

SHORT COMMUNICATION

Nutrition

Tolerance development in cow's milk-allergic children receiving amino acid-based formula with synbiotics: 36-Months follow-up of a randomized controlled trial (PRESTO Study)

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Abstract

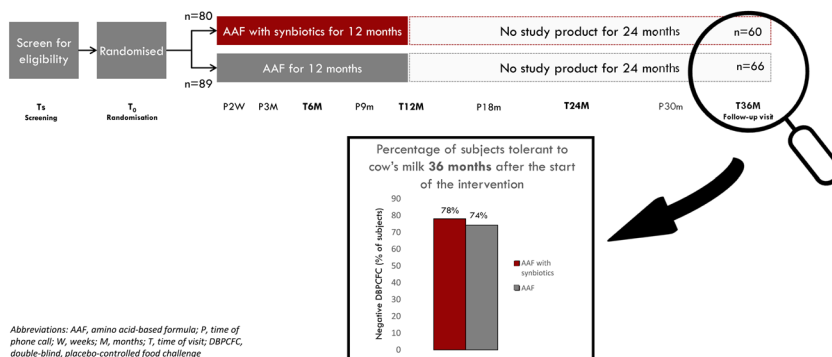
The objective of the present study is to assess the rates of acquired tolerance to cow's milk (CM) after 36 months in subjects who consumed amino acid-based formula with synbiotics (AAF-S) or amino acid-based formula without synbiotics (AAF) during a 1-year intervention period in early life as part of the PRESTO study (Netherlands Trial Register number NTR3725). Differences in CM tolerance development between groups were

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analysed using a logistic regression model. Results show that the proportion of subjects (mean $\pm$ SD) age, 3.8 ± 0.27 years) who developed CM tolerance after 36 months was similar in the group receiving AAF-S (47/60 [78%]) and in the group receiving AAF (49/66 [74%]) ($p=0.253$), that is, figures comparable to natural outgrowth of CM allergy. Our data suggest that the consumption of AAF and absence of exposure to CM peptides do not slow down CM tolerance acquisition.

Rates of cow's milk allergy outgrowth in children receiving amino acid-based formula



Tolerance Development in Cow's Milk-Allergic Children Receiving Amino Acid-based Formula with Synbiotics: 36-Months Follow-up of a Randomized Controlled Trial (PRESTO Study), Chatchatee et al., 2023

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KEYWORDS

cow's milk allergy, elemental formula, prebiotics, probiotics

1 | INTRODUCTION

Amino acid-based formulas (AAF) with a specific blend of prebiotics and probiotics (synbiotics) are used in the dietary management of cow's milk allergy (CMA). These formulas are proven to be well-tolerated and safe, are effective in symptom resolution and are associated with an improved gut microbiota composition and fewer (severe) infections.^{1–5} We recently published the results of the randomized double-blind controlled PRESTO study indicating that the development of tolerance to cow's milk (CM) was similar between infants with confirmed immunoglobulin E (IgE)-mediated CMA receiving an AAF with synbiotics and those receiving an AAF without synbiotics. The rates of acquired tolerance to CM were similar to rates observed in previous randomized dietary intervention studies in infants with IgE-mediated CMA receiving extensively hydrolysed formula and in line with natural outgrowth.⁶ The initial publication⁶ reported prevalence of CM tolerance development after 12 months (end of intervention period) and after 24 months (follow-up period). In the present paper, results on CM tolerance development after 36 months are reported.

What is Known

- The randomized double-blind controlled trial PRESTO showed that infants receiving amino acid-based formula (AAF) with or without synbiotics for 12 months in early life demonstrated effective symptom resolution.
- After 12 and 24 months, development of tolerance to cow's milk (CM) was in line with natural outgrowth.

What is New

- This study shows that, 36 months after the start of the intervention, a high proportion of children (about three-quarters) developed tolerance to CM.
- These data suggest that the consumption of AAF, with or without synbiotics, and the absence of exposure to CM peptides do not slow down CM tolerance acquisition.

2 | METHODS

2.1 | Study design

The PRESTO Study is a multicentre, prospective, double-blind, randomized controlled trial registered as NTR3725 in the Netherlands Trial Register. Details on the design of the study, subject recruitment, in- and exclusion criteria, conduct of the study and demographic characteristics of the study participants can be found in Chatchatee et al.⁶ Figure 1 illustrates the study design. In short, infants aged ≤ 13 months with confirmed IgE-mediated CMA were randomly assigned to receive either a hypoallergenic AAF (produced by Nutricia) containing synbiotics (AAF-S) or an AAF without synbiotics (AAF). The synbiotic blend comprised of a prebiotic mixture of chicory-derived neutral oligofructose and long-chain inulin (BENEO-Orafti SA; 9:1 ratio at a total concentration of 0.63 g/100 mL formula), and a probiotic strain *Bifidobacterium breve* M-16 V (Morinaga Milk Industry at a concentration of 1.47×10^9 colony forming units/100 mL formula). The AAF was nutritionally similar to the AAF-S but lacked the synbiotic blend. Suggested minimum amounts of daily study product intake volumes were age-dependent, that is, 450 mL/d for 0–8-month-olds, 350 mL/d for 9–18-month-olds, and 250 mL/d for >18-month-olds. The intervention period was 12 months and clinical visits were scheduled 6, 12, 24, and 36 months after inclusion. During the study visits at 12, 24, and 36 months, the proportion of subjects who developed tolerance to CM (primary outcome of the study) was measured by a double-blind, placebo-controlled food challenge (DBPCFC) with CM powder. Subjects with a negative outcome to the DBPCFC were challenged to fresh (pasteurized) cow's milk. If the infant reacted to the DBPCFC or fresh milk challenge, the DBPCFC was repeated at the subsequent visit.

The PRESTO study was conducted in accordance with the World Medical Association Declaration of Helsinki and the International Conference on Harmonization guidelines for Good Clinical Practice, and approved

by the relevant Institutional Ethics committees. Written informed consent was obtained from each subject's parent/caregiver before study entry.

2.2 | Statistical analysis

All statistical analyses were performed in the all-subjects-randomized (ASR) population, including all infants who were randomized and received at least one sip of the study product. Differences in tolerance development to CM between groups were analysed using a logistic regression model including treatment, age at baseline, CM IgE at baseline, and the stratification factors study site and CM skin prick test (SPT) wheal size at baseline, as fixed factors.⁶ CM-related symptoms were analysed using a proportional odds regression model with adjustment for the stratification factors study site and CM SPT wheal size. $p < 0.05$ were considered statistically significant. Statistical analyses were performed using SAS Enterprise Guide v4.3 or higher software for Windows (SAS Institute).

3 | RESULTS

The initial study population of the PRESTO study included 169 infants (mean $\pm$ SD age at baseline: 9.4 ± 2.53 months) (Figure 1). Of those, 126 subjects (60 in AAF-S and 66 in AAF) completed the 36-month follow-up visit. Mean ($\pm$ SD) age of these subjects at the time of the visit was $3.8 (\pm 0.27)$ years. DBPCFC was performed as part of the 36-month follow-up visit in 48 subjects (38%). A total of 78 subjects already showed a negative reaction to the DBPCFC and fresh milk challenge at the 12- or 24-month follow-up visit, and were not challenged again at 36 months follow-up. Results show that the percentage of subjects who had developed tolerance to CM after 36 months was similar in the group receiving AAF-S (47/60 [78%]) and in the group receiving AAF (49/66 [74%]) ($p = 0.253$). Figure 2 shows the trajectory of

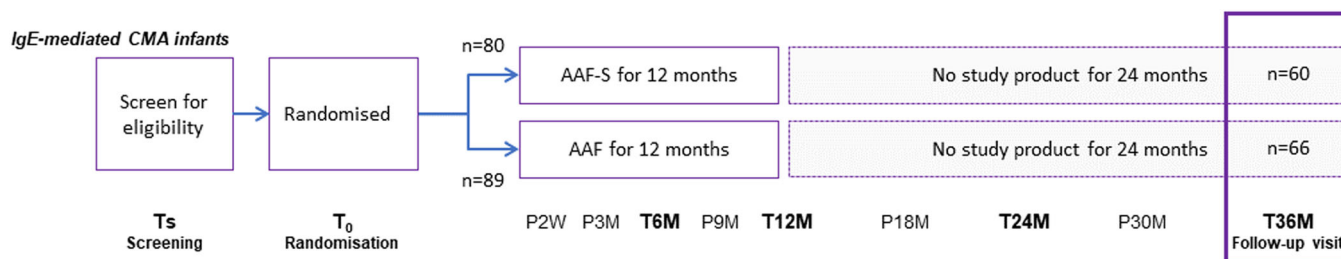


FIGURE 1 Subjects are randomized to receive either amino acid-based formula with synbiotics or amino acid-based formula and stratified by study site and cow's milk skin-prick test wheal size at entry, being 0–5 mm and ≥ 6 mm. M, months; P, time of phone call; T, time of visit; W, weeks.

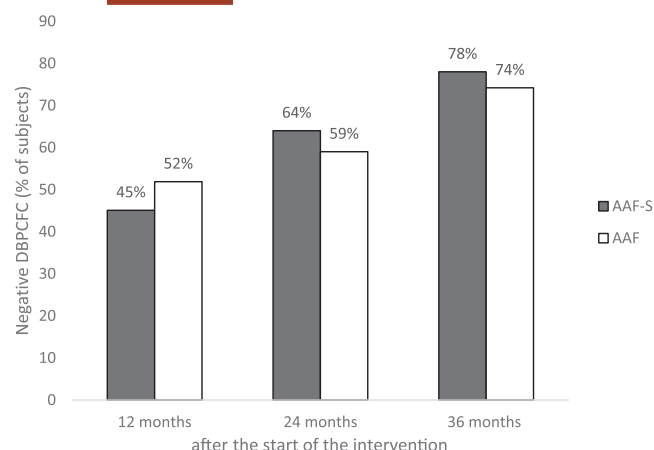


FIGURE 2 Percentage of subjects tolerant to cow's milk (CM) as defined by a negative response to an oral double-blind, placebo-controlled food challenge (DBPCFC) with CM powder after 12 (end of intervention period, mean $\pm$ SD age: 21.5 $\pm$ 2.73 months), 24 months (follow-up period, mean $\pm$ SD age: 33.8 $\pm$ 3.00 months) and 36 months (follow-up period, mean $\pm$ SD age: 3.8 $\pm$ 0.27 years) for subjects receiving amino acid-based formula with synbiotics (AAF-S) or without synbiotics (AAF).

acquisition of tolerance to CM over the study duration. CM-related symptoms (i.e., redness, oozing, crusting/flaking, itchiness and dryness of the skin, blocked nose, sneezing, coughing, wheezing, vomiting, spitting up, bowel habits, bloating, abdominal pain, rhinitis, and watery/itchy eyes) after 36 months were prevalent, but generally mild (Table S1). The most frequently reported symptoms after 36 months were gas/wind (66.7%), skin dryness (49.6%), sneezing (45.0%), skin itchiness (40.3%), blocked nose (38.8%), coughing (38.8%), rhinitis (36.8%), and constipation (24.6%). There were no differences in the prevalence or severity of CM-related symptoms between the AAF-S and AAF groups. We observed a decrease in the number of subjects who reported skin symptoms (including skin redness, crusting/flaking, itchiness, and dryness) and diarrhea over the duration of the study, whereas an increase in the number of subjects reporting respiratory symptoms (nasal congestion, rhinitis) and constipation was observed between 12 and 36 months after the start of the intervention (Table S1).

CM SPT results after 36 months suggest persistent sensitization to CM (CM-SPT wheal size ≥ 3 mm) in 34% (19/56) of subjects randomized to AAF-S compared to 45% (26/58) of subjects randomized to AAF (odds ratio: 0.490; 95% confidence interval: 0.189–1.270; $p = 0.142$). Median (Q1; Q3) total- and CM-specific serum IgE after 36 months were similar in both groups (total IgE: AAF-S, 184 kU/L [85; 473] vs. AAF, 235 kU/L [82; 1004], $p = 0.695$ and CM-specific IgE: AAF-S, 1.3 kU/L [0.7; 3.3] vs. AAF, 1.2 kU/L [0.1; 5.2], $p = 0.342$).

4 | DISCUSSION

The present results indicate that 36 months after the start of a 12-month intervention period with AAF with or without synbiotics for the dietary management of IgE-mediated CMA, about three-quarters of the subjects developed tolerance to CM. This is in line with findings from Host et al.⁷ and Saarinen et al.⁸ who reported natural outgrowth of IgE-mediated CMA in respectively 76% and 65% of children at 3 years of age. In contrast, others have reported lower recovery rates of CMA, ranging from around 50%–55% at 4 to 5 years^{9–12} to as low as 19% at 4 years of age¹³ and 22% at the age of 5.¹⁴ This variation is likely due to the population under study (e.g., a highly selected population of CMA children who were referred to a specialized tertiary care clinic in the study of Santos et al.¹⁴), as well as other characteristics of the study design, such as the age of the subjects at inclusion and the prescribed dietary management.

In line with the higher proportion of children achieving tolerance to CM over the 36 months period (Figure 2), most skin- and gastrointestinal-related symptoms of CMA decreased over time (Table S1). On the contrary, rhinitis and rhinitis-related symptoms such as nasal congestion, cough, and watery/itchy eyes, were more frequently observed after 36 months. This supports the concept of the atopic march, where allergic diseases in early life progress from skin symptoms and food allergies in early life to the later development of allergic rhinitis and asthma.¹⁵

To conclude, a high proportion of children (about three-quarters) who consumed an AAF with or without synbiotics for 12 months in early life, developed tolerance to CM in the 36 months after the start of the intervention. There were no differences in acquisition of tolerance to CM between the AAF groups. Although this study did not include a comparison arm of infants receiving a hypoallergenic formula with CM peptides and hence firm conclusions cannot be drawn, our data suggest that the consumption of AAF and absence of exposure to CM peptides do not slow down CM tolerance acquisition.

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CONFLICT OF INTEREST STATEMENT

A.N.W. reports royalty payments from UpToDate; research grants from Nutricia, Nestlé, Astellas Pharma, NIAID, and DBV Technologies; personal fees from Nestlé, Nutricia/Danone, Novartis, and Regeneron; serves the American College of Allergy, Asthma, and Immunology as deputy editor of the *Annals of Allergy, Asthma, and Immunology* and is a member of the American Board of Allergy and Immunology outside the

submitted work; and is on the medical advisory board (unpaid) of the International FPIES Association. L.L. received lecture fees from Nutricia, Nestlé Nutritional Institute, Allergopharma, Infectopharm, HAL Allergy, and DBV Technologies; and received consulting fees from Nestlé Nutritional Institute, DBV Technologies, Infectopharm, and Aimmune outside the submitted work. SRBME, MTJvA*, MMON, and JEL are (*former) employees of Danone Nutricia Research. V.T. received lecture fees from Danone/Nutricia. C.D. receives research grant support from the National Institutes of Health/National Institute of Allergy and Infectious Disease, Food Allergy Research and Education, DBV Technologies, Aimmune Therapeutics, Nutricia North America, Regeneron Pharmaceuticals, and the Scurlock Foundation; and is a consultant for Moonlight Therapeutics. A.M. has received speaker's fees from DVB Technologies, Aimmune, Sanofi, Viatrix, and Nestlé Health Institute, and is part of the advisory boards of Novartis, Sanofi, Regeneron, and Viatrix. M.E.L. has undertaken clinical research with Danone/Nutricia and Abbott Nutrition and was a member of the IMAP milk allergy guidelines group. A.T.F. has received research funding from ALK-Abello and Danone and consultancy fees from Stallergenes Greer, DBV, Aimmune, Danone, and Mead Johnson; and is president of BSACI, previous director of KCL Allergy Academy, and trustee of Allergy UK, all of which receive commercial sponsorship. L.J.M. reports consultant arrangements with advisory boards at Danone and Novartis, and speakers' bureau participation for Danone, Mead Johnson, and Regeneron; involvement in commercial clinical trials at Danone and Regeneron; and membership in BSACI, EAACI, and BPAIIG. K.B. has received lecture fees from Aimmune, Allergopharma, Bencard, Danone/Nutricia, Infectopharm, Meda Pharma/Mylan, Nestlé, and ThermoFisher, and consulting fees from Aimmune, ALK, Bausch & Lomb, Bencard, Danone/Nutricia, DBV, Hipp, Hycor, Infectopharm, Mabyon, Meda Pharma/Mylan, Nestlé, and Novartis. The rest of the authors declare that they have no relevant conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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