

Review Article

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Soy- And Rice-Based Formula And Infant Allergic To Cow's Milk

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Running title: grain based formulas and cow's milk allergy

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Abstract

Soy milk formula has limited medical indications for infants feeding, although in several parts of the world it has been used as a source of nutrition in a large number of children. It used to be the main alternative feeding for infants allergic to cow's milk that did not breastfed before the introduction of extensively hydrolyzed formulas. Although there is a debate, the fact that some children are allergic to soy or some children with cow's milk allergy can present with concomitant soy allergy, restricted the use of soy formulas for treatment of infants allergic to cow's milk. Other grain-based formulas like the rice-based ones are promising in infants with cow's milk allergy. Grain-based formulas could be an alternative and cheaper way of nutrition for infants allergic to cow's milk than extensively hydrolyzed formulas. Further large scale longitudinal clinical studies are required to clarify the safety of soy and other grain-based formulas for treatment of cow's milk allergy.

Keywords: children, cow's milk allergy, rice formulas, soy formulas

Introduction

Among grain-based formulas, soy- and rice-based formulas are the only that have been extensively studied. These formulas could be an alternative source of feeding in infants who cannot tolerate cow's milk. Breastfeeding is the optional choice of nutrition in infancy, but extensively hydrolyzed formulas (EHF) are suggested in infants with cow's milk allergy who do not breastfeed [1, 2]. Taking into account the high cost of extensive hydrolysed formulas, there is a question whether grain-based formulas could be an alternative choice in the management of cow's milk allergy (CMA). There is a debate, though, especially regarding the safety of soy formulas in children allergic to cow's milk and data, as it will be discussed, are limited and have provided conflicting results. Since, among several grains, only soy and rice have been used as a vegan protein in the production of formulas that officially can be an alternative source of feeding in infancy, we analyze the data that concern these formulas and their relationship with CMA [1, 2, 3, 4]. So far, there are no other grain-based formulas, i.e. almond-, oat- or coconut-based, which are recommended as nutritional supplements in infancy, and therefore we will refer only to all relevant information for soy- and rice-based formulas. The current review summarizes the composition and the allergenicity of soy- and rice-based formulas, and provides data from several studies which investigated the potential risk of allergy when grain-based formulas were used as a substitute in children with CMA.

Soy milk formulas

CMA affects approximately 2-3 % of infants [5, 6, 7] and IgE-mediated allergic reactions are more frequently presented than non-IgE mediated [8, 9]. Current recommendations for CMA treatment are either breastfeeding with elimination of milk and milk products from mother's diet or the use of EHF [1]. Soy and grain-based formulas can be an alternative source of nutrition in children who cannot tolerate cow's milk. However, especially for soy milk formulas, there is a debate whether they can be used as substitutes of cow's milk, since its components can act as allergens too [1, 2]. According to guidelines published in 2012 by the Nutrition Committees of the European Society of Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) [1], soy milk formulas can be used only under specific circumstances. These include galactosemia, persistent lactose intolerance, and religious or other ethical considerations, whereas soy milk is contraindicated in preterm infants [10]. In infants with CMA, soy milk formulas can be used only after the age of 6 months, but first clinical challenge to soy protein should be performed. Position of the American Academy of Paediatrics is different, and recommends that soy milk formulas could be used for CMA treatment although the hypoallergenic milk formulas are preferred regardless of age [2].

Soy milk formulas composition

Soy protein biological value is lower to that of cow's milk, due to the different amino acid pattern between them. Soy protein contains lower amounts of lysine, methionine and proline and higher amounts of glycine, arginine, aspartate and cysteine [11]. Only soy proteins should be used for the preparation of soy milk formulae, and they are

derived from soy flour in which carbohydrates, mineral salts and fat are eliminated [12]. According to ESPGHAN recommendations regarding soy milk formula composition, the minimum protein content should be 2.25 g/100 kcal which is higher than that of the cow milk formula (1.8 g/100kcal), and therefore is possible that the soy protein has lower bioavailability compared to that of cow's milk. Furthermore, in order to be nutritionally adequate for infants growth, soy milk formula should be supplemented with L-carnitine, taurine and methionine (soy based products contain low amount of these amino acids). Soy phytates can impair the absorption of minerals and trace elements, and soy milk formulae are fortified with calcium, phosphorus, iron, zinc and iodine [13, 14]. It is also recommended that soy phytates in infant's formulas should be effectively reduced by phytase treatment or with precipitation methods [15]. Fat content varies by manufacturer and it usually ranges from 5.02-5.46g/100 kcal or 3.4-3.6g/100kcal. Supplementation with docosahexanoic and arachidonic acid is usual. Sucrose, corn syrup solids and corn maltodextrin are carbohydrate sources for soy milk formulae, and their content ranges 10.26-10.95 g/100 kcal or 6.9-7.4 g/100 kcal according to manufacturer [2]. Bone density of infants fed a soy formula is comparable to the one of infants fed a cow's milk one [15].

Soy protein allergenicity

Soy formula could be an alternative source of feeding for infants with CMA. However, soy allergy is also common, since soybeans are considered one of the eight most common food allergens [16]. Many soy proteins are binding IgE in patients allergic to soy, but only a few of them are considered to be immunodominant allergens (table 1). These are the birch pollen allergens Gly m 3, a profilin, and Gly m

4, a Bet v 1-related pathogenesis-related protein 10 which is the major allergen in patients with birch pollen and soy allergy [17]. Soy hull antigens, named Gly m 1 and gly m 2 are aeroallergens and they have been implicated in respiratory soy allergy [18, 19]. The proteins Gly m 5 (beta-conglycinin) and Gly m 6 (glycinin) have been implicated with severe allergic reactions to soy [20, 21]. A study conducted in Northern European children revealed that IgE-binding to Gly m 5 or Gly m 6 was found in 86% of children with anaphylaxis to soy, in 55% of children with moderate and only 33% of subjects with mild symptoms [20]. Another possibly major soy allergen is protein P34 (Gly m Bd 30K) and among soy products, soymilk presents the highest P34 antigenicity, ranging from 7 to 23 mg/g extracted protein [22]. On the other hand, sensitization to soy allergens does not always translate into clinical symptoms. The clinical and immunological basis of soy allergy seems to be complex, and this was revealed in a double-blind, placebo-controlled food challenge study, in which it was found that only 1% of patients with soy allergy react subjectively (symptoms referred by the patient) and objectively (symptoms observed by physicians) with 0.21 and 37.2 mg of soy protein, respectively [23]. About 50% of children allergic to soy protein become tolerant by age 7 years [24].

Soy milk allergy clinical manifestations

In children with soy milk allergy, non-IgE-mediated clinical manifestations are more frequent than IgE-mediated reactions. The frequency of adverse reactions to soy has been estimated to be <1% in children fed to soy milk formula [2], whereas the occurrence of allergy to cow's milk has been found to be 3.4% in the general pediatric population [2]. Anaphylactic reactions due to soy are much rarer than those elicited by cow's milk. Severe IgE-mediated reactions to soy are usually described in patients

with concomitant peanut and birch pollen allergy or in those with coexisting severe asthma [17]. Clinical studies regarding IgE-mediated allergic reactions to soy provided conflicting results, others showed severe allergic reactions in some patients allergic to soy [17, 25] whereas others claim the opposite [26].

On the other hand, soy protein is a major causative factor, along with cow's milk, of non-IgE-mediated reactions, like food protein induced enterocolitis syndrome (FPIES) and protein induced allergic enterocolitis, proctitis, proctocolitis syndrome [27, 28]. Several studies have documented that a high percentage of infants, ranging from 30 to 65%, with cow's milk induced enterocolitis presented with concomitant soy allergy [29, 30]. The role of soy protein in other delayed non-IgE-mediated reactions like constipation or infantile colic is questioned, because clinical studies did not provide benefit from substitution of cow's milk formulae with soy ones [31].

Soy formula and cow's milk allergy

Before the introduction of hydrolyzed formulas for treatment of infants allergic to cow's milk protein, soy milk was the only option used. Soy bean based formula for feeding infants was first introduced in the United States in the early 1900s [32, 33]. Since the 1960s, soy milk formulas composition improved with the addition of nutritional elements necessary for the normal growth and development of infants, as mentioned above. Soy milk is very popular in countries like the United States or Israel [34], whereas in European countries is much less frequently used for infant feeding [12, 35].

Cross-reactivity between cow's milk and milk derived from other mammals, like sheep or goat, exists since mammalian milk proteins share amino acid sequence

homology [36]. Therefore, these milks cannot be used as an alternative source of feeding in children with cow's milk allergy. Although, cross-reactivity between soy and cow's milk proteins has been found (e.g. in casein and A5-B3 glycinin molecule), clinical co-allergy between cow's milk and soy has not been established [37, 38, 39].

Current knowledge about infants with non-IgE-mediated gastrointestinal symptoms like enterocolitis or proctocolitis suggests that about half of them present with concomitant soy allergy [30, 40]. Therefore, the American Academy of Pediatrics recommended in 1998 that in infants with documented cow's milk protein enteropathy soy formula should be avoided [41]. Recommendations about infants with IgE-mediated cow's milk allergy have been a controversial issue, with different positioning from the American Academy of Pediatrics and the ESPGHAN Committee on Nutrition [1, 2]. Guidelines by ESPGHAN (2012) consider the use of soy milk after 6 months of age and only if tolerance to soy protein has been established by clinical challenge. On the other hand, recommendations published by the American Academy of Pediatrics in 2008 are less clear, although they propose the use of EHF for treatment of cow's milk allergy regardless of age, they do not exclude the use of soy formulas.

The reason for the above mentioned controversies are the very few number studies conducted (table 2). In a double blind placebo-controlled study of 93 infants with IgE-mediated cow's milk allergy, concomitant soy allergy was detected in 14% of the individuals studied [42]. In another prospective randomized study conducted in 170 infants with cow's milk allergy, adverse reactions were more frequent in soy formula compared to EHF [43] and these reactions were more frequent to infants less than 6 months of age. A recent prospective study evaluated the effect of different dietary

managements in acquisition of tolerance in 260 children with cow's milk allergy. EHF was found to be better in tolerance acquisition compared to soy protein formulas [44]. Another prospective study, though, showed the opposite; soy or rice formulas were better than EHF in acquisition of tolerance in children with CMA (45).

As far as the prevention of atopic dermatitis is concerned, soy formulas should not be recommended [46], and this opinion was drawn after a meta-analysis of five randomized or quasi-randomized trials which all compared prolonged soy formula to cow's milk formula feeding in prevention of eczema, rhinitis and asthma in allergic infants. None of these studies compared soy formula with hydrolyzed ones regarding this topic. The conclusion was that there was no benefit from the use of soy formula in the prevention of atopic disease. Current recommendation from the American Academy of Pediatrics for the prevention of atopic diseases is exclusive breastfeeding for at least 4 months [47].

Peanut and soy are both members of the legume family and soy bean storage proteins display significant homology with peanut allergens. As far as peanut allergy is concerned, regarding soy consumption and the risk of peanut allergy appearance, results from a limited number of studies are contradictory. The study from Klemola et al [48] showed that in children with CMA the use of soy formula during the first 2 yr of life did not increase the risk of development of peanut-specific immunoglobulin E antibodies or of clinical peanut allergy. Koplin J et al [49] did not find any causal relationship between soy milk consumption and peanut sensitization in infants with personal or family history of cow's milk allergy. Only one study found association between feeding with soy milk and development of peanut allergy [50]. Further studies are required in order to clarify this topic.

Besides the limited and controversial medical indications of soy formulas in children with cow's milk allergy, other reasons that could justify the use of soy milk could be economic, religious and philosophical [51]. EHF are far more expensive than soy ones and therefore soy formula can be an alternative choice for families with low income. As far as religious reasons are concerned, some religions exclude the use of hydrolysates because the enzymes used in some of them originate from pork pancreas [51]. Philosophical reason for the use of soy milk is the choice of vegan diet and the exclusion of foods that originate from animals.

It should be taken into account though, that there are several other considerations, besides allergy, for the safety of soy milk in infancy. These include for instance phytoestrogens which, under certain conditions, they are bioactive. Concerns have been raised regarding their role in the reproductive system because they act as endogenous estrogens [52]. Phytates also interfere with iodine metabolism and despite the supplementation of soy formulas with iodine, the use of soy formulas in infants with congenital thyroid insufficiency is problematic because such cases when fed with soy milk need high doses of levothyroxine and close monitoring [53, 54, 55]. The higher amounts of aluminum in soy formulas are another major consideration, since aluminum is accumulated in bones and the central nervous system [56]. On the other hand, taking into account these above mentioned questions and especially the role of isoflavones in central nervous system development, a recent prospective study compared the development of infants (mental, psychomotor, language skills) among breastfed, infants fed with milk-based formula and infants with soy-protein formula during the first year of life. No differences were detected between the two groups of

bottle-fed infants, and only the breastfed infants had a higher Psychomotor Development Index Score [57].

Rice-based formulas

Rice (*Oryza sativa*) is one of the most common cereals produced and consists a major source of protein in many parts of the world. It accounts for as much as for half of the daily calories for half of the world's population and is among the first solid foods fed to infants in many cultures [58].

Rice based formula as a milk substitution for children with CMA is discussed for almost half a century [59, 60]. Rice is known to be a relatively low allergenic food [61] and there are few reports on immediate hypersensitivity reactions upon ingestion of rice in the West [62]. Considering that optimal management of CMA should include the use of safe, affordable and nutritionally adequate substitutes, milk formula oriented from rice protein appears as an appealing alternative in children with CMA.

Rice as an allergen

Rice allergy is not infrequent in Eastern Asia countries where rice is commonly eaten. Frequency of IgE mediated rice allergy reaches up to 10% in atopic subjects in Japan and India population [63]. Prevalence is much lower in Europe and the USA [62].

In rice, proteins with molecular weight of 14-16, 26, 33, and 56 kDa have been demonstrated to be potentially allergenic. The majority of the allergic components are albumins with molecular weights between 14 and 16 kDa [64] (Table 3, 4). The 15.5, 16, 19, 25, 50, 90 kDa rice protein has been reported to be a major allergen and responsible for cross-allergenicity between cereal grains (Poaceae family) [63]. Other allergens partially characterized have been designated RAP, RAG 1, RAG 2, RAG 5, RAG 14, and RAG 17 [64]. Raw rice is substantially more allergenic than cooked,

although some of the allergens are heat stable and resist proteolysis. Rice is known to contain a 9 kDa lipid transfer protein (LPT) [66]. LPTs are heat-stable proteins and may account for allergy to cooked rice. A yet unidentified 56 kDa glycoprotein was implicated at a case report of rice induced anaphylaxis [67]. To date, two rice allergens have been fully characterized: Ory s 1, a 35 kD beta-expansin homologous to grass pollen group 1 allergens and Ory s 12, a 14 kD profilin A, a food allergen [68].

Rice is considered to be with relatively low allergenicity at least in the Western countries, although the incidence of rice allergy seems to be increasing. Lactoferrin form in rice is found to be 40-fold less immunogenic and at least 200-fold less allergenic than the one in native human milk [69]. Both forms are with identical amino acid sequences, but different glycosylation patterns. It is suggested that different glycosylation patterns may selectively inhibit IgE responses and impact on antigen uptake, processing and/or presentation, as well as the balance between Th1 and Th2 responses [69].

Sensitivity to rice proteins is found in 0.7-35% [65, 70] of patients with atopic diseases and up to 69% in cereal allergic patients [71]. Even though rice is considered of low allergenicity, several IgE-mediated symptoms have been reported in rice-allergic individuals including anaphylaxis [72].

No- IgE-mediated allergy to rice

Non-IgE mediated symptoms can occur in consistence with rice consumption, particularly in the form of Food Protein Induced Enterocolitis Syndrome (FPIES). FPIES is a potentially severe non-IgE-mediated food hypersensitivity more usually to milk and soy, which has been recognized for decades but has received relatively little

attention. The presentation of this clinical entity varies from mild (mild emesis and/or diarrhea) to severe, repetitive emesis, diarrhea and systemic inflammatory response, with progression to dehydration and shock in 15–20% of patients [73]. Although much more work is needed to elucidate the immunologic basis of this disorder, it is hypothesized that local inflammation induced upon food allergen ingestion leads to increased intestinal permeability and fluid shift. A central role of T cells in the local intestinal inflammation has been implicated and humoral immune response may also be involved in the pathophysiology of FPIES [74].

Rice is the single most common solid food that induces FPIES [75]. Interestingly, rice-induced FPIES has been referred to be more frequently associated with fluid resuscitation and a longer delay in diagnosis than FPIES associated with CMP and soy [76]. In a case report study of an infant with rice induced FPIES, a mixed TH1 and TH2 immunologic response was demonstrated [77]. More specifically rice-stimulated peripheral blood lymphocytes from the patient revealed increased IFN- γ , IL-5, TNF- α and IL-10 synthesis, while the patient's duodenal lymphocytes stimulated with rice also showed elevated IFN- γ and IL-5 synthesis (but not IL-10, TNF- α , and TGF- β) synthesis, indicating all together elevated TH1 and TH2 cytokine synthesis.

Rice protein-based infant formulas as a substitutive in CMA

The simplest way to deal with CMA is avoidance of cow's milk proteins. Before tolerance to CM proteins can be achieved, a CM substitute of adequate nutritional value is necessary. For nonbreastfed infants, available substitutes include extensively hydrolyzed cow's milk whey and/or casein formula, soy formula, rice hydrolysates,

and amino acid-based formula. Current guidelines define a therapeutic formula as one that is tolerated by at least 90% of CMA infants [78]. These criteria are met by some extensively hydrolyzed cow's milk whey and/or casein formula, soy and rice hydrolysates as well as by amino acid-based formula (AAF).

In a study from Italy, the tolerance of hydrolysed rice protein formula (HRF) was examined in 116 children with CMA [79]. In the present series rice specific IgE was demonstrated at skin prick test (SPT) in 4.04% of subjects sensitive to cow's milk. CAP and immunoblotting also showed a lower, although significant, level of sensitization to rice, without clinical relevance for patients who could all eat rice without undesirable effects. Specific rice IgE (SPTs, CAP and immunoblottings) appeared even more rarely with HRF (3%, 4,3% and 6,2% respectively). Moreover, immunoblottings with HRF were negative even in children sensitized to rice, suggesting that hydrolysis modifies rice protein antigenicity in as much as their IgE-binding capability is abolished. It is noteworthy that all challenges with HRF were uneventful. The fact that the presence of specific IgE to rice did not generally translate into symptoms suggested that sensitivity to these allergens is associated with poor diagnostic predictivity.

Another study examined the tolerance of HRF in 18 CMA children [61]. Sensitization to rice proteins (skin prick tests, Cap system) was found in 39% of CMA. Challenge with HRF was without consequences in all children. It was also shown that specific IgE for rice may not translate into clinical symptoms in most cases and is not a reliable index of suspicion for allergy manifestations.

A recent study [3] including 92 children assessed the clinical tolerance of a partially HRF in infants with IgE-mediated cow milk allergy. All CMA infants showed negative results to the initial SPTs to rice extract and HRF, while determination of

specific IgE to rice in serum also proved negative. The HRF was well tolerated by infants with symptoms of IgE-mediated CMP allergy, similarly to a control group that was given an EHF. Children that developed CM tolerance during the course of the study (~ 24 months) were similar in both groups, confirming the adequacy of HRF when compared to EHF.

The later matter of possible influence of the choice of different formulas on the rate of acquisition of tolerance in CMA patients has been addressed by other two studies. The first examined the rate of patients acquiring tolerance to CM after 12 months of exclusion diet with different formulas [EHF, EHF plus lactobacillus rhamnosus GG (LGG), HRF, soy formula(SF) and AAF] [44]. Only those receiving EHF containing LGG achieved tolerance more frequently than those receiving other formulas. The rate of patients acquiring tolerance at the end of the study period was similar for children receiving RHF compared with children receiving EHF alone, SF, or AAF. The second study compared EHF (casein or whey proteins), soy formula and RHF in CMA children [80]. Despite small numbers of patients in each group there were no differences between formula groups in the rate of acquisition of tolerance to CMP after 12 months.

One major disadvantage of hypoallergenic formulas and the cause of frequent complaints by parents is rejection by children due to bad taste, which is related to the formation of bitter peptides during proteolysis. Peptides released by proteolysis have a bitter taste that depends on the size of the peptide and its hydrophobicity, as the alcohol soluble part is the most bitter. It has been shown that HRF substitutes are of adequate tolerance in CMA children. The palatability of several hydrosylate and other substitution formulas [a partially hydrolyzed formula, 2 casein hydrolysates, 2 whey hydrolysates, and 2 mixed casein-whey hydrolysates, soy formulas (hydrolyzed and

nonhydrolyzed) and a rice hydrolysate were included] were examined in a study a few years ago [81]. HRF (along soy formulas) were found to have the best taste scores and a satisfactory palatability as a whole.

Nutritional value of rice protein based formula

One major concern in using rice based formula as a milk substitution is whether it's adoption as a basic nutrient source in daily diet interferes with adequate growth and nutritional sufficiency for children with CMA. This concern emanates from the fact that rice milk is extremely low in protein content. In a case series of four infants the use of rice milk formula (duration 5-13 months) resulted in severe malnutrition presenting with hypoalbuminemia and poor weight gain in three cases, and multiple secondary infections in another one [82]. This was due to daily protein intake of only 25% of the recommended dietary allowance.

Several studies have addressed the matter of the nutritional value of a rice hydrolysate in infants diagnosed with CMA (Table 5) [3, 80, 83, 84, 85]. Even though most of the studies found no important deficits in growth parameters in children who adopted HRF, these findings are not consistent with another study that demonstrated growth impairment in a group of children with atopic dermatitis and CMA who received a HRF compared to another formula. The later finding creates an ambiguity about safety and uneventful use of HRF in children with CMA.

Conclusions

Soy-based formulas have limited medical indications and there are several concerns regarding their safety in infants with CMA. It is surprising the fact that studies investigating this topic are sparse and therefore additional studies should be

performed in large cohorts of children in order to clarify whether they could be a safe and cheap substitute in children with CMA or not.

On the other hand, it has been well demonstrated that the HRF substitute is an interesting alternative option in children with CMA. First of all HRF fulfills current guidelines that define a therapeutic formula as one that is tolerated by at least 90% of infants with CMA. Also children with CMA may react to residual allergens in partially or extensively hydrolyzed formulas. Cross reaction with soy formula can even be noticed at a small but not negligible percentage of such patients (10-14%). Taking into consideration that soy milk is not suggested in CMA infants < 6 months old, as well as low palatability of amino acid based formula, rice protein based formula constitutes a quite appealing substitute in certain CMA children.

Another concern regarding rice-based formula is its nutritional sufficiency, mostly referring to low protein concentration. It has been suggested that the suitability for use in infant formula of other proteins sources and their adequate minimum and maximum amounts should be documented on a case-by-case basis. Long-term trials assessing growth parameters through various age groups could be helpful in confirming the nutritional adequacy of HRF across different age groups.

Current guidelines from World Allergy Organization ESPGHAN Gastrointestinal Committee suggest HRF as a suitable substitution for children with CMA under certain conditions, such as failure of other alternative formulas (e.g allergic manifestations or uptake refusal), or vegan families, recommending that a hydrolyzed rice formula may be considered in a selected group of infants.

Abbreviations

CMA	Cow's Milk Allergy
CMP	Cow Milk Protein
EHF	Extensively Hydrolyzed CMP Formula
AAF	Amino Acid-based Formula
LPT	Lipid Transfer Protein
FPIES	Food Protein Induced Enterocolitis Syndrome
HRF	Hydrolysed Rice Protein Formula

Conflict of interest

Authors declare no conflict of interest

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Soy allergenic proteins		
Name	MW	Allergenicity
Gly m 1	7-8 Kda	aeroallergen
Gly m 2	8 Kda	aeroallergen
Gly m 3	14 Kda	birch pollen allergen
Gly m 4	17 Kda	birch pollen allergen
Gly m 5	140-180 Kda	related with anaphylaxis to soy
Gly m 6	320-360 Kda	related with anaphylaxis to soy
Protein P34	34 Kda	the highest P34 antigenicity is found in soymilk

Table 1. Among several soy proteins that bind IgE in patients allergic to soy, only a few of them are considered to be immunodominant allergens and are shown above (16-24). MW: molecular weight.

Reference	Type of study	Number of subjects	Purpose	Conclusions
Zeiger et al, 1990	Cohort study	93 infants with CMA	Evaluation of frequency of soy allergy in children with CMA (14% concomitant soy allergy)	Soy milk safe alternative for children with CMA
Klemola et al, 2002	Prospective randomized study	170 infants with CMA	Evaluation of adverse reactions frequency in children with CMA between soy milk and EHF milk	EHF safer than soy milk in CMA infants
L. Terracciano et al, 2010	Prospective study	72 children with CMA	Comparison of EHF, rice and soy milk for acquisition of tolerance in children with CMA	Acquisition of tolerance better with rice or soy milk than EHF
Berni Canani R et al, 2013	Prospective study	260 children with CMA	Comparison of EHF, rice and soy milk for acquisition of tolerance in CMA children	Acquisition of tolerance better with EHF than soy or rice milk

Table 2. Studies conducted in children with CMA regarding either a) the safety of soy milk in these children or b) acquisition of tolerance in children with CMA receiving soy or rice milk.

Proteins/Glycoproteins	Amount of total protein (%)
Soluble proteins	
Albumins (water-soluble)	10,8
Globulins (salt-soluble)	9,7
Prolamines (70%-ethanol soluble)	2,2
16 kDa Allergen (phosphate buffered saline-soluble fraction)	~ 1,5% in seeds
Insoluble proteins	
Glutelins	77,3

Table 3. Rice protein fraction. *From Internet Symposium on Food Allergens 2001;3: 1615-168.*

Rice Proteins/Glycoproteins	
14-16 kDa rice allergen	<i>Isoallergens and Variants</i> At least 7 isoallergens of 14-16 kDa rice allergens which share > 67% amino acid sequence identity fulfilling the definition of isoallergens of the WHO/IUIS Allergen Nomenclature Subcommittee. <i>Frequency of Sensitization</i> IgE-binding to 14-16 kDa rice allergens in 67-100% of patients IgE-binding to 14-16 kDa isoallergens: a) 14-15.5 kDa allergen in 64% b) RA14 (~16 kDa) gene family, 3 isolated fractions: 41% (for 1 fraction) and 29% (other 2 fractions) c) RA17 (14-15.5 kDa) in 29%
33 kDa allergen	
60 kDa allergen	
Major Allergens: 15.5, 16, 19 kDa	
Major Allergens: 16, 25, 50, 90 kDa	
Allergens: 12,5 & 8 kDa	

Table 4. Allergens of rice. *Modified from: Internet Symposium on Food Allergens 2001;3:1615-1682*

Year (Rf)	Formula used (N)	Observation Time	Remarks
2003 (9)	SF (8) RHF (8)	6 months	Infants in both groups showed normal growth patterns during the study.
2005 (79)	SF (17) eCHy (26) RHF (15) CM (30, healthy)	~ 24 months	Significantly lower growth pattern in in RHF infants between 9 mo and 1,5 year compared to controls.
2006 (85)	RHF (32) CMF (33)	4 months	Growth and plasma biochemistry comparable in CMF and partially HRF in healthy infants.
2007 (84)	SF (32) CHy (31) RHF (30) BF (32)	~ 6 months	Infants with CMA fed hydrolyzed products showed a trend toward higher WA z-core increments in the 6 month period .
2010 (3)	EHF (46) HRPF (46)	~ 24 months	No statistical difference between the groups in growth. Growth of HPRF Infants was within normal parameters for both weight and height (WHO

Table 5. Growth of children with CMA using a RHF substitutive. Rf: reference, N: number of patients, SF: soy formula, RHF: rice hydrosylate formula, eCHy: extensively hydrosylate casein formula, CMF: cow milk formula, BF: breast fed, EHF: extensively hydrosylate formula, HRPF: hydrolysed rice protein formula, n: number of patients.