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The Impact of Formula Choice for the Management of Pediatric Cow's Milk Allergy on the Occurrence of other Allergic Manifestations:

The Atopic March Cohort Study

(ATMA II Trial - ClinicalTrials.gov ID: NCT03861910)

Prepared with thanks to Professor Roberto Berni Canani

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EHCF + LGG® is effective in preventing future allergic manifestations and in accelerating the return to milk products (immune tolerance acquisition) in infants affected by CMA.

VIEW FULL STUDY

What is cow's milk allergy (CMA)?

With an **estimated prevalence of up to 3%, CMA is one of the most common food allergies** and one of the main causes of food-induced anaphylaxis in the paediatric age population.

CMA results from a **breakdown of immune tolerance mechanisms, leading to an abnormal immune-mediated response to proteins in cow's milk** that occurs consistently with ingestion. The condition imposes a **significant cost to healthcare systems, as well as to families**.

Elimination of cow's milk proteins from the diet is the mainstay of treatment. If breastfeeding is not available, the child must be fed a special formula adapted to CMA dietary management. This type of formula must be adequate in terms of allergic and nutritional safety.

STUDY BACKGROUND

The most used formulas for CMA are extensively hydrolysed whey formula (EHWF) or casein formula (EHCF), soy formula (SF), rice hydrolysed formula (RHF) or amino acid-based formula (AAF). Data suggest that **early-life CMA could be the first stage of the "allergic march", leading to other atopic manifestations (AMs), especially asthma, atopic eczema, urticaria and rhinoconjunctivitis, later in life**.

Formulas for CMA treatment differ mainly in the protein fraction features, such as source (cow's milk, soy or rice) and degree and procedure of hydrolysis. It has been suggested that selected milk protein hydrolysates may be able to not only reduce allergic symptoms in CMA children, due to the destruction of IgE epitopes, but may also have immune-modulating properties, such as the induction of T-cell tolerance and the prevention of sensitisation.

EHCF-derived casein protein fraction is able to elicit a tolerogenic effect through, in part, an epigenetic modulation of genes expression. The **addition of the probiotic *Lactobacillus rhamnosus* GG (LGG®) is able to elicit positive modulation of the gut microbiome with increased production of the short-chain fatty acid butyrate**, a powerful metabolite able to exert a strong epigenetic-mediated regulation of the **main mechanisms involved in immune tolerance acquisition**.

Data suggest a potentially different impact on immune tolerance acquisition induced by EHCF + LGG®. There is also evidence that **EHCF + LGG® may have a long-lasting preventive effect on the development of allergy in children at risk for atopy**. In children with CMA, dietary intervention with EHCF

Study Design

In a **36-month prospective cohort study**, the **occurrence of other AMs** including eczema, urticaria, asthma, and rhinoconjunctivitis (primary study outcome), and the **time of immune tolerance acquisition** (secondary study outcome) were comparatively **evaluated in immunoglobulin E (IgE)-mediated CMA children treated with:**

- extensively hydrolysed casein formula + LGG® (**EHCF + LGG®**)
- rice hydrolysed formula (**RHF**)
- soy formula (**SF**)
- extensively hydrolysed whey formula (**EHWF**)
- amino-acid based formula (**AAF**).

*Allergic manifestation incidence (Bonferroni corrected 95% confidence interval [CI]) at 36 months:
- **0.22** (0.09 to 0.34) for the **EHCF + LGG® cohort**
- 0.52 (0.37 to 0.67) for the RHF cohort
- **0.58** (0.43 to 0.72) for the **SF cohort**
- 0.51 (0.36 to 0.66) for the EHWF cohort
- **0.77** (0.64 to 0.89) for the **AAF cohort.**

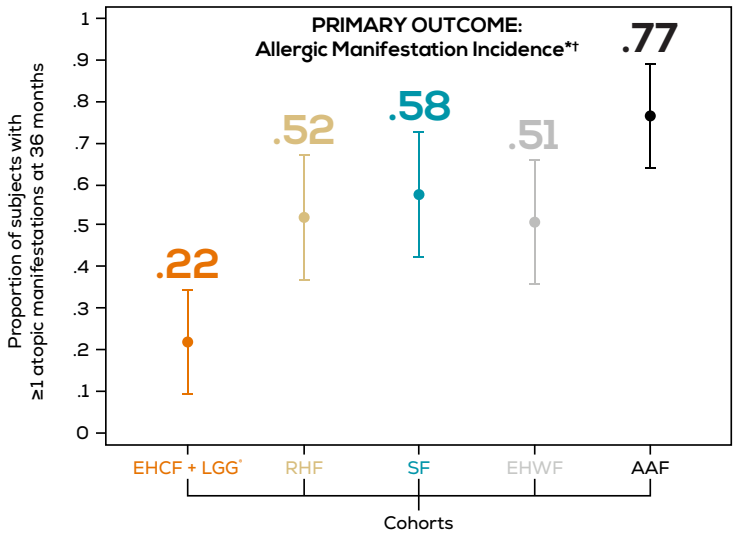
†Rice hydrolysate formula is not available in the UK.

supplemented with LGG® has benefits in **decreasing inflammation and gastrointestinal symptoms and in reducing disease duration, the occurrence of functional gastrointestinal disorders, and other AMs later in life,** compared with EHCF without LGG®. **The present study was designed to assess the incidence of AMs later in life in children with CMA treated with different special formulas.**

STUDY RESULTS

This is the first cohort study evaluating the occurrence of AMs later in life in children with CMA treated with different formulas. Some 365 subjects were enrolled into the study, with 73 assigned per formula cohort.

Regarding the primary outcome (see Figure below), **the incidence of other AMs in the EHCF + LGG® cohort was significantly lower, compared with the other cohorts**.



The ability of EHCF + LGG® to prevent allergy is supported by the results of the GINI study in which infants at high risk of allergic diseases were protected from AMs when they received EHCF + LGG®.[1–6]

Conclusion

This cohort study performed in a well-characterised population of children with CMA shows that **EHCF + LGG® is effective in preventing the allergic march and in accelerating the time of immune tolerance acquisition in paediatric patients affected by CMA**.

*Based on evidence using THIN (The Health Improvement Network), real world evidence from clinical practices (>11 million anonymised patients entered by GPs from >560 practices across the UK).
†Immune tolerance acquisition (Bonferroni corrected 95% confidence interval [CI]) at 36 months:
- **0.81** (0.69 to 0.93) for the **EHCF + LGG cohort**
- 0.41 (0.26 to 0.56) for the RHF cohort
- **0.40** (0.25 to 0.54) for the **SF cohort**
- 0.42 (0.28 to 0.57) for the EHWF cohort
- **0.19** (0.07 to 0.31) for the **AAF cohort.**

‡Rice hydrolysate formula is not available in the UK.

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These data are consistent with those of a recent retrospective study, based on real world evidence, revealing that the first-line management of newly diagnosed CMA infants treated with **EHCF + LGG® may slow down the allergic march when compared with infants treated with extensively hydrolysed whey formula (EHWF)**.[7*]

Secondary outcome results (see Figures below) of this cohort study confirm that **EHCF + LGG® has a greater potential in stimulating immune tolerance acquisition**. In other words, reducing disease duration and returning patients to milk. We provide additional evidence on the positive effect elicited by EHCF + LGG® on immune tolerance acquisition in children with CMA.