

Hydrolyzed Proteins in Allergy

Silvia Salvatore and Yvan Vandenplas

Hydrolyzed proteins are used worldwide in the therapeutic management of infants with allergic manifestations and have long been proposed as a dietetic measure to prevent allergy in at-risk infants.

Cow's milk (CM) allergy (CMA) is the most frequent food allergy in early childhood and affects about 0.5–6% of infants, but the disease range varies according to patient selection, type of feeding (breast- or bottle fed) and criteria of diagnosis (symptom based or challenge proven) [1]. CM presents two different fractions of proteins: casein and whey, with both having allergenic properties. Immunoreactive epitopes and peptide fragments of both β -lactoglobulin and casein have been well characterized [2]. Milk allergenicity is reduced by various processes but mainly by hydrolysis. Hydrolyzed formulas (HFs) differ according to the methods of hydrolysis (such as enzymatic hydrolysis, ultraheating, ultrafiltration, pressure and glycation), the timing of hydrolysis, the degree of hydrolysis (i.e. intact protein molecules are broken down into peptides of various molecular weights), the protein source (casein, whey, rice or soy) and other nonprotein components. Based on all the above-mentioned characteristics, the *in vitro* results and the clinical effects of one formula cannot be transferred to another one, and commercial old and new formulas, even if from the same manufacturer, are not always comparable. There is no general agreement on unique standards to specifically define partially (pHFs) or extensively hydrolyzed formulas (eHFs), but the distinction is generally made by the molecular weight and percentage of the peptide fragments. A pHF contains peptides with a molecular weight generally <6 kDa, ranging from 3 to 10 kDa, with some commercial pHFs containing 18% of peptides >6 kDa; an eHF usually has more than 90% of peptides <3 kDa, with 1–5% of peptides >3.5 kDa [3]. In contrast, the molecular weight of whole CM protein ranges from 14 kDa (α -lactalbumin) to 24 kDa (casein) up to 67 kDa (bovine serum albumin) [2]. The weight of peptides has immune and clinical relevance because the 'bigger' the peptide the 'more allergenic' it can be. Peptides >6 kDa, and predominantly those >10 kDa, frequently act as allergens [4], but already those in the

range between 0.97 and 1.4 kDa are able to bind IgE in vitro, those >1.4 kDa can produce skin reactivity and those >3 kDa can cause a type I reaction in sensitized patients [5]. pHF s have been developed with the aim of minimizing the number of sensitizing epitopes within CM proteins, while at the same time retaining peptides with sufficient size and immunogenicity to possibly stimulate the induction of oral tolerance. Two different meta-analyses [6, 7] showed that a specific whey-based pHF offers a valid option for primary allergy prevention, mainly for atopic dermatitis, in high-risk infants who are not exclusively breastfed. In one meta-analysis, it significantly halves the incidence of atopic dermatitis [11 trials; summary relative risk (RR) estimate 0.56, 95% CI 0.4–0.77] up to 3 years of life compared to a standard CM formula [6]. In the other meta-analysis involving 3,284 participants (1,027 in pHF and 2,257 in control groups), a reduction in all allergic diseases of 52% [5 randomized controlled trials (RCTs); RR 0.48, 95% CI 0.23–1.00] was found at 3 and 6 months of age, 38% at 12 months (4 RCTs; RR 0.62, 95% CI 0.45–0.85; number needed to treat 12) and 58% at 30–36 months (1 RCT; RR 0.42, 95% CI 0.19–0.90) compared to a standard formula [7]. For atopic dermatitis or atopic eczema (8 RCTs), using a random-effect model, the use of pHF compared with standard formula statistically significantly reduced the incidence of eczema at 1 year (4 RCTs; RR 0.68, 95% CI 0.48–0.98; I^2 ¼0%), but not at 4–6 months (5 RCTs), 2 years (3 RCTs) or 30–36 months (2 RCTs) [7].

In the (so far) largest dietary intervention study (GINI) that prospectively investigated in a randomized and double-blind design the allergy-preventive effect of three different HF s compared with a standard (CM) formula in a cohort of 2,252 infants with at least one first-degree allergic relative, a significant reduction in eczema was noted at all study points (1, 3, 6 and 10 years) when using pHF [odds ratio (OR) 0.56; 95% CI, 0.32–0.99] or a casein-based eHF (OR 0.42, 95% CI, 0.22–0.79) but not a whey-based eHF or a standard CM formula [8]. More studies are needed to determine the nutritional effect and the real benefit of pHFs in the prevention of CMA in both high- and low-risk infants.

Because pHFs contain large CM peptides that can cause severe reactions in CMA patients, pHFs are not recommended for treatment of CMA [1, 9], and CM protein-based eHF is the preferred option in CMA infants who are not breastfed [1, 9–11]. eHF s have been extensively hydrolyzed in order to destroy allergenic epitopes. However, the molecular weight profile only enables to differentiate protein characteristics of formulas, but does not clearly determine the allergenic formula properties and clinical response that should be tested in vivo. Although lower than in pHF, residual allergenicity is present even in eHF whilst the only anallergic formulas are the elemental ones based on free amino acids that cannot determine an immune stimulation [1, 9]. Amino-acid-based formulas (AAFs)

are recommended in infants who refuse or do not tolerate eHF or in the most severe cases of CMA [1, 9, 11]. Compared to eHFs, AAFs have, in most countries, higher costs, different taste and possibly different long-term nutritional effects [9, 10].

There is limited evidence that the addition of probiotics (e.g. *Lactobacillus rhamnosus* GG or *Bifidobacterium breve*) to an eHF offers additional benefit [12, 13]. In a recent prospective trial in 38 infants with CMA (confirmed by food challenge) fed for 6 months a new rice protein-based eHF (with more than 95% rice peptides <3 kDa) without lactose but enriched with pectin, lysin and tryptophan, clinical tolerance and normal growth were noted in all patients [14].

The maintenance of a decreased well-balanced diet is not easy, especially in more severe cases of CMA, but is mandatory for each child. The choice of the eHF should be based on scientific evidence of efficacy, tolerance and nutritional adequacy [10].

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