Allergies in high-risk schoolchildren after early intervention with cow's milk protein hydrolysates: 10-year results from the German Infant Nutritional Intervention (GINI) study

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Background: The long-term effect of nutritional intervention with hydrolysate infant formulas on allergic manifestations in high-risk children is uncertain.

Objective: We sought to investigate the effect of hydrolysate infant formulas on allergic phenotypes in children with family history of allergies at school age.

Methods: We analyzed data from participants of the prospective German Infant Nutritional Intervention study after 10 years of follow-up. At birth, children were randomly assigned to receive, for the first 4 months, one of 4 blinded formulas as breast milk substitute, if necessary: partially hydrolyzed whey formula (pHF-W), extensively hydrolyzed whey formula (eHF-W), extensively hydrolyzed casein formula (eHF-C), or standard cow's milk formula. Outcomes were parent-reported, physician-diagnosed allergic diseases. Log-binomial regression models were used for statistical analysis.

Results: The relative risk for the cumulative incidence of any allergic disease in the intention-to-treat analysis (n = 2252) was 0.87 (95% CI, 0.77-0.99) for pHF-W, 0.94 (95% CI, 0.83-1.07) for eHF-W, and 0.83 (95% CI, 0.72-0.95) for eHF-C compared with standard cow's milk formula. The corresponding figures for atopic eczema/dermatits (AD) were 0.82 (95% CI, 0.68-1.00), 0.91 (95% CI, 0.76-1.10), and 0.72 (95% CI, 0.58-0.88), respectively. In the per-protocol analysis (n = 988) effects were stronger. The period prevalence of AD at 7 to 10 years was significantly reduced with eHF-C in this analysis, but there was no preventive effect on asthma or allergic rhinitis.

Conclusion: The significant preventive effect on the cumulative incidence of allergic diseases, particularly AD, with pHF-W and eHF-C persisted until 10 years without rebound, whereas eHF-W showed no significant risk reduction. There is insufficient evidence of ongoing preventive activity at 7 to 10 years of age. (J Allergy Clin Immunol 2013;131:1565-73.)

Key words: *Birth cohort, double-blind randomized trial, nutritional intervention, cow's milk protein hydrolysate infant formulas, long-term allergy prevention*

Early nutritional intervention with cow's milk protein hydrolysate infant formulas (CMPHIFs) has shown a significant reduction of allergic manifestation in children with a family history for atopy.[1-8] Most of the studies demonstrated a preventive effect mainly on atopic eczema/dermatitis (AD)[6-8] but also on food allergy and early wheezing.[9-12] Because only a few studies could follow the children into school age, little is known about the long-term effects of early intervention with CMPHIFs on the persistence and development of allergic phenotypes at school age.[9,13,14]

Recently, we have shown that high-risk 6-year-old children have a reduced risk for AD but not for asthma or allergic rhinitis if they were fed in the first 4 months of life either exclusively or as a supplement to breast milk with one of 3 CMPHIFs, a partially hydrolyzed whey formula (pHF-W), an extensively hydrolyzed whey formula (eHF-W), or an extensively hydrolyzed casein formula (eHF-C), compared with standard cow's milk formula (CMF).[6] Although CMPHIFs are generally recommended for children at risk as a

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*Members of the GINIplus study group at 10 years are listed in the Online Repository.

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Abbreviations used

AD: Atopic eczema/dermatitis
AM: Allergic manifestation
aRR: Adjusted relative risk
CMF: Standard cow's milk formula
CMPHIF: Cow's milk protein hydrolysate infant formula
eHF-C: Extensively hydrolyzed casein formula
eHF-W: Extensively hydrolyzed whey formula
GEE: Generalized estimating equations
GINI: German Infant Nutritional Intervention
ISAAC: International Study on Asthma and Allergy in Childhood
ITT: Intention-to-treat
mITT: Modified intention-to-treat
NNT: Number needed to treat
pHF-W: Partially hydrolyzed whey formula
PP: Per protocol
RR: Relative risk

supplement for breast-feeding in the first 4 to 6 months in Europe, and pHF-W has been used recently in the United States,[15-17] this recommendation has been questioned for several reasons, such as lack of blinding; lack of double-blind, placebo-controlled food challenges; no effect on objective markers, such as specific IgE levels; lack of a universally accepted biologic mechanism to explain the effect[18]; and no or only modest evidence that allergic symptoms are truly prevented rather than only delayed.[18,19] One recent small study showed no preventive potential of pHF-W on AD,[20] and another study has favored introduction of CMF in the first 14 days of life for allergy prevention.[21] Because these 2 study results were based on small numbers, had severe limitations, or both,[22] we used the large dataset of the 10-year follow-up of the German Infant Nutritional Intervention (GINI) study to investigate the effect of early feeding with CMPHIFs on the allergic phenotypes of any allergic manifestation (AM), atopic eczema/dermatitis (AD), asthma, and allergic rhinitis at school age. Specifically, we were interested whether the previously observed preventive effect of the hydrolysate formulas on AD persists until school age and whether childhood asthma can be prevented by nutritional intervention through the oral route.

METHODS

Study design and population

The GINI study is an ongoing birth cohort study set up to investigate the preventive effect of different CMPHIFs in children with first-degree allergic heredity. Details of design, sample size, recruitment, outcome definitions, and follow-up have been published previously.[4-6] In brief, between September 1995 and July 1998, healthy term newborns were recruited at birth in 2 regions of Germany (rural Wesel and urban Munich). High-risk infants, who were defined as having at least 1 parent or biological sibling with a history of allergic disease, were selected by questionnaire (n = 2252). If the parents agreed to participate in the prospective, double-blind intervention trial, newborns were randomly allocated at birth by a computer-generated list to one of 3 hydrolyzed study formulas: pHF-W (Beba HA; Nestlé, Vevey, Switzerland); eHF-W (Hipp HA; Hipp, Pfaffenhofen, Germany, until 1999 on the German market and identical to Nutrilon Pepti, Nutricia/Numico, Zoetermeer, The Netherlands), and eHF-C (Nutramigen; Mead Johnson, Diezenbach, Germany) or CMF (Nutrilon Premium; Nutricia/Numico, Zoetermeer, The Netherlands) to be administered if breast-feeding needed to be supplemented or discontinued. Randomization was conducted stratified for uniparental or biparental allergic heredity and study region.[4] The infants were enrolled before any formula supplementation was necessary and at the latest at 14 days of age. Mothers were advised to feed the randomized formula as the only substitute to breast milk during the strict intervention period of 4 months, if necessary. The strict intervention period was defined as 16 weeks, although study formula was provided for 6 months. The aim was to avoid modification of the formula effect by solid foods. The study protocol was approved by local ethic committees, and written informed consent was obtained from all participating families. Ethics approval was repeated for the follow-up examinations at 6 and 10 years.

Follow-up examination

The follow-up examination at 10 years was divided into 2 steps. First, an International Study on Asthma and Allergy in Childhood (ISAAC) modified questionnaire[23] was sent to parents to collect information on health outcomes, allergic symptoms, physician's diagnosis of allergic diseases, and several covariates.[6] In a second step, all children were invited to the study center for physical examination and blood sampling.

Determination of outcomes and covariates by using questionnaires

The outcome of interest for this analysis was the cumulative incidence until 10 years and the period prevalence at age 7 to 10 years of parent-reported physician's diagnosis of any allergic manifestation (AM), which was defined by any of the following diseases: atopic eczema/dermatitis (AD), urticaria and food allergy/intolerance, asthma, and hay fever/allergic rhinitis.[24] The parents were asked the following: "Did a physician diagnose any of the following diseases during the 1st/2nd/3rd/4th/5th/6th/7th/8th/9th/10th year of life: […] asthma, allergic or atopic eczema/dermatitis, hay fever/allergic rhinitis, urticaria, food allergy? […]." A specific disease (asthma, eczema, or rhinitis) at school age was defined as present if, at 10 years, the parents reported a physician's diagnosis during the last 4 years, treatment in the last 12 months, or both for that specific disease.

The following covariates were reported at birth and regarded as potential confounders: sex; study region (Munich or Wesel); heredity of family allergy; family history of eczema, asthma, and hay fever; parental education (3 categories by years of schooling); and number of older siblings. Information on furry pets in the home was gathered yearly by using questionnaires, and passive tobacco smoke exposure was queried on and after the second year.

Symptoms of "wheezing" were defined by the ISAAC questions[25] as wheezing and whistling in the chest ever or in the last 12 months. Flexural rash was defined as an itchy rash that came and went for at least 6 months, affecting the elbow or knee bends, the front of the ankles, or the skin under the buttocks and around the neck, ears, or eyes. Symptoms of rhinitis were defined as a problem with sneezing or a runny or blocked nose without cold or flu accompanied by itchy-watery eyes. Parent-reported allergies were defined by using the following question: "Has your child ever had atopic dermatitis/atopic eczema, asthma, hay fever?"

Additionally, for asthma and eczema, age at the beginning and, if applicable, end of the symptoms and whether these symptoms were present at the time of the examination were queried.

Levels of specific IgE to the most common food and inhalant allergens were measured with the CAP System (Pharmacia, Freiburg, Germany) at the age of 10 years. We used the screening test "Kindernahrung" (FX5, children's food, containing hen's egg, milk protein, codfish, soybean, peanut, and wheat) and "Inhalation-mix" (SX1, containing *Dermatophagoides pteronyssinus*, rye, timothy grass, mugwort, birch pollen, *Cladosporium* species, and cat and dog dander). Single allergens were tested in the case of positive results. Additionally, we measured levels of specific IgE to ragweed. Sensitization was defined as positive if at least 1 specific IgE level was 0.35 kU/L or greater (ie, CAP class 1).

Statistics

Intention-to-treat (ITT) and per-protocol (PP) analyses were performed. The ITT population consisted of all primarily randomized children (n = 2252). Additionally, a modified intention-to-treat (mITT) analysis was done in which the population was restricted to those with certain or uncertain exposure to any study formula (n = 1615) by excluding all children who did