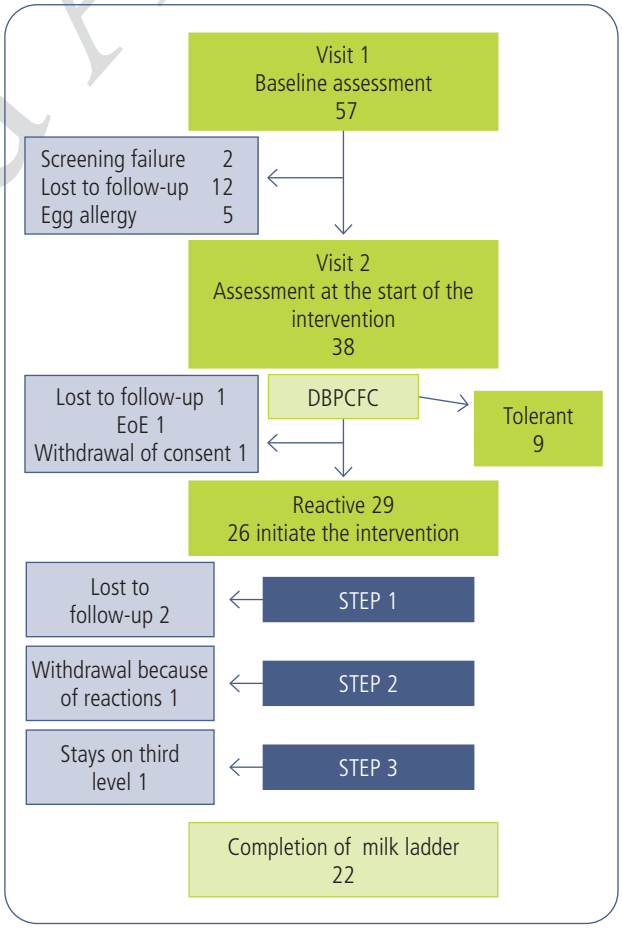

Figure. Patient flowchart showing how patients progressed throughout the study. DBPCFC indicates double-blind placebo-controlled food challenge.

A total of 57 patients were assessed at baseline. Of these, 38 were evaluated at the second visit. The Figure shows the patient participation flowchart; Table s1 describes the baseline characteristics. While the initial sample size estimate was higher, only 3 centers of the initial 5 could recruit patients owing to COVID-19, which also caused significant loss to follow-up (12 out of the 57). All 38 patients underwent double-blind placebo-controlled food challenge, which yielded positive results in 29. Three children did not initiate the intervention (1 was diagnosed with eosinophilic esophagitis, 1 withdrew consent, and 1 was lost to follow-up), leaving a total of 26 patients who started the milk ladder. Two patients abandoned the study at step 1, although both tolerated the foods of that step. Overall, 22 patients successfully completed the intervention and were able to tolerate milk in any form (22/29 [76%]). One patient did not finish owing to reactions.

A total of 220 step-up oral challenges were performed at the participating centers. Of these, 30 elicited a reaction (13.6%). Four additional reactions occurred during home dosing. All the reactions occurred in 8 patients (8/22 [36.4%]). The remainder, 63.6%, did not experience any reaction during hospital up-dosing or during home dosing (Table s2). Out of the 8 patients who presented reactions, 7 were able to progress across the ladder and now currently tolerate milk. One patient had only local oral reactions (grade 1), while the rest presented at least 1 systemic reaction. There were 8 grade 1 reactions (8/34 [23.5%]), 6 grade 2 reactions (6/34 [17.6%]), and 20 grade 4 reactions (20/34 [58.8%]). Five reactions in 4 patients required adrenaline, and 12 reactions in 5 patients required inhaled salbutamol. Of note, 1 patient (03010) experienced several reactions in step 2 that were related to the presence of partially cooked egg in the pancake used in step 2. The child had previously tolerated hard-boiled egg but had never consumed raw or soft-boiled egg. He tolerated the subsequent steps by avoiding egg.

Four reactions in 3 patients occurred at home to foods that had previously been tolerated. Two of the reactions were grade 1 and resolved without treatment, 1 was grade 2 (erythema and pruritus) and was controlled with oral antihistamine and a corticosteroid, and the third was grade 4 (only cough) and was controlled with inhaled salbutamol. Patient 03010 had an additional grade 4 reaction after consuming a pastry containing milk (not included in the study). None of the other patients experienced reactions at home. None of the patients developed persistent gastrointestinal symptoms or were diagnosed with EoE during or after finishing the milk ladder. Table 6s describes the symptoms of each reaction in detail.

The overarching goal of this study was to evaluate the effect of the milk ladder on the development of tolerance in IgE-mediated CMPA. The recipes were well-received by the families, who found them easy to follow. The participants adhered to the protocols, with 1 exception, namely, a patient who missed doses at home.

The safety of ladder-based protocols gives cause for concern, since limited data are available and safety data reports are not standardized across studies. In our study, 36.4% of the patients had reactions, most of which were grade 4 (severe), as opposed to previous reports, where reactions were mostly mild or moderate, with no anaphylaxis [11,12]. The respiratory symptoms recorded were mostly cough (18/20), with wheezing in one patient and mild laryngeal edema in another. Also concerning regarding the safety of the milk ladder are the practicalities of the intervention. These include food-specific factors, such as allergen quantity (as compared to oral immunotherapy, where the dose is very precise), heating time, and even distribution of the allergen throughout the food being prepared [13]. However, in our study, most of the reactions happened in the hospital, and most participants did not have any reactions at home once tolerance was confirmed at the hospital. It is important to confirm tolerance to the ingredients used in the recipes in order to avoid reactions unrelated to the food under treatment (as was the case of the patient who did not tolerate soft-boiled egg in our study).

According to our experience, the milk ladder seems safe for most patients. However, clinicians should be aware that some patients may experience severe reactions. Fortunately, most reactions (30/34 [88.2%]) happened in the hospital during the step-up dosing, and those that appeared at home with previously tolerated doses were milder and easy to control by the families. We found that the patients who experienced reactions during the milk ladder had significantly higher levels of sIgE to whole milk and its components (Table 5s), although the severity in the initial milk reactions was similar. More studies with larger samples are needed to identify this severe phenotype. As some patients may experience severe reactions, it is of the utmost importance to confirm tolerance of each step-up dose in a clinical setting under the supervision of a trained allergist. Families must also be well-informed, trained, and committed for the duration of the intervention.

Funding

This work was supported by the ARADyAL Research Network (RD16/0006/0009) and project PI16/00819 funded by the Instituto de Salud Carlos III (ISCIII) of Ministerio de Ciencia e Innovación of the Spanish Government and cofunded by FEDER (European Regional Development Fund).

NPFS holds a contract from the "Río Hortega" program (CM21/00080) of the ISCIII and grants cofunded by the European Social Fund.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

1. Schoemaker AA, Sprikkelman AB, Grimshaw KE, Roberts G, Grabenhenrich L, Rosenfeld L, et al. Incidence and natural history of challenge-proven cow's milk allergy in European children – EuroPrevall birth cohort. Allergy. 2015;70:963-72.
2. Turner PJ, Campbell DE, Motosue MS, Campbell RL. Global Trends in Anaphylaxis Epidemiology and Clinical Implications. J Allergy Clin Immunol Pract. 2020;8(4):1169-76.
3. Tejedor-Alonso MA, Moro-Moro M, Mosquera González M, Rodriguez-Alvarez M, Pérez Fernández E, Latasa Zamalloa P, et al. Increased incidence of admissions for anaphylaxis in Spain 1998–2011. Allergy. 2015;70:8803.

4. Baseggio Conrado A, Ierodiakonou D, Gowland MH, Boyle RJ, Turner PJ. Food anaphylaxis in the United Kingdom: analysis of national data, 1998-2018. BMJ. 2021 Feb 17;372:n251. Erratum in: BMJ. 2021;19:372:n733.
5. Levy MB, Goldberg MR, Nachshon L, Tabachnik E, Katz Y. Lessons from cases of mortality due to food allergy in Israel: cow's milk protein should be considered a potentially fatal allergen. Isr Med Assoc J. 2012;14:29-33.
6. Pajno GB, Fernandez-Rivas M, Arasi S, Roberts G, Akdis CA, Alvaro-Lozano M, et al. EAACI Guidelines on allergen immunotherapy: IgE-mediated food allergy. Allergy. 2018;73:799-815.
7. Venter C, Brown T, Shah N, Walsh J, Fox AT. Diagnosis and management of non-IgE-mediated cow's milk allergy in infancy - a UK primary care practical guide. Clin Trans Allergy. 2013;3:23.
8. Venter C, Meyer R, Ebisawa M, Athanasopoulou P, Mack DP. Food allergen ladders: A need for standardization. Pediatr Allergy Immunol. 2022;33:e13714
9. Cerecedo I, López-Picado A, Hernández-Núñez MG, Rubio-Herrera MA, de la Hoz B, Infante S, et al. Milk Ladder for Cow's Milk Reintroduction in infants with IgE-mediated Cow's Milk Allergy: version adapted to the Spanish population. J Investig Allergol Clin Immunol. 2024;34(1):51-3.
10. Fernández-Rivas M, Gómez García I, Gonzalo-Fernández A, Fuentes Ferrer M, Dölle-Bierke S, Marco-Martín G, et al. Development and validation of the food allergy severity score. Allergy. 2022;77:1545-58.
11. Ball HB, Luyt D. Home-based cow's milk reintroduction using a milk ladder in children less than 3 years old with IgE-mediated cow's milk allergy. Clin Exp Allergy. 2019;49:911-20.
12. Cronin C, McGinley AM, Flores L, McKiernan A, Velasco R, O'B Hourihane J, et al. Primary care as a setting for introducing milk using the milk ladder in children with IgE-mediated cow's milk protein allergy. Clin Transl Allergy. 2023;13:e12286
13. Mack DP, Greenhawt M, Anagnostou A. Are There Hidden Dangers Associated With Milk and Egg Dietary Advancement Therapy? J Allergy Clin Immunol Pract. 2023;11:1056-62.

Manuscript received August 11, 2023; accepted for publication May 20, 2024.

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