Milk Ladder for Reintroduction of Cow’s Milk in Infants With IgE-Mediated Cow’s Milk Allergy: Version Adapted to the Spanish Population

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The prognosis of cows’ milk protein allergy (CMPA) is favorable, although CMPA may persist into adulthood and be severe [1]. Recent reports on anaphylaxis show that food-related anaphylaxis is increasingly frequent and that milk is increasingly identified as the culprit allergen in severe anaphylaxis [2-3] because of accidental exposure to cow’s milk, which is ubiquitous, particularly in prepacked foods containing milk. As a result, it is of the utmost importance to develop strategies for inducing tolerance in infants and children with CMPA.

Various observational studies have evaluated the success of early intervention protocols in food allergy [4-7]. However, it was not until the publication of the findings of the LEAP study [8] and other well-designed randomized trials that we had stronger clinical evidence that the early introduction of peanut and cooked egg might prevent the development of allergy to those foods [9].

In 2011, a NICE guideline on the diagnosis and management of food allergies was published [10-11]. Based on the evidence summarized in this document and on the available data on allergenicity and the effects of food processing, we designed an intervention to reintroduce milk and other dairy products into the diets of infants and children with mild-to-moderate non-IgE-mediated CMPA [12]. The “Milk Ladder” is a plan in which milk products are reintroduced gradually and in stages, starting with foods that contain only a small amount of well-cooked milk in a carbohydrate matrix and progressing towards uncooked dairy products and fresh milk [10].

We designed a study to evaluate the feasibility of adapting the “Milk Ladder” intervention to children with IgE-mediated CMPA. The study is registered at clinicaltrials.gov (NCT03466931). In the present article, we describe this adapted reintroduction plan and provide recipes to ensure appropriate implementation. Efficacy and safety data will be included in upcoming publications.

As a first step, a multidisciplinary team comprising allergists, endocrinologists, and nutritionists reviewed the original protocol and recipes of the Milk Ladder. Our endocrinologist and dietician evaluated the original recipes, some of which are seldom consumed in Spanish households. Therefore, they developed recipes adequate to each step that include the same amount of milk protein as in the original ones.

In parallel, they looked for commercial alternatives that were readily available in Spanish grocery stores. The recipes are balanced, with low or no refined sugar content and adequate fats and can be part of a healthy diet (Table 1, supplementary material).

The adapted version of the Milk Ladder (AVML) consists of the progressive introduction into the participants’ diet (4 different levels) of meals cooked with increasing amounts of cow’s milk. To ensure correct implementation and development, 7 medical visits were programmed throughout the study (Figure 1, supplementary material). The intervention plan is described below and in Table 2, supplementary material. The Table shows protein content and cooking temperature for each recipe. Safety assessments were performed throughout the study. Stop criteria (box 1, supplementary material) were established for study termination when required. Exhaustive safety monitoring was carried out at different time points by an External Safety Committee set up ad hoc for the study. The timing of the visits is shown below.

Visit 1 (baseline assessment): Demographic data and baseline characteristics were collected. An allergy history was taken, and SPT with commercial extract of cow’s milk and fractions (α-lactalbumin, β-lactoglobulin, and casein) was performed. Blood samples were collected for the measurement of total IgE, sIgE, and IgG4 (Thermo Fisher Scientific) and for the determination of linear IgE and IgG4 epitopes by peptide microarray–based immunoassays [13]. Quality of life was...
were scheduled to confirm the tolerance of each level of the AVML. Participants’ tolerance level if reactions occurred at home or the patient could not progress through all the steps of the AVML. Patients were then classified as tolerant (negative results) or reactive (positive results).

An early-in-life intervention such as the AVML proposed in our study, if shown to deliver effective and safe results, could modify the natural history of the disease towards early resolution and acquisition of tolerance in those who would normally outgrow their allergy on their own, or as a modified form of oral immunotherapy in those with persistent allergy. These outcomes are also expected to be associated with clear and positive benefits in the quality of life of patients and their families.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

Is Pru p 7 (Peamaclein) Sensitization a Predominant Cause of Cypress Pollen–Associated Peach Allergy in Spain?

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The Cupressaceae tree family includes about 160 different species of trees distributed in 5 genera worldwide [1]. Cupressus sempervirens is the most common species in the Mediterranean. The prevalence of sensitization to cypress pollen has increased in recent decades, ranging from 9% to 65% [1,2]. Madrid has one of the highest prevalence values in Spain [3,4], with a cumulative rate of 11,023 grains/m$^3$ in 2021, ie, twice that of 2020 (www.polenes.com).

Four Cupressus sempervirens allergens have been characterized (www.allergen.org), namely, Cup s 1 (pectate lyase), Cup s 2 (polygalacturonase), Cup s 3 (thaumatin-like protein), and Cup s 7 (gibberellin-regulated protein). High sequence identity and cross-reactivity between Cupressaceae pollen allergens have been demonstrated [5,6].

In 2013, peamaclein (Pru p 7) was identified as the first gibberellin-regulated protein and registered as a peach allergen (www.allergen.org). Peach allergy has been associated with cypress pollen allergy in certain areas, such as France [7,8] and Japan [9], owing to cross-reactivity between Cup a 7 and Pru p 7. In these areas, Pru p 7 was established as a major peach allergen.

In Spain, peach was the most frequent fruit eliciting allergy and Pru p 3 was reported to be the major peach allergen [10].

The aim of this study was to assess the frequency of sensitization to Pru p 7 (peamaclein) and Pru p 3 (nonspecific lipid transfer protein), as well as other peach allergens (Pru p 1 and Pru p 4), among cypress-allergic patients from Madrid (Spain), an area with high exposure to Cupressus tree pollen.

Sera were collected from 153 consecutive patients with Cupressus pollen allergy who had been treated at Fundación Jiménez Díaz Hospital, Madrid, Spain from September 2021 to June 2022. The methods are summarized in Supplementary Table I.

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