Efficacy and safety of hydrolyzed rice-protein formulas for the treatment of cow's milk protein allergy

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Short title: Efficacy and safety of hydrolyzed rice-protein formulas for the treatment of CMPA

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ABBREVIATIONS

AAF: amino acid formula

CF: complementary feeding

CMP: cow's milk protein

CMPA: cow's milk protein allergy

CMP-eHF: cow's milk protein-based extensively hydrolyzed formulas

FSMP: foods for special medical purposes

HRP: hydrolyzed rice proteins

HRPF: hydrolyzed rice-protein formula

OFC: oral food challenge

RAST: radioallergosorbent test

SBS: symptom-based score

SF: soy formula

SPT: skin-prick test

ABSTRACT

Foods for special medical purposes (FSMPs) with a protein fraction made of hydrolyzed rice proteins (HRPs) have been on the market in Europe since the 2000s for the treatment of cow's milk protein allergy (CMPA). HRPF formulas (HRPFs) are proposed as a plant-based alternative to cow's milk protein-based extensively hydrolyzed formulas (CMP-eHF) beside the soy protein formulas whose use in CMPA is controversial. HRPFs do not contain phytoestrogens and are derived from non-genetically modified rice. HRPFs are strictly plant-based apart from the addition of vitamin D_3 (cholecalciferol). As the amino acid content of rice proteins differs from that of human milk proteins, the protein quality of these formulas is improved by supplementation with free lysine, threonine, and tryptophan.

The consumption of HRPFs has risen: for example, in France HRPFs account for 4.9% in volume of all formulas for children aged 0–3 years.

Several studies have shown the adequacy of HRPFs in treating CMPA. They ensure satisfactory growth from the 1st weeks of life for infants and toddlers, both in healthy children and in those with CMPA. HRPFs can be used to treat children with CMPA either straightaway or in second intention in cases of poor tolerance to CMP-eHF for organoleptic reasons or for lack of efficacy. In France, the cost of HRPFs is close to that of regular infant or follow-on formulas.

Key words: cow's milk allergy; hydrolyzed formulas; hydrolyzed rice-protein formulas; extensively hydrolyzed cow's milk protein formula; growth

1. INTRODUCTION

In the European Union, the only protein sources allowed in infant and follow-on formulas are cow's milk proteins (CMP), goat's milk proteins (since 2013), soy protein isolates, and hydrolyzed proteins [1]. For the treatment of cow's milk protein allergy (CMPA), soy protein-based formulas have been widely used as an alternative to CMP-based extensively hydrolyzed formulas (CMP-eHF), but up to 14% of infants with CMPA also react to a soy formula [2]. In addition, soy formulas contain significant amounts of phytoestrogens such as isoflavones, which might have untoward effects as endocrine disrupting compounds, although the long-term deleterious consequences are unproven [3-5]. Guidelines of the Nutrition Committee of the French Society of Pediatrics (SFP), the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the American Academy of Pediatrics (AAP) recommend the use of soy protein-based formulas when parents wish to exclude products of animal origin or during CMPA after the age of 6 months, when complementary feeding has been initiated and in the absence of allergy to soy [2, 6, 7].

Foods for special medical purposes (FSMPs) with hydrolyzed rice proteins (HRPs) as a protein source have been in use since the early 2000s in several European countries (Italy, Spain, and France) for the treatment of CMPA. Hydrolyzed rice-protein formulas (HRPFs) do not contain phytoestrogens and the rice used is not genetically modified. HRPFs are strictly plant-based apart from the addition of vitamin D_3 (cholecalciferol). The content of arsenic, heavy metals, and pesticides is strictly regulated for foods intended for children under 3 years of age, according to Directive EU 2013/46 of 28 August 2013 amending Directive 2006/141 [1]. Manufacturers are required to respect safety limits. The Nutrition Committee of the ESPGHAN published recommendations in 2015 [8]. Since 2016 (EU 2015/1006 of 25 June 2015) the maximum level of inorganic arsenic for rice intended

to produce foodstuffs for children under 3 years of age is 0.10 mg/kg (a limit twice as low as that for white rice) [9].

Among FSMP used for CMPA in France, CMP-eHFs account for 48.4% in volume of the total, HRPFs 39.3%, and preparations based on amino acids (AAFs) 12.3%, i.e., 6.0%, 4.9%, and 1.5%, respectively, of all formulas for children aged 0–3 years, [10]. Due to the very low prescription of soy formulas (SF), their production was stopped in France in the first half of 2018. Given the widespread use of HRPF, the current review, focuses on 1) the efficacy of HRPFs in the treatment of CMPA and 2) the quality of growth in children on prolonged use of these HRPFs.

2. METHODOLOGY

A PubMed search was performed using the following key words: cow's milk protein allergy, extensively hydrolyzed cow's milk protein formula, hydrolyzed rice protein formula, rice-hydrolyzate formula, and partially hydrolyzed rice protein formula. The objective was to find studies published in peer-reviewed journals regarding the efficacy and safety of HRPFs. There was no starting date for this literature search and its end was October 2018. The articles selected were original articles. Eleven clinical trials on HRPFs in children and one animal study were identified and ranked according to the level of evidence of the Oxford Centre for Evidence-based Medicine (CEBM) [11] (Table 1). A study on palatability (level 1b), absent from the table, not dealing with efficacy and performed in adults, will be discussed later in the text. Most of the studies in children with CMPA involved exclusively IgE-mediated CMPA: the diagnosis was based on serum determination of specific antibodies by the radioallergosorbent (RAST) test, skin-prick tests (SPT) and oral food challenge (OFC); non-IgE-mediated CMPA was diagnosed only by OFC. Only two studies [12, 13] included both IgE-mediated CMPA and non-IgE-mediated CMPA.

3. THE HRPFs

3.1 Overview on the products available on the market

Published studies tested HRPFs from five different brands in Italy (*n*=1), the USA (*n*=1), Spain (*n*=1), and France (*n*=2). In Italy, Plasmon Risolac® 1 and 2 (Heinz, Milan) have been on the market since 2000. This brand is currently available as a single formula (Risolac®) for infants and toddlers aged 0–3 years. The Italian Health authorities consider this product as a FSMP for children with CMPA or soy allergy. In Spain, Blemil Plus Arroz Hidrolizado® 1 and 2 (Ordesa, Barcelona) have been on the market since 2008. These formulas are

reimbursed by the Spanish Health insurance under the category "lactose-free hydrolysates," i.e., FSMPs to be used in case of CMPA, primary or secondary lactose intolerance, chronic or acute diarrhea, and refeeding after an episode of acute diarrhea. In France, Modilac Expert Riz® 1 and 2 (Sodilac, Paris) have been on the market since 2009. Their composition is identical to that of Blemil Plus Arroz® 1 and 2. Modilac Expert Riz AR® has been on the market since 2013 for the treatment of the CMPA with regurgitations. Modilac Expert Riz® 3 has been marketed since 2016 for children 1–3 years of age. Novalac Riz® (Novalac, Paris) for infants and young children 0–3 years old was launched in 2012. In contrast to CMP-eHFs, the HRPFs mentioned above are not reimbursed by the French health insurance. Picot Riz® 1 and 2 (Lactalis nutrition santé, Laval) launched in 2012, Premiriz® 1, 2, and 3 (Candia-Baby, Paris), and Bébé Mandorle riz® 1 and 2 (La Mandorle, Paris) are not proposed as treatment for CMPA and will not be discussed further in this paper because of the complete lack of clinical trials. Another HRPF (Ross Products, Abbott) evaluated in a clinical trial published in 2006 [14] has not been marketed to date (Table 2).

According to European legislation: "dietary foods for special medical purposes" means a category of foods for particular nutritional uses, specially processed or formulated and intended for the dietary management of patients, and to be used under medical supervision. They are "intended for the exclusive or partial feeding of patients with a limited, impaired or disturbed capacity to take, digest, absorb, metabolize or excrete ordinary foodstuffs or certain nutrients or metabolites, or with other medically-determined nutrient requirements, whose dietary management cannot be achieved only by modification of the normal diet, by other foods for particular nutritional uses, or by a combination of the two." These indications are demonstrated by generally accepted scientific data and their efficacy and safety for young children must be shown by high-quality scientific studies [7]. It should be noted that a formula indicated for the treatment of CMPA must be tolerated by at least 90% of the children who are allergic to CMP, with a 95% confidence level [15, 16].

3.2 Composition of the HRPFs

3.2.1 Energy content

The energy content of HRPFs is comparable to that of regular infant or follow-on formulas (Table 2).

3.2.2 Protein content

The protein source is a HRP obtained through enzymatic hydrolysis. Most rice proteins (80% glutelin and 10% globulin) are insoluble in water and hydrolysis makes them water soluble [14,17]. In HRPFs peptides have a low

molecular weight (MW). In Risolac®, 44% of peptides have a MW < 1000 Daltons (Da), 43% < 1000–2000 Da, and 13% < 2000–4000 Da. In Blemil Plus Arroz® and Modilac Expert Riz®, 96.6% of peptides have a MW < 5000 Da (26.8% < 300 Da, 29.9% with 300–1000 Da, 35.2% 1000–5000 Da), and up to 10% are free amino acids. Novalac Riz® contains peptides with a lower MW, with 95% of peptides at a MW < 1000 Da, and 99.4% MW ≤ 5000 Da [12].

While rich in essential amino acids, the grain of rice has limited amounts of three essential amino acids: lysine, 36 mg vs. 67 mg for 1 g of protein in human milk; threonine, 37 mg vs. 44 mg; and tryptophan, 9 mg vs. 17 mg [18,19]. The protein composition of the outer layer of the rice grain differs from that of the polished rice (endosperm) since its content in some essential amino acids is higher: lysine (45.5 vs. 33.1 mg/g of protein), tryptophan (11. 7 vs. 8.2 mg/g of protein). Rice outer hull proteins thus can partly compensate for the amino acid deficiencies of the grain [20] (Table 3). Supplementation with free L-lysine, L-threonine, and L-tryptophan makes it possible to make the aminogram of HRPs close to that of human milk in order to meet infants' amino acid requirements [21] (Table 3).

The nutritional value of a protein is influenced not only by its amino acid composition, but also by its digestibility coefficient (DC) (ingested nitrogen – excreted nitrogen / ingested nitrogen × 100). The DC of rice proteins is lower than that of CMP: 93 vs. 100% [22]. Due to this difference in DC, the protein content of infant HRPFs, follow-on HRPFs, and growing-up HRPFs is slightly higher than the current average protein content of infant formulas (1.4 g/100 mL), follow-on formulas (1.5 g/100 mL), and growing-up formulas (1.7 g/100 mL) [23] (Table 2).

3.2.3 Carbohydrate and lipid composition of HRPFs

The lipid composition of HRPFs is identical to that of standard formulas.

Currently HRP formulas are lactose-free: the formula with lactose used in one study [24] is no longer available. The carbohydrate fraction is composed of dextrin maltose for the most part and cornstarch in Blemil®, Modilac®, and Novalac®. In Plasmon Risolac® glucose syrup and sucrose are present alongside a majority of dextrin maltose and some cornstarch. Ross's HRPF contains 40% rice syrup (rich in simple maltose and low in glucose and fructose) and 60% sucrose (Table 2).

3.3 Rice protein and HRP allergenicity

Rice protein allergy is rare in Western countries [25]. Rice is considered the least allergenic cereal because it triggers undesirable reactions in less than 1% of children with allergies [26]. Rice proteins can be the cause of the non-IgE-mediated food protein-induced enterocolitis (FPIES) but more rarely than CMP or soy proteins. The diagnostic delay and symptom severity are greater than for CMPA [27,28]. Children with rice-induced FPIES are more likely to develop the same syndrome with other foods (oats, barley, wheat, and other non-cereal foods) than children whose FPIES was caused by cow's milk or soy. From 1963 to 2009, 42 cases of FPIES involving rice were reported [29], i.e., less than one case per year. In all these studies, the rice was eaten in grain and not in the form of HRP. To date, there is no published report of allergy to HRPFs, but no post-marketing information on the tolerance of HRPFs is available.

The allergenicity of HRPF (Risolac®) was evaluated by Piacentini et al. [30] in 130 young guinea pigs fed *ad libitum* for 37 days either with HRPF or with a conventional CMP formula. After this sensitization period, guinea pigs received intravenously isolated whole proteins (CMP and rice) or ultra-centrifuged formulas (uCMPF and uHRPF). Specific IgG against beta globulin, casein, and whole rice protein were measured. In the CMP formula-fed group, the injection of β-lactoglobulin, casein, or whole uCMPF induced significantly more reactions than those of the HRPF-fed group injected with the same proteins ($p < 0.001$). In the HRPF-fed group, no reaction was observed after challenge with uHRPF, and only two mild reactions occurred after challenge with rice protein. Very low levels of rice-protein-specific IgG antibodies were noted in all groups, including animals fed the HRPF, with no significant differences between the groups.

Grain rice is known for its low allergenicity, and the results of this animal study suggest that the HRPF used had a very low sensitization capacity.

3.4 Clinical efficacy of HRPFs

3.4.1 HRPFs for treatment of CMPA

In a trial by Fiocchi et al. [31], 18 children with CMPA who developed clinical reactions to a soy-based formula confirmed by positive double-blind placebo-controlled OFC, mean age 5 years (range, 1–9 years), were fed a HRPF (Risolac®). SPTs were positive in all for CMPs (casein in 13, alpha-lactalbumin in 10) and soy, in eight out of 18 for rice and in two out of 18 for HRP. Serum-specific IgE were positive for cow's milk in all children, for soy in 13, and for rice in seven, while HRP-specific IgE were negative in all children. The rice formula was assessed by double-blind, placebo-controlled OFC with a HRPF: it was negative in all cases, thus supporting the HRPF use in soy and CMP allergy.

In another prospective study by Fiocchi et al. [32], 100 children, mean age 3.2 ± 2.93 years, with CMPA and immediate reactions to cow's milk confirmed by a double-blind placebo-controlled OFC were fed a HRPF (Risolac®). SPTs were positive for cow's milk and/or a cow's milk protein fraction in 87 out of 99 children, four out of 90 for rice proteins and in four out of 86 for HRP. Specific IgE were present (> 0.35 KU/L) in 92 out of 95 children for cow's milk and/or a cow's milk protein fraction, in 21 out of 91 children for rice proteins, and in four out of 91 children for HRP. Specific IgE against rice were found in 21 out of 91 by the FEIA CAP system (Pharmacia & Upjohn Diagnostic) and in 70 out of 96 by immunoblotting, whereas weak positive responses to HRP were observed in only six children. All double-blind placebo-controlled OFCs with HRPF were negative. This study concluded that HRP is a possible alternative for children with CMPA.

In a prospective, open, randomized clinical trial by Reche et al. [33], 92 infants (mean age, 4.3 months; range 1.1–10.1), with CMPA characterized by an immediate clinical reaction, SPT, specific IgE, and positive OFC, were fed a HRPF (Blemil Arroz®) (n = 46/92) or a CMP-eHF (n = 46/92). The HRPF was well tolerated in all children in the HRPF group, and the CMP-eHF induced urticaria and vomiting in one child in the CMP-eHF group. During the 2 years of the study, the number of children who remained allergic and the time course of total IgE and CMP-specific IgE was similar in both groups. The HRPF was shown to be effective in the treatment of CMPA since a formula indicated for the treatment of CMPA must be tolerated by at least 90% of children allergic to CMP [15,16].

In these three studies HRPF provided adequate management of IgE-mediated CMPA.

In a prospective trial conducted without randomization or control group by Vandenplas et al. [12], 40 infants (mean age, 3.4 months; range, 1–6 months) with CMPA confirmed by an OFC were fed a HRPF (Novalac Riz®) for 6 months. CMPA was IgE-mediated (immediate reaction: 14/40 and positive prick test: 15/40) or non-IgE-mediated. Clinical tolerance was evaluated with a symptom-based score (SBS) proposed by the author but not currently validated [34]. All infants tolerated the HRPF and all parameters composing the SBS had decreased significantly after 1 month of dietary treatment with the study formula, and this evolution was confirmed after 3 and 6 months, but the methodological limitations of this study make it impossible to draw firm conclusions.

3.4.2 The duration of CMPA

The duration of CMPA depending on the type of formula used to feed infants has been addressed in three studies.

In the study conducted by Reche et al. [33], the percentage of children remaining allergic to CMP decreased during the study, but the percentage of children who became tolerant was the same in both groups, HRPF and CMP-eHF, after 12, 18, and 24 months.

In a prospective, randomized, cohort study by Terraciano et al. [35,36], 72 children aged 14.1 ± 8.6 months at diagnosis were followed up for a median duration of 26 months. The estimated median disease duration, i.e., time before tolerance was achieved, was 56 months [95% CI not indicated] (mean ± SE: 40.2 ± 4.8) in the CMP-eHF group, 28 [11–37] (24.3 ± 2.6) months in the soy formula (SF) group, and 20 [10–33] (24.3 ± 3.6) months in the HRPF group. In the same study, this beneficial effect was not observed in polysensitized children (CMP and soy).

In a retrospective multicenter observational study reported by Berni Canani et al. [37,13], 260 children with CMPA confirmed by positive double-blind placebo-controlled OFC, with a positive SPT to CMP in 96 at enrollment, were divided into five different feeding groups: CMP-eHF + *Lactobacillus rhamnosus* GG (LGG) (n = 71), CMP-eHF (n = 55), HRPF, (Risolac®) (n = 46), soy formula (n = 55), and AAF (n = 33). The percentage of patients showing tolerance to CMP during an OFC after 12 months of exclusion diet was higher with CMP-eHF + LGG than with CMP-eHF (OR 4.8; 95% CI, 2.2–10.5; $p < 0.001$). Acquisition of tolerance to CMP with the CMP-eHF did not significantly differ from the outcome of other dietary regimens: HRPF, SF, and AAF. This study was observational, with a higher percentage of IgE-mediated CMPA / non-IgE-mediated CMPA in the HRPF group compared to the CMP-eHF + LGG and CMP-eHF groups (50% vs. 38 and 44%), which could account for a longer spontaneous duration in the HRPF group: the acquisition of tolerance in of IgE-mediated CMPA is delayed compared to non-IgE-mediated CMPA [38,39].

Regarding the duration of CMPA, these three studies do not allow any conclusion on the influence of the formula used to treat CMPA.

3.5 Growth studies of infants and children fed a HRPF

3.5.1 Growth of healthy infants

In a randomized, double-blind trial by Lasekan et al. [14], 65 healthy infants enrolled from birth to 16 weeks of age were fed a HRPF (Ross) or a regular infant formula. During a 4-month follow-up, height, weight, BMI, and head circumference were within normal ranges and there was no significant difference between the two groups.

In a prospective open multicenter study by Girardet et al. [24], 78 healthy full-term infants were fed a HRPF containing lactose (Modilac®) from the 1st month of life and were followed until initiation of complementary

feeding (CF), i.e., up to 4–6 months of age. The mean daily weight gain was 23.2 ± 4.3 g (per protocol population), which did not differ from WHO standards [40] in the same age range (22.2 ± 1.8 g, $p = 0.09$). The Z-scores of weight, height, and BMI (ITT population) remained between +1.1 and −0.5 SD during the study period.

The results of these two studies on the growth of healthy infants fed a HRPF from birth to initiation of CF show appropriate growth.

3.5.2 Growth of infants and children with CMPA

Growth failure affecting weight, height, or BMI in children with proven CMPA was identified in the early 1990s. Growth may be affected by CMPA before CMPA is diagnosed and treatment is initiated and may persist during the elimination diet. The frequent delay in the diagnosis of CMPA increases the risk of undernutrition [41,42]. Five studies evaluated the growth of infants with CMPA and fed a HRPF from the 1st months of life to 2 years of age. A significant growth retardation existed at inclusion in three out of five studies compared to reference growth curves: ANTRHO Atlanta 1990 in the Agostoni study [43], Spanish reference tables in the Reche study [33], and Growth Standards 2006 WHO in the Vandenplas study [12].

In a prospective, randomized, single-center clinical trial by D'Auria et al. [44], 16 infants with CMPA and atopic dermatitis, aged 6–14 months (median, 11 months) were fed with a HRPF (Risolac®) (n=8) or a SF (n = 8) for 6 months. The diagnosis of CMPA was based on SPT and double-blind placebo-controlled OFC or open challenge when appropriate. Weight and height z-scores based on growth standards (ANTHRO Atlanta 1990) [45] were similar in both groups at enrollment and at 1, 2, 4, and 6 months, and remained within expected values. Average (median) weight-for-age z-scores ranged from −0.30 (−0.34) to −0.09 (−0.08) and −0.21 (−0.14) to 0.11 (0.15), in the HRPH group and in the SF group, respectively, and length-for-age Z-scores from −0.10 (−0.21) to 0.07 (0.12), and −0.12 (−0.23) to 0.27 (0.37), respectively.

In a prospective, nonrandomized, open, single-center clinical trial conducted by Savino et al. [46], 58 infants with CMPA and atopic dermatitis (according to clinical symptoms and allergy tests upon admission: RAST, SPT, and patch tests, and open OFC) were enrolled from the 1st month of life to the age of 2 years: 15 children received a HRPF (Risolac®), 17 a SF, and 26 a CMP-eHF while 30 healthy infants without CMPA, receiving a free diet without eviction of milk and dairy products, served as controls. No significant differences between the HRPF, SF, and CMP-eHF groups were observed for the z-score of weight-for-age during the first 2 years of life, but a significantly lower difference was seen in the HRPF group compared to the control group in the intervals

9–12 months ($p = 0.025$) and 12–18 months ($p = 0.020$) of age. In contrast, the SF and CMP-eHF groups were comparable to the control group, but the CMP-eHF group was significantly lower ($p = 0.000$) in the 1st trimester of life. The HRPF contained 15–20% less protein (1.5 g/100 mL) than the soy formula (1.8 g/100 mL) and the CMP-eHF (1.9 g/100 mL) with almost identical energy content, (67.8, 67.6, and 67.6 kcal/100 mL, respectively), a difference that may explain the lower weight gains [17]. However, during the exclusive bottle feeding period, weight gain was comparable in the HRPF and the control groups, with the lower growth rate observed only between 9 and 18 months when the CF covered most of the needs, suggesting a role for the elimination diet of the CMP: growth may be affected by CMPA during the elimination diet [41,42].

In a prospective, randomized, comparative, unblinded, multicenter trial published by Agostoni et al. [43], 93 infants with CMPA diagnosed between ages 6 and 12 months by specific IgE blood test, SPT, and double-blind placebo-controlled OFC were exclusively breastfed for at least 4 months, gradually weaned at 5–6 months and randomized into three groups: soy protein formula ($n = 32$), CMP-eHF ($n = 31$), and HRPF (Risolac®) ($n = 30$). The protein content of these formulas (2.3, 1.9, and 2.1 g/100 mL, respectively) as well as their energy content, (69, 68, and 68 kcal/100 mL) were similar. A fourth group ($n = 32$) was breastfed until age 12 months with CF starting at 5 months. Weight-for-age z-scores were negative in the four groups at enrollment (6 months), presumably due to CMPA. There were no significant differences between the groups throughout the duration of the study for weight gain and height-for-age z-scores,

In the study published by Reche et al. [33], 92 infants with CMPA were fed a HRPF (Blemil Arroz®) or a CMP-eHF. At enrollment, all infants had a weight below the average of the Spanish reference charts, probably because of CMPA (z-score for weight: −0.51 ± 0.82 in the HRPF group and −0.74 ± 0.96 in the CMP-eHF group). There were no statistically significant differences in weight gain, length gain, and final weight and height at 18 months between the two groups.

In the observational Vandenplas study [12], 40 infants with CMPA were fed a HRPF (Novalac Riz®) for 6 months. Growth z-scores were compared to the 2006 WHO growth standards [40]. At inclusion, weight-for-age, weight-for-length, and BMI average z-scores were all negative, probably due to CMPA. Weight-for-age, weight-for-length, and BMI z-scores had significantly increased at 1 month of HRPF feeding with a complete catch-up growth at the end of the study (weight for age z-score at inclusion: −0.7 ± 1.0; at 1 month: −0.5 ± 0.9; $p < 0.001$; at 6 months: −0.1 ± 1.0; $p < 0.001$; BMI for age z-score at inclusion: −0.7 ± 0.9; at 1 month: −0.6 ± 0.8 $p = 0.012$; at 6 months: 0.0 ± 0.8 $p < 0.001$).

Taken in aggregate, these seven studies show that HRPFs allow for satisfactory growth patterns in healthy children and for catch-up growth in those suffering from CMPA. However, it should be noted that most of the studies focused on small samples and relatively short durations of use.

3.5.3 Protein nutritional status

Two studies were conducted to determine protein nutritional status. The Lasekan study [14] compared healthy children fed a HRPF (Ross) or a regular CMP formula; it showed comparable plasma protein concentrations, particularly in total plasma protein, serum albumin, and pre-albumin/transthyretin. In the study conducted by D'Auria et al. [44], the plasma concentrations of biochemical markers of protein homeostasis (albumin, pre-albumin, total plasma protein, urea) were similar among children with CMPA fed either a HRPF (Risolac®) or a SF.

3.5.4 Bone mineralization

CMPA can reduce bone mineral density due to significantly reduced calcium intake [47]. Two studies [13,43] found similar plasma calcium, magnesium, and alkaline phosphatase concentrations in healthy children fed HRPF or regular CMP, but these are very indirect signs of bone health. No studies have been published on the impact of HRPF feeding during CMPA on bone density.

Studies on the bioavailability of minerals and micronutrients in children fed a HRPF would be welcome.

3.6 HRPFs tolerance

3.6.1 Digestive tolerance

The hydrolysis of proteins increases the osmolarity of the formula, which could increase regurgitations due to delayed gastric emptying and render the stools softer and more frequent, sometimes greenish, due to increased intraluminal water secretion [48]. To limit these effects, HRPFs are thickened with cornstarch in Risolac®, Blémil®, and Modilac®, and with pectin in Novalac®. In the study reported by Lasekan et al. [14], the digestive tolerance of a HRPF in healthy infants was good and comparable to that of a standard nonhydrolyzed CMP formula; the HRPF did not alter the number or the consistency of stools. Infants fed HRPF tended to have less regurgitation and vomiting than infants fed standard milk-based infant formula. In the D'Auria et al. study [44], in infants with CMPA, the HRPF did not induce any adverse event. Only 5.3% of infants with CMPA had

normal stools at baseline in the Vandenplas study [11], whereas stool normalization was observed in 52.6% of infants after 1 month of HRPF feeding and in 77.8% after 3 months, but this was an observational study that did not allow any firm conclusions to be drawn.

3.6.2 Acceptability of HRPFs

A double-blind study by Pedrosa et al. [49] tested the palatability (taste, odor, texture) of 12 different formulas in 50 randomized adult subjects: these tests demonstrated a clear superiority of HRPFs and soy formulas compared with various CMP-eHFs. In children, the palatability of HRPFs turned out to be superior to that of the CMP-eHFs [50]. The reported overall acceptance of the HRPFs in the studies reported was good in the studies from Lasekan et al. (Ross) [14], D'Auria et al. (Risolac®) [44], Fiocchi et al. (Risolac®) [32], and Girardet et al. (Modilac®) [38]. In the Reche et al. study (Blemil Arroz®) [33], two infants out of 46 refused to take HRPF, and two infants out of 46 refused to take CMP-eHF. In the Vandenplas study (Novalac®) [12], 18.8% of parents felt that their infant did not like or did not accept the study formula and preferred the formula used before the study, leading to three drop-outs out of 40 infants enrolled: a possible explanation could be a higher degree of hydrolysis of the proteins, increasing the bitter taste [48].

3.7 Use of HRP formulas during CMPA

HRPFs are currently marketed mainly in Italy, France, and Spain. They are found in a growing number of world regions such as North Africa, the Middle East, and South America, though they are unavailable in many countries in Europe, in the USA, Canada, Australia, and New-Zealand. The existing guidelines recommend the use as first management of CMP-eHFs (from whey or casein) in children with CMPA while HRPFs are not mentioned or only in second intention, since they are unavailable in many countries. HRPFs are gaining popularity, because they have been shown to be effective and safe, have good acceptability, and are cheaper than the CMP-eHFs [51]. The cost of HRPFs is close to that of regular infant or follow-on formulas. In comparison, CMP-eHFs are nutritionally adequate and well tolerated by children allergic to CMP and other foods, but may have drawbacks: a bitter taste [52], a higher cost (two to three times that of a standard formula), and a potential risk of anaphylaxis in some children. AAFs, offered in severe clinical situations or in children not responding to CMP-eHF, are safe, but more expensive (six to eight times the cost of CMP-eHFs) [53,54]. The ESPGHAN Committee on Gastroenterology stated in 2012 that the use of a HRPF is an option if it has proven safety and efficacy in infants with CMPA [55].

Based on studies published to date, HRPFs are effective for the management of children with CMPA and provide satisfactory nutritional security. No data are available on the use of HPRF during allergy to CMP-eHFs, which, at the moment, requires the use of AAFs. The effect of HRPFs on the duration of CMPA, noticeably compared to CMP-eHFs, remains unknown.

4. CONCLUSION

HRPFs are not available in many countries while they are widely used in others such as Italy, Spain, and France. Evidence from clinical trials published to date shows that HRPFs are a feasible treatment option in children with CMPA, either in first intention or in case of palatability issues with CMP-eHFs. HRPFs allow a satisfactory growth from birth through the first few years of life in healthy children as well as in children suffering from CMPA. Such conclusions are, however, valid only for the products reported in the studies reviewed. Another aspect of HRPFs is a relatively low cost compared to CMP-eHFs. No data are available to draw any conclusions on the use of HPRFs in cases of allergy to CMP-eHFs, which today require the use of AAFs. On the other hand, it is not currently possible to conclude on the influence of the formula used to treat infants with CMPA on the duration of the CMPA.

RECOMMENDATIONS FOR CHILDREN WITH CMPA

- The Committee on Nutrition of the French Society of Pediatrics reiterates its 2012 recommendations: HRPFs can be considered as an alternative to CMP-eHF as a first-line treatment for infants with CMPA because of their effectiveness, in terms of allergic symptoms and nutritional adequacy, their palatability, and their lower cost.
- HRPFs therefore represent an option, either as a first-intention regimen for a child with CMPA or as second intention if CMP-eHFs are either not accepted or poorly accepted for organoleptic reasons.

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Alain Bocquet: Clinical Trials, Nestlé, Novalac; Lectures Blédina, Nestlé, Novalac, Sodilac.

Christophe Dupont: Scientific Advisory Board, Nestlé, Nutricia; Clinical Trials, Novalac.

Jean-Pierre Chouraqui: Lectures, Mead-Johnson, Nestlé.

Dominique Darmaun: Lectures, Danone, Nestlé.

François Feillet: Scientific Advisory Board, Nutricia, Vitaflo; Lectures, Nutricia, Vitaflo.

Alexandre Lapillonne: Lectures, Nestlé, Mead-Johnson.

Umberto Simeoni: Scientific Advisory Board, Sodilac; Lectures, Danone, Nestlé.

André Briend, Marie-Laure Frelut, Jean-Philippe Girardet, Régis Hankard, Jean-Christophe Rozé, and Dominique Turck declare that they have no competing interests.

Table 1
Summary of clinical studies

Level of evidence	Author year, reference	Type of study	Number of subjects	Age at inclusion * *mean age*	Duration of study	Infant health status	Number of children fed a HRPF	Number of infants fed another formula used in groups used for comparison	Control groups	Outcome measure
1b	D'Auria 2003 [44]	prospective, randomized, single center, control group	16	6–16 months	6 months	CMPA	8	8 SF		Growth
1b	Lasekan 2006 [14]	prospective, randomized, blinded, single center, control group	80	2 days	4 months	healthy	32	33 infant cow's milk formula		Growth
2b	Agostoni 2007 [43]	prospective, randomized, unblinded, multicenter, control group	160	5.3 months *	6 months	CMPA	30	31 CMP-eHF 32 SF	32 breast fed	Growth
2b	Reche 2010 [33]	prospective, open study, randomized, multicenter, control group	92	4.3 months *	2 years	CMPA	41	40 CMP-eHF		Growth Allergen-icity Duration of CMPA
2b	Terraciano 2010 [36]	prospective, randomized, cohort MICMAC	72	14.1 ± 8.6 months	26 months	CMPA	25	18 CMP-eHF 29 SF		Duration of CMPA
4	Fiocchi 2003 [31]	prospective, open study, multicenter,	18	5 years *	1 test	CMPA	18			Allergen-icity
4	Savino 2005 [46]	prospective, open study, nonrandomized, single center, control group	88	3.3 ± 32 months	2 years	CMPA	15	26 CMP-eHF 17 SF	30 healthy	Growth
4	Fiocchi 2006 [32]	prospective, open study, multicenter,	100	3.2 ± 2.9 years	1 test	CMPA	100			Allergen-icity
4	Girardet 2013 [24]	prospective, open study, multicenter, z-score WHO curves	85	< 1 month	4 months	healthy	78			Growth

4	Berni Canani 2013 [13]	open study, nonrandomized, multicenter,	260	3.4 ± 1.5 months	12 months	CMPA	46	55 CMP-eHF 71 CMP-eHF+LGG 23 SF 33 AAF		Duration of CMPA
4	Vandenplas 2014 [12]	prospective, open study, without control group, z-score WHO curves	40	< 6 months	6 months	CMPA	40			Growth Allergen-icity
5	Piacentini 2003 [30]	guinea pigs allergenicity study after sensitization	130				130			Allergen-icity

AAF: amino acid formula, CMPA: cow's milk protein allergy, CMP-eHF: cow's milk protein-based extensively hydrolyzed formulas, HRPF: hydrolyzed rice-protein formula, LGG: Lactobacillus GG, SF: soy formula

Table 2

Comparison of different HRPFs: energy, protein, chemical index, amino acid supplements, and carbohydrates

Formula	**Risolac** 1® *Initial*	**isolac** 2® *Initial*	**Risolac®** *Current* 0–3 years	**Blemil plus** Arroz 1® **Modilac** Expert Riz 1®	**Blemil plus** Arroz 2® **Modilac** Expert Riz 2®	**Novalac Riz ®** 0–3 years (Novarice)	**Ross** formula
Energy kcal/100 mL	**68**	**71**	**69**	**71**	**69**	**68**	**68**
Proteins g/100 mL	**1.5**	**2.1**	**2.1**	**1.7**	**2.0**	**1,8**	**1.9**
Chemical index	**117**	**106**	**106**	**109**	**105**		**99**
***Supplement* Lysine**	**+**	**+**	**+**	**+**	**+**	**+**	**+**
***Supplement* Threonine**	**+**	**+**	**+**	**+**	**0**	**0**	**+**
***Supplement* Tryptophan**	**0**	**0**	**+**	**+**	**+**	**+**	**0**
Carbohydrates g/100mL	**7.7**	**8.5**	**7.3**	**7.6**	**8.1**	**7.6**	**6.7**
Maltose dextrin			5.3	6.0	6.4	5.7	
Cornstarch			0.5	1.6	1.7	1.9	
Simple carbohydrates			1.5 *				6.7 **

***** glucose syrup and sucrose

** rice syrup (rich in simple maltose and low in glucose and fructose) and 60% sucrose

Table 3

Comparison of essential or conditionally essential amino acid (AA) content in rice and breast milk protein.

Essential or semi-essential amino acids (mg amino acid/g protein)				
	Grain of rice [17]	Rice endosperm [19]	Rice bran [19]	Breast milk [18]
Arginine	83.3			38
Histidine	23.4	24.6	44.8	25
Isoleucine	43.1	38.0	36.1	40
Leucine	82.5	81.5	76.9	85
Lysine	***36.1***	***33.1***	***45.5***	***67***
Methionine	23.4	38.8 *	27.0 *	16
Cysteine	20.4			13
Phenylalanine	53.5	100.9 **	82.4 **	34
Tyrosine	33.5			32
Threonine	***35.7***	***34.6***	***36.8***	***44***
Tryptophan	***11.5***	***8.2***	***11.7***	***17***
Valine	60.9	51.2	55.3	45

* sum of methionine and cysteine ** sum of phenylalanine and tyrosine

Three limiting essential amino acids are identified in rice: lysine. threonine, and tryptophan.