OPEN ACCESS

An extensively hydrolysed rice protein-based formula in the management of infants with cow's milk protein allergy: preliminary results after 1 month

Yvan Vandenplas, Elisabeth De Greef, Bruno Hauser, Paradice Study Group

▶ Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/archdischild-2013-304727).

Universitair KinderZiekenhuis Brussel, Vrije Universiteit Brussel, Brussels, Belgium

Correspondence to
Professor Yvan Vandenplas, Department of Pediatrics, UZ Brussel, Laarbeeklaan 101, Brussels 1090, Belgium; yvan.vandenplas@uzbrussel.be

Received 24 June 2013
Revised 19 March 2014
Accepted 9 May 2014
Published Online First 9 June 2014

ABSTRACT

Background Guidelines recommend extensively hydrolysed cow's milk protein formulas (eHF) in the treatment of infants diagnosed with cow's milk protein allergy (CMPA). Extensively hydrolysed rice protein infant formulas (eRHFs) have recently become available, and could offer a valid alternative.

Methods A prospective trial was performed to evaluate the clinical tolerance of a new eRHF in infants with a confirmed CMPA. Patients were followed for 1 month. Clinical tolerance of the eRHF was evaluated with a symptom-based score (SBS) and growth (weight and length) was monitored.

Results Thirty-nine infants (mean age 3.4 months, range 0.5–6 months) diagnosed with CMPA were enrolled. All infants tolerated the eRHF and experienced a normal growth.

Conclusions In accordance with current guidelines, this eRHF is tolerated by more than 90% of children with proven CMPA with a 95% CI, and is an adequate alternative to cow's milk-based eHF.

Trial registration number ClinicalTrials.gov NCT01998074.

What is already known about this topic

- Extensive cow's milk-based hydrolysed formulas are the first choice in the treatment of cow's milk protein allergy.
- Extensive hydrolysates are not everywhere available, are expensive, have a poor palatability, and some infants are still allergic to the cow's milk peptides present in the hydrolysate.
- Soy infant formula has been proposed as second option, but the negative perception of the high levels of phytoestrogens present in soy hampers their use. Moreover, 10–15% of the infants allergic to cow's milk also do not tolerate soy.

What this study adds

- An extensive rice protein-based hydrolysed formula is shown to be effective in the treatment of cow's milk protein allergy.
- Since rice is much cheaper and has a better palatability than cow's milk-based extensive hydrolysates, and since it does not contain phytoestrogens, it may become a first option in the treatment of cow's milk protein allergy if the efficacy and acceptability are confirmed in future studies.

INTRODUCTION

Guidelines for the dietary management of infants diagnosed with cow's milk protein allergy (CMPA) recommend the substitution of cow's milk with extensively hydrolysed casein or whey protein formulas (eHF).[1–4] Up to 14% of infants with CMPA will also react to soy-based formulas,[3] even though it appears less likely in immunoglobulin E (IgE)-mediated CMPA compared to non-IgE-mediated CMPA.[5] Therefore, the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) recommends not using soy-based infant formula before the age of 6 months.[6] Consequently, soy is not considered as first-line option in the treatment of CMPA in the Western world.[5] eHFs Are substantially more expensive than standard infant formula and soy formula, and generally have a bitter taste which often hampers their acceptability.[7] Some infants may still be intolerant or allergic to these eHFs.[3 8] In those cases, amino acid-based formulas are an effective dietary treatment in infants intolerant to eHF,[1 2 5] but are substantially more expensive than eHF.

As a result, affordable and better tasting dietary options in the treatment of CMPA would be welcomed as an alternative. Hydrolysed formulas based on rice protein, supplemented with L-lysine and L-threonine to achieve an optimal amino acid profile similar to that of mother's milk, may offer such an option.[9 10] Therefore, the efficacy of this new extensively hydrolysed rice protein infant formula (eRHF) was evaluated in infants with CMPA.

MATERIALS AND METHODS

Infants who initially presented to paediatricians with symptoms suggesting CMPA were selected. Diagnostic criteria to suspect CMPA were based on the presence of a combination of the following symptoms: general discomfort (persistent distress or colic≥3 h/day, wailing/irritability at least 3 days/week since at least 1 week), gastrointestinal signs and symptoms (frequent regurgitation, vomiting, diarrhoea, constipation with or without perianal rash, blood in the stools), respiratory symptoms (runny nose, otitis media, chronic cough, wheezing unrelated to infection) and dermatological

To cite: Vandenplas Y, De Greef E, Hauser B, *et al*. *Arch Dis Child* 2014;**99**:933–936.

manifestations (atopic dermatitis, angio-oedema, urticaria unrelated to acute infections, drug intake).[11] A symptom-based score (SBS) was developed, and the severity of each presenting symptom was scored[12] (e-Table).

Infants were included after the diagnosis of CMPA was confirmed by a positive open challenge, except if a challenge test was contraindicated according to recent guidelines.[2] The challenge was performed with cow's milk protein infant formula, according to a standardised challenge test procedure.[1] The paediatricians determined a SBS before the food challenge, after the food challenge and 1 month after dietary treatment with the eRHF. The challenge procedure lasted for half a day. If no reaction occurred, parents administered at least 250 mL/day of standard infant formula during 1 week. During that week, the physician followed the symptoms on a daily basis. Parents had to report any change/reaction they noticed. If any, the child was presented at the outpatient clinic and the physician evaluated the evolution of the SBS. The challenge was considered as positive if symptoms increased immediately or a few days (up to 7 days) after the start of the food challenge.

Infants with a positive challenge were included in the study. During the 1-month study period, only the formula was changed to exclusive formula feeding with the new eRHF (Novarice, United Pharmaceuticals; nutritional information (/100 mL): proteins 1.8 g; lipids 3.4 g; carbohydrates 6.6 g; fibres 0.5; energy 65.7 kcal). Paediatricians advised parents to not change or start solids during the 1 month of intervention. Infant formulas are the only recommended foods for infants below 6 months. The SBS was used to follow these infants.[11–13] Growth was monitored and evaluated as z scores according to the WHO Child Growth Standards.[14]

The test formula contains extensively hydrolysed-rice proteins supplemented with lysine and tryptophan to improve the nutritional quality by providing an amino acid profile similar to that of mother's milk, in compliance with the recommendation of the EU directive on infant formulas. It also contains a thickening complex using pectin due to the fact that formulas based on extensively hydrolysed protein are particularly liquid. The formula complies with EU regulation. Feeding tolerance and adverse events were registered throughout the month during which this formula was administered exclusively to the infants.

The treating physician could perform a skin prick test (SPT) and measure specific IgE, according to their preference. The evaluation of the SPT was conducted according to the standard criteria, that is, a papula of 3 mm induration compared to a negative control with saline solution.[15]

The study was approved by the ethical committee of the UZ Brussel, acting as the leading centre, and of each participating centre or investigator; 14 investigators (all paediatricians with more than 10 years of practice (CH, MNR, NB, MPM, TC, ED, JFQ, JC, FH, RL, LV; MNR being also allergist) and two paediatric gastroenterologists (A l'H, BH) from 11 centres participated in the trial. A written informed consent was obtained from all parents. The trial is registered as ClinicalTrials.gov NCT01998074.

In order to be considered hypoallergenic, a therapeutic formula must demonstrate in a clinical study that with 95% CI, it does not provoke allergic reactions in 90% of infants or children with confirmed cow's milk allergy.[4] In case of no reaction, the lower 95% CI for the proportion of patients with no reaction should be greater than 90%; a sample size of 29 participants is sufficient to show hypoallergenicity. Considering possible drop-outs or deviations to inclusion criteria, the target was to recruit 36 patients. Statistical analysis was carried out using SAS V.9.2 software. For qualitative parameters classified in two categories, McNemar's test was used; in case of more than two categories, symmetry test was used; paired Student t test was used for quantitative parameters. The normality of distribution was systematically checked using Shapiro Wilk's test and the Wilcoxon's test was used in case of non-normality.

RESULTS

The first 39 infants fulfilling the inclusion criteria of whom the parents accepted to participate in the study and signed the informed consent, were recruited (21 boys, 18 girls; age 3.3 ±1.5 months (mean±SD), range 0–6 months). The mean and median weight gain over 1 month were 600 g and 700 g, respectively (at inclusion: 6.1±1.2 kg (mean±SD); 6.2 kg (median); 3.0–9.4 kg (range); after 1 month: 6.7±1.1 kg; 6.9 kg; 3.8–9.7 kg). The mean and median growth were 2.3 cm and 3.0 cm, respectively (at inclusion: 61.9±3.8 cm; 62 cm; 50–69 cm; after 1 month: 64.2±3.7 cm; 65 cm; 53–70.5 cm).

Two patients did not have a CMP-challenge because of an initial anaphylactic reaction. The CMP-challenge was positive in the remaining infants; 13 infants had an immediate type of reaction. A SPT was performed in 15 infants and was positive in 14 (mean wheal 11.5±5.6 mm; median 10 mm; range 5–20 mm; mean rash 11.9±4.4 mm; median 12 mm; range 5–25 mm).

Two parents decided to stop the trial because according to their opinion the infant did not like or accept the study formula and preferred the "initial" formula (which was given before the challenge): one infant was on soy formula, the other on a cow's milk-based eHF. In both cases, this was a parental decision. According to the treating physician, these drop-outs were due to low-acceptance (taste) of study formula.

The SBS was significantly lower after 1 month of eHF feeding than during the challenge (table 1, $p<0.0001$).

During the challenge, at inclusion time, 51.3% of the infants had either hard or watery stools (27.0% and 24.3%, respectively), while after 1 month feeding with the eHRF, only 10.8% of the infants had hard or watery stools (8.1% and 2.7%, respectively) according to the Bristol scale ($p<0.0001$). At the time of inclusion, 56.7% of the infants were crying more than 3 h/day, whereas, after 1 month, none of the infants were crying more than 3 h/day ($p<0.0001$), and 64.9% were crying less than 1 h/day. The regurgitation score decreased by 75% over 1 month (from 2.4 to 0.6, $p<0.0001$). All parameters composing the score had decreased after 1 month of dietary treatment with the study formula (table 1), the evolution for urticaria and eczema on head, neck and trunk being statistically significant.

All the 37 children successfully completed the study and tolerated the rice-based formula. After 1 month of feeding with the study formula, the mean weight-for-age z-score (±SD) was −0.48±0.85 vs −0.71±0.97 at inclusion. The mean weight-for-length z-score went from −1.1±1.2 to −0.8±0.9; the mean length-for-age z-score from 0.2±0.9 to 0.2±1.0 and the mean Body Mass Index for age z-score from −1.1±1.2 to −0.8±0.9. The average total weight gain over the course of the 1 month observation period was 701±292 g, that is, 22.8±8.7 g/day. This is within the standard range for growth according to the WHO Child Growth Standards.[14]

DISCUSSION

We demonstrated that the tolerance of this formula, containing hydrolysed rice proteins, was excellent in infants with CMPA, and that weight and length gains were normal. Up to now, all studies with hydrolysed rice protein formulas were performed with a partial hydrolysate (pRHF). Nevertheless, these studies

Table 1 Evolution of the symptom-based score (SBS)

	Before challenge (n:39)	Inclusion (n:37)	1 month (n:37)	p Value
Global-score				
Mean±SD (CI 95%)	9.4±6.1 (7.4 to 11.4)	13.0±5.2 (11.3 to 14.7)		<0.0001*
		13.0±5.2 (11.3 to 14.7)	3.5±2.3 (2.7 to 4.3)	<0.0001*
Crying (%), (CI 95%)				
<1 h/day		13.5 (2.5 to 24.5)	64.9 (49.5 to 80.2)	
1.5 h/day		5.4 (0.0 to 12.7)	21.6 (8.4 to 34.9)	
2 h/day		5.4 (0.0 to 12.7)	10.8 (0.8 to 20.8)	
2–3 h/day		18.9 (6.3 to 31.5)	2.7 (0.0 to 7.9)	
3–4 h/day		18.9 (6.3 to 31.5)	0.0	
4–5 h/day		5.4 (0.0 to 12.7)	0.0	
>5 h/day		32.4 (17.3 to 47.5)	0.0	
Crying (%), (CI 95%)				
Crying <3 h/day		43.2 (27.3 to 59.2)	100.0 (100.0 to 100.0)	<0.0001†
Crying ≥3 h/day		56.7 (40.8 to 72.7)	0.0	
Crying score‡				
Mean±SD, (CI 95%)		3.7±2.1 (3.0 to 4.4)	0.5±0.8 (0.2 to 0.8)	<0.001§
Regurgitations score[27]‡				
Mean±SD, (CI 95%)		2.4±2.2 (1.6 to 3.1)	0.6±0.9 (0.4 to 0.9)	<0.0001*
Stools (%), (CI 95%)[28]				
Type I/II (hard)		27.0 (12.7 to 41.3)	8.1 (0.0 to 16.9)	
Type III/IV (normal)		5.4 (0.0 to 12.7)	54.1 (38.0 to 70.1)	
Type V (soft)		10.8 (0.8 to 20.8)	8.1 (0.0 to 16.9)	
Type VI (mushy)		32.4 (17.3 to 47.5)	27.0 (12.7 to 41.3)	
Type VII (watery)		24.3 (10.5 to 38.1)	2.7 (0.0 to 7.9)	
Stools (%), (CI 95%)				
Normal stools (types III, IV)		5.4 (0.0 to 12.7)	54.1 (38.0 to 70.1)	<0.0001†
Non-normal stools (types I, II, V, VI)		94.5 (87.3 to 100)	45.9 (29.9 to 62.0)	
Urticaria (%), (CI 95%)				
Present		16.2 (4.3 to 28.1)	0.0	0.0143†
Absent		83.8 (71.9 to 95.7)	100.0 (100.0 to 100.0)	
Eczema (%), (CI 95%)				
Head, neck, trunk				
Absent		51.4 (35.2 to 67.5)	78.4 (65.1 to 91.6)	0.0348¶
Mild		18.9 (6.3 to 31.5)	18.9 (6.3 to 31.5)	
Moderate		18.9 (6.3 to 31.5)	2.7 (0.0 to 7.9)	
Severe		10.8 (0.8 to 20.8)	0.0	
Arms, hands, legs, feet				
Absent		64.9 (49.5 to 80.2)	86.5 (75.5 to 97.5)	0.1557¶
Mild		10.8 (0.8 to 20.8)	13.5 (2.5 to 24.5)	
Moderate		13.5 (2.5 to 24.5)		
Severe		10.8 (0.8 to 20.8)		
Respiratory symptoms (%), (CI 95%)				
No		75.7 (61.9 to 89.5)	81.1 (68.5 to 93.7)	0.5062¶
Mild		18.9 (6.3 to 31.5)	13.5 (2.5 to 24.5)	
Moderate		5.4 (0.0 to 12.7)	5.4 (0.0 to 12.7)	

Stools were scored according to the Bristol stool scale[28].
*Paired Student t test.
†McNemar test.
‡Sub-scores included in the calculation of the SBS score.
§Wilcoxon test.
¶Symmetry test.

also focused on their tolerance in infants with CMPA.[13–15] Two studies by Fiocchi *et al*[16] have shown that infants with CMPA and other food allergies tolerated pRHF.[17] Reche *et al*[18] demonstrated a 95% efficacy rate with a pRHF in infants with CMPA. We observed a 100% efficacy rate with this eRHF. The molecular weight profile of the proteins in Novarice is comparable to that of cow's milk-based eHF.[16]

In spite of the doubts raised by a publication[17] regarding the nutritional adequacy of pRHF, growth was shown to be adequate in this trial and also in other studies carried out using a pRHF in infants diagnosed with CMPA.[18 19] A normal weight and length evolution was observed. Furthermore, the nutritional adequacy of a pRHF was also shown in a double-blind randomised trial in healthy infants who had normal growth parameters.[20] Other trials confirmed these findings.[21–23]

Rice has also recently been criticised regarding its possible arsenic content. However, this concerned mainly organic brown rice syrup, and was not related to infant formula based on

extensively hydrolysed rice protein. There is no EU regulation fixing limits to arsenic in infant formulas. In particular, this study formula contains less than 10 μg/L of arsenic, which is the maximum content allowed in drinking water according to EU regulation (drinking water being the only food in which arsenic content is regulated) and infant formulas are reconstituted with approximately 86–87% of water.[24] The authors agree with UK Food Standards Agency advice that rice drink is not a suitable substitute for breast or formula milk at any stage of infancy or early childhood as it is nutritionally inadequate.[25] However, this trial evaluated a rice-based infant formula, whose nutritional composition conforms to the European regulations, particularly regarding the amino acid profile, and thus differs in all aspects from rice drinks. The arsenic content of the rice-based infant formula is much lower (<10 μg/L) than the level of arsenic in rice drinks (23 μg/L) mentioned by the UK Food Standard Agency.[25]

In this study, the rice protein-based formula was well tolerated overall. The parents of two patients said their infant did not like the taste of the formula. In general, one of the main complaints of parents was that infants refuse hydrolysed formulas because of the unpleasant bitter taste. A recent double-blind study evaluating the palatability of different formulas used to feed infants with CMPA showed that soy and rice-based formulas had better taste scores than CMP hydrolysed formulas.[26] Good oral tolerance because of its pleasant odour, taste and flavour was confirmed for rice formulas in healthy infants.[18 26] In the absence of a control group it is not possible to show superiority of one dietetic therapeutic intervention over another; however, the goal of this study was to demonstrate the efficacy of a dietary intervention with a new therapeutic formula in infants with proven CMPA.

In conclusion, the preliminary data with this new extensively hydrolysed rice protein formula showed that the formula was tolerated by more than 90% of infants with a demonstrated CMPA, with a 95% CI. Its good acceptability makes this kind of formula an interesting option in the treatment of CMPA. However, more data on a larger number of children and a longer follow-up are needed. Infants were followed for 6 months, and data on this longer follow-up will be available soon.

Collaborators Paradice Study Group: C Halut, MN Robberecht, N Balduck, A l'Homme, MP Mohring, T Carvelli, B Hauser, E Defontaine, JF Questiau, J Christens, F Henckens, R Lemmens, L Vercammen, E De Greef.

Contributors The protocol was developed by YV. All authors, including all members of the Study Group included patients. Data were collected and the manuscript was written by BH, EDG and YV.

Competing interests YV is consultant for United Pharmaceuticals and Biocodex.

Ethics approval Ethics Committee UZ Brussels.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Vandenplas Y, Koletzko S, Isolauri E, *et al*. Guidelines for the diagnosis and management of cow's milk protein allergy in infants. *Arch Dis Child* 2007;92:902–8.
2 Koletzko S, Niggemann B, Arato A, *et al*.; European Society of Pediatric Gastroenterology, Hepatology, and Nutrition. Diagnostic approach and management of cow's-milk protein allergy in infants and children: ESPGHAN GI Committee practical guidelines. *J Pediatr Gastroenterol Nutr* 2012;55:221–9.
3 Bhatia J, Greer F; American Academy of Pediatrics Committee on Nutrition. Use of soy protein-based formulas in infant feeding. *Pediatrics* 2008;121:1062–8.
4 No authors listed]. American Academy of Pediatrics. Committee on Nutrition. Hypoallergenic infant formula. *Pediatrics* 2000;106:346–9.
5 Zeiger RS, Sampson HA, Bock SA, *et al*. Soy allergy in infants and children with IgE-associated cow's milk allergy. *J Pediatr* 1999;134:614–22.
6 Agostoni C, Axelsson I, Goulet O, *et al*.; ESPGHAN Committee on Nutrition. Soy protein infant formulae and follow on formulae a commentary by the ESPGHAN. *J Pediatr Gastroenterol Nutr* 2006;42:352–61.
7 Høst A, Koletzko B, Dreborg S, *et al*. Dietary products used in infants for treatment and prevention of food allergy. Joint Statement of the European Society for Paediatric Allergology and Clinical Immunology (ESPACI) Committee on Hypoallergenic Formulas and the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) Committee on Nutrition. *Arch Dis Child* 1999;81:80–4.
8 Klemola T, Vanto T, Juntunen-Backman K, *et al*. Allergy to soy formula and to extensively hydrolyzed whey formula in infants with cow's milk allergy: a randomised study with a follow-up to the age of 2 years. *J Pediatr* 2002;140:219–24.
9 Koletzko B, Baker S, Cleghorn G, *et al*.; ESPGHAN Committee on Nutrition. Global Standard for the composition of infants formula: recommendations of an ESPGHAN coordinated international expert group. *J Pediatr Gastroenterol Nutr* 2005;41:584–99.
10 Commission Directive 2006/141/CE of 22 December 2006 on infant formulae and follow-on formulae and amending Directive 1999/21/EC. OJ L 401, 30.12.2006, p.1.
11 Vandenplas Y, Steenhout P, Planoudis Y, *et al*.; Althera Study Group. A double-blind randomized trial comparing two extensively hydrolyzed formulas with probiotics for the treatment of cow's milk protein allergy. *Acta Paediatr* 2013;102:990–8.
12 Vandenplas Y, Steenhout P, Grathwohl D; Althera Study Group. A pilot study on the application of a symptom-based score for the diagnosis of cow's milk protein allergy. *SAGE Open Med* 2014;2.
13 Vandenplas Y, De Greef E; ALLAR Study Group. Extensive protein hydrolysate formula effectively reduces regurgitation in infants with positive and negative challenge tests for cow's milk allergy. *Acta Paediatr* 2014;103:e243–50.
14 WHO Multicentre Growth Reference Study Group. WHO Child Growth Standards: Length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age: Methods and development. Geneva: World Health Organization, 2006.
15 Dreborg S, Frew A. EAACI position paper: allergen standardization and skin tests. *Allergy* 1993;48(Suppl 14):48–82.
16 Fiocchi A, Travaini M, D'Auria E, *et al*. Tolerance to a rice hydrolysate formula in children allergic to cow's milk and soy. *Clin Exp Allergy* 2003;33:1576–80.
17 Fiocchi A, Restani P, Bernardini R, *et al*. A hydrolyzed rice-based formula is tolerated by children with cow's milk allergy: a multi-centre study. *Clin Exp Allergy* 2006;36:311–16.
18 Reche M, Pascual C, Findaor A, *et al*. The effect of a partially hydrolyzed formula based on rice protein in the treatment of infants with cow's milk protein allergy. *Pediatr Allergy Immunol* 2010;21:577–85.
19 Comité de Nutrition de la Société Française de Pédiatrie. Utilisation des formules à charge antigénique réduite. *Arch Pediatr* 2000;7:302–61.
20 Savino F, Castagno E, Monti G, *et al*. Z-score of weight for age of infants with atopic dermatitis and cow's milk allergy fed with a rice-hydrolysate formula during the first two years of life. *Acta Paediatr* 2005;94:115–19.
21 D'Auria E, Sala M, Lodi F, *et al*. Nutritional value of a rice-hydrolysate formula in infants with cows' milk protein allergy: a randomized pilot study. *J Int Med Res* 2003;31:215–22.
22 Agostoni C, Fiocchi A, Rive E, *et al*. Growth of infants with IgE-mediated cow's milk allergy fed different formulas in the complementary feeding period. *Pediatr Allergy Immunol* 2007;18:599–606.
23 Lasekan JB, Koo WK, Walters J, *et al*. Growth, tolerance and biochemical measures in healthy infants fed a partially hydrolyzed rice protein-based formula: a randomised, blinded prospective trial. *J Am Coll Nutr* 2006;25:12–19.
24 Council Directive 98/83/EC of 3 November 1998 on the quality of water intended for human consumption. OJ L 330, 5.12.1998, p.32.
25 United Kingdom Food Standards Agency. Food Survey Information Sheet 02/09. Survey of total and inorganic arsenic in rice drinks. http://multimedia.food.gov.uk/multimedia/pdfs/fsis0209arsenicinrice.pdf
26 Pedrosa M, Pascual CY, Larco JI, *et al*. Palatability of hydrolysates and other substitution formulas for cow's milk-allergic children: a comparative study of taste, smell, and texture evaluated by healthy volunteers. *J Investig Allergol Clin Immunol* 2006;16:351–6.
27 Vandenplas Y, Hachimi-Idrissi S, Casteels A, *et al*. A clinical trial with an anti-regurgitation formula. *Eur J Pediatr* 1994;153:419–23.
28 Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. *Scand J Gastroenterol* 1997;32:920–4.