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An extensively hydrolysed casein-based formula for infants with cows' milk protein allergy: tolerance/hypo-allergenicity and growth catch-up

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Abstract

Children with cows' milk protein allergy (CMPA) are at risk of insufficient length and weight gain, and the nutritional efficacy of hypo-allergenic formulas should be carefully assessed. In 2008, a trial assessed the impact of probiotic supplementation of an extensively hydrolysed casein-based formula (eHCF) on acquisition of tolerance in 119 infants with CMPA. First analysis of the study results showed that the studied formula allowed improvement of food-related symptoms. The scoring of atopic dermatitis (SCORAD) index was assessed at randomisation and after 6 months of feeding. A *post hoc* analysis was performed using WHO growth software's nutritional survey module (WHO Anthro version 3.2.2). All infants who were fed the study formula tolerated it well. The SCORAD index significantly improved from randomisation to 6 months of feeding with the study formula. Anthropometric data indicated a significant improvement in the weight-for-age, length-for-age and weight-for-length z scores, as well as in the restoration of normal BMI. The probiotic supplementation did not show any impact on these parameters. The present data showed that this eHCF was clinically tolerated and significantly improved the SCORAD index and growth indices.

Key words: Anthropometric data: Infant development: Scoring of atopic dermatitis: Hypo-allergenic formulas

Cows' milk (CM) proteins are the most frequent cause of food allergy during infancy. Depending on diagnostic criteria and study design, estimates of the prevalence of cows' milk protein allergy (CMPA) vary from 2 to 7·5%[1].

The first-line treatment for food allergy disorders is avoidance of the suspected allergen. In the particular case of CMPA, guidelines recommend the use of formulas in which CM proteins are extensively hydrolysed[1,2]. By reducing the number of conformational and sequential epitopes, extensive hydrolysis dramatically reduces allergenicity of CM proteins. This avoidance of contact to allergens is the primary objective of using extensively hydrolysed formulas and most often allows infants to thrive while progressively outgrowing CMPA. Thus, hypo-allergenic formulas should ensure a normal development of the infant; however, data relating to the impact of these formulas on infants' growth are insufficient[3–5].

In 2008, the Cow's Milk Allergy Modified by Elimination and Lactobacilli (CAMEL) study was a randomised, double-blind, placebo-controlled trial, funded by the Dutch Ministry of Economic Affairs, that aimed at determining whether acquisition of tolerance to CM would be affected by supplementation to the infant formula with a combination of two probiotics (*Lactobacillus casei* CRL431 and *Bifidobacterium lactis* Bb-12)[6]. This study included 119 allergic infants fed with an extensively hydrolysed casein-based formula (eHCF) either supplemented with probiotics or without probiotics for 6 months. The probiotic supplementation did not improve acquisition of tolerance. However, although collected, the data concerning tolerance of the formula and growth parameters of all infants included in the study did not appear in the initial analysis.

Therefore, the objective of this *post hoc* analysis was to capitalise on the data pertaining to a population of infants

Abbreviations: AD, atopic dermatitis; CAMEL, Cow's Milk Allergy Modified by Elimination and Lactobacilli; CM, cows' milk; CMPA, cows' milk protein allergy; DBPCFC, double-blind, placebo-controlled food challenge; eHCF, extensively hydrolysed casein-based formula; SCORAD, scoring of atopic dermatitis.

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† See the Appendix for a full list of the CAMEL study group members.

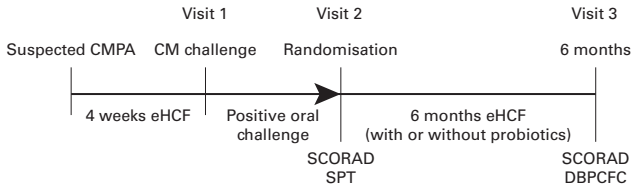

Fig. 1. Design of the study adapted from the Cow's Milk Allergy Modified by Elimination and Lactobacilli study[6]. CMPA, cows' milk protein allergy; eHCF, extensively hydrolysed casein-based formula; CM, cows' milk; SCORAD, scoring of atopic dermatitis; SPT, skin prick test; DBPCFC, double-blind, placebo-controlled food challenge.

with validated CMPA in order to assess the tolerance/hypo-allergenicity of the formula along with its safety for growth in infants fed this eHCF for 6 months.

Methods

Population and design

The present randomised, double-blind, placebo-controlled study enrolled infants with a diagnosis of CMPA, aged less than 6 months, followed up by the paediatricians of the CAMEL study group. The present study was conducted according to the guidelines laid down in the Declaration of Helsinki, and all procedures involving human subjects were approved by the local ethics committee of the Erasmus MC, Rotterdam. At least, one parent in each family provided written informed consent before inclusion.

Interventions

Details of the procedure have been described previously[6]. In brief, upon identification, infants with suspected CMPA were prescribed an eHCF for at least 4 weeks (Fig. 1). Following this, CMPA was then confirmed at visit 1 using a food challenge performed according to the current guidelines[7,8]. All infants with positive challenge were randomised at visit 2 (inclusion visit) to the supplemented or the non-supplemented eHCF group. Skin prick tests against milk, egg and soya were performed at visit 2, and a double-blind, placebo-controlled food challenge (DBPCFC) was performed after 6 months of eHCF feeding (visit 3).

Study products

The eHCF was a commercially available formula especially designed for infants with CMPA (Allernova, Allergy Care; United Pharmaceuticals). The probiotic-supplemented formula used the same eHCF but with *L. casei* CRL431 and *B. lactis* Bb-12. Nutritional composition of the eHCF conforms to the essential composition set by the European Directive 1999/21 for foods for special medical purposes and by the European Directive 2006/141 for infant and follow-on formulas, particularly regarding the amino acid profile. The energy content in the formula is 276·9 kJ/100 ml (66·3 kcal/100 ml), and the protein, lipid and carbohydrate contents are 1·6, 3·5 and 7·2 g/100 ml, respectively. The extensive casein hydrolysate has a median peptide size of 267 Da, with more than 95 % of peptides less than 1500 Da.

Measurements

Allergic symptoms were registered after food challenge, at visits 1 and 3. The scoring of atopic dermatitis (SCORAD) index, assessing the severity of the eczema, was measured at visits 2 and 3[9]. Weight and length were measured at visits 2 and 3. Weight-for-age, length-for-age, weight-for-length and BMI-for-age z scores were computed for each infant, based on the WHO 2006 reference data[10].

Statistical analyses

Normality of distributions was assessed using the Shapiro–Wilk test. Quantitative parameters were compared within groups between visit 2 (randomisation) and visit 3 using Student's t test (normally distributed data) or Wilcoxon's test (non-normally distributed data), and were compared between groups using ANCOVA based on ranks with the baseline value as a co-variable. Statistical analyses were conducted using SAS version 9.2 (SAS Institute Inc.). Statistical tests were two-sided, and the level of significance was set at 5 %. Sample size calculation showed that ninety-seven patients were required to demonstrate an increase of +0·5 in the weight-for-age z score, considering 1·5 SD and assuming a type-I error of 5 % and a power of 90 %[3]. Distributions of z scores compared with normal reference values were represented using WHO Anthro version 3.2.2 software.

Results

Study population

Of the 193 infants with suspected CMPA referred to the CAMEL study, 119 met the criteria to continue the study following

Table 1. Baseline characteristics of included infants

(Mean values and standard deviations; number of subjects and percentages)

	eHCF (*n* 60)		eHCF + probiotics (*n* 59)		Total (*n* 119)	
	n	%	*n*	%	*n*	%
Boys	36	60·0	30	50·8	66	55·5
Age at inclusion (months)						
Mean	4·1		4·3		4·2	
SD	1·5		1·2		1·4	
Birth weight (g)						
Mean	3445		3456		3451	
SD	556		504		529	
Gestational age (weeks)						
Mean	39·6		39·5		39·6	
SD	1·7		1·6		1·6	
Caesarean delivery	10	16·7	12	20·7	22	18·6
Positive SPT against milk	12	20·7	6	10·3	18	15·5
Positive SPT against egg	13	22·4	10	17·2	23	19·8
Positive SPT against soya	2	3·4	1	1·7	3	2·6

eHCF, extensively hydrolysed casein-based formula; SPT, skin prick test.

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Table 2. Symptoms that developed during oral food challenge at visit 1 by allergic infants
(Number of subjects and percentages)

		eHCF (*n* 59)		eHCF + probiotics (*n* 59)		Total (*n* 118)	
		n	%	*n*	%	*n*	%
Skin symptoms	Urticaria	3	5·1	4	6·8	7	5·9
	Rash	31	52·5	24	40·7	55	46·6
	Pruritus	6	10·2	10	16·9	16	13·6
	Eczema	5	8·5	8	13·6	13	11·0
Gastrointestinal symptoms	Vomiting	16	27·1	14	23·7	30	25·4
	Diarrhoea	9	15·2	6	10·2	15	12·7
Respiratory symptoms	Sneezing	0	0·0	0	0·0	0	0·0
	Wheezing	1	1·7	2	3·4	3	2·5
Subjective symptoms (crying and irritability)		27	45·8	25	42·4	52	44·1

eHCF, extensively hydrolysed casein-based formula.

a confirmed CMPA. The mean age was 4·2 months (minimum 1·4, maximum 6·0), and males represented 55 % of included patients. The baseline characteristics of the study population included are summarised in Table 1. At visit 1, the allergic symptoms on oral challenge with a CM formula were urticaria, worsening of atopic eczema/atopic dermatitis (AD) syndrome, vomiting, diarrhoea, physician-diagnosed wheezing or convincing behavioural symptoms. Among the 119 included infants, 54·2 % had skin reactions; 33·9 % had gastrointestinal reactions; 44·1 % had subjective symptoms, such as crying and irritability; and 2·5 % had airway reactions on oral challenge at visit 1 (Table 2). Among infants who had subjective symptoms, 32·7 % expressed also skin symptoms, 36·5 % gastrointestinal symptoms and 1·9 % airway reactions; 23·1 % had two or more other symptoms than subjective symptoms, and 9·6 % expressed symptoms in two organ systems.

Hypo-allergenicity/tolerance

All the 193 screened infants were fed the eHCF for at least 4 weeks or more. All of them clinically tolerated the eHCF well, including the 119 infants who had an overt CMPA and could eventually be maintained in the follow-up, 6-month study.

During the following 6 months, eight subjects dropped out: five lost to follow-up; two consents retracted by the parents; one study formula stopped by the paediatrician. Of the 111 included infants who completed the 6-month feeding period, sixty-one became tolerant to CM and fifty were still allergic to CM at 6 months according to a DBPCFC.

At visit 3, among the fifty infants still allergic to CM, 59·2 % had skin reactions, 36·7 % gastrointestinal reactions, 51·0 % subjective symptoms and 4·1 % airway reactions after the DBPCFC. Details of each item are described in Table 3. Among the infants who had subjective symptoms, 27·8 % expressed also skin symptoms, 77·8 % gastrointestinal symptoms and 5·6 % airway reactions; 27·8 % had two or more other symptoms than subjective symptoms, and 27·8 % expressed symptoms in two organ systems.

Evolution of the scoring of atopic dermatitis index at 6 months

The mean SCORAD index of infants fed the eHCF for 6 months significantly improved (Table 4), and decreased from 9·9 (SD 14·2) at randomisation to 5·6 (SD 9·5) at 6 months ($P<0·001$, Wilcoxon's test). In the sub-population of infants with eczema (SCORAD >0), the SCORAD index decreased

Table 3. Symptoms that developed during double-blind, placebo-controlled food challenge at 6 months (visit 3) by still allergic infants
(Number of subjects and percentages)

		eHCF (*n* 25)		eHCF + probiotics (*n* 24)		Total (*n* 49)	
		n	%	*n*	%	*n*	%
Skin symptoms	Urticaria	4	16·0	3	12·5	7	14·3
	Rash	16	64·0	9	37·5	25	51·0
	Pruritus	1	4·0	3	12·5	4	8·2
	Eczema	6	24·0	4	16·7	10	20·4
Gastrointestinal symptoms	Vomiting	4	16·0	8	33·3	12	24·5
	Diarrhoea	6	24·0	7	29·2	13	26·5
Respiratory symptoms	Sneezing	1	4·0	0	0·0	1	2·0
	Wheezing	0	0·0	1	4·2	1	2·0
Subjective symptoms (crying and irritability)		10	40·0	8	33·3	18	36·7

eHCF, extensively hydrolysed casein-based formula.

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Table 4. The scoring of atopic dermatitis (SCORAD) index at randomisation and at 6 months
(Mean values and standard deviations)

		Randomisation		6 months		Evolution			
	Treatments	Mean	SD	Mean	SD	Mean	SD	*P* (intra-group)	*P* (inter-group)
All subjects included (*n* 110)	eHCF	9·0	12·9	5·3	8·0	−3·7	10·3	0·011*	0·630†
	eHCF + probiotics	10·9	15·5	6·0	10·8	−4·9	12·5	0·008*	
	Total	9·9	14·2	5·6	9·5	−4·3	11·4	<0·001*	
Subjects with SCORAD > 0 (*n* 72)	eHCF	15·0	13·7	8·8	8·8	−6·2	12·8	0·009‡	0·836†
	eHCF + probiotics	15·3	16·4	8·4	12·0	−6·9	14·4	0·008*	
	Total	15·2	15·1	8·6	10·6	−6·6	13·6	<0·001*	

eHCF, extensively hydrolysed casein-based formula.
* Wilcoxon's test.
† ANCOVA based on ranks.
‡ Student's *t* test.

significantly by −6·6 (SD 13·6; $P<0·001$). Probiotic supplementation to the eHCF had, however, no significant effect on the evolution of the SCORAD index.

Anthropometric data

At birth, the mean weight-for-age *z* scores of included infants were all higher than 0·0 (Table 5). From birth to randomisation in the study, the mean weight-for-age *z* scores decreased significantly by −1·5 (SD 1·1) in the entire study population, subgroup analysis showing no difference between the two groups.

Following the 6-month feeding of eHCF, a significant improvement was observed for the weight-for-age, length-for-age and weight-for-length *z* scores, as well as restoration of a normal BMI (Table 6). Subgroup analyses did not show any benefit from the probiotic supplementation. In addition, proportions of infants with length-for-age and weight-for-age *z* scores below −2·0 were significantly reduced (Table 7). The distribution of *z* scores for weight-for-age, length-for-age and weight-for-length at randomisation and after 6 months is shown in Figs. 2–4. At randomisation, the weight-for-age curve followed an expected dispersion but a deviation to the left. The length-for-age curve also showed a deviation to the left but a greater value of dispersion. The weight-for-length curve followed the expected dispersion but showed a slight deviation to the left. A 6-month feeding with the eHCF allowed normalisation of these three distributions.

Discussion

This *post hoc* analysis of the CAMEL study assessed, in a well-characterised population of infants with CMPA proved by oral challenge, the tolerance/hypo-allergenicity of the eHCF and its nutritional adequacy.

A total of 193 infants suspected of having CMPA were fed with the eHCF for at least 4 weeks. All of them, including the 119 infants with CMPA, clinically tolerated the eHCF well for 4 or more weeks, which is more than a sufficient period to detect late-onset allergic reactions according to the American Academy of Paediatrics[11].

Previously published data mainly reported changes in the SCORAD index in infants fed an extensively hydrolysed whey-based formula. Previously, two studies have shown an improvement in this index after 6 and 8 months of extensively hydrolysed whey-based formula treatment[12,13], as also observed in the present study after 6 months of eHCF feeding. These results are in opposition to those reported by Niggemann *et al.*[14]. The SCORAD index results were registered at randomisation and after approximately 28, 60, 90 and 180 d. They did not show any significant improvement and remained constant throughout the trial period. As already evidenced by the CAMEL study group in 2008, the probiotic supplementation had no effect on the evolution of the SCORAD index. Since 2008, Gore *et al.*[15] confirmed the lack of effect that probiotics have on eczema, as they found no benefit from supplementation with *B. lactis* or *Lactobacillus paracasei* in the treatment of eczema, in infants aged 3–6 months.

Table 5. Weight-for-age *z* scores at birth and at randomisation
(Mean values and standard deviations)

		Birth		Randomisation		Evolution			
Treatments	*n*	Mean	SD	Mean	SD	Mean	SD	*P* (intra-group)	*P* (inter-group)
eHCF	57	0·3	1·2	−1·2	1·2	−1·5	1·1	<0·001*	z0·679†
eHCF + probiotics	53	0·3	1·0	−1·1	1·1	−1·5	1·2	<0·001‡	
Total	110	0·3	1·1	−1·2	1·2	−1·5	1·1	<0·001‡	

eHCF, extensively hydrolysed casein-based formula.
* Wilcoxon's test.
† ANCOVA based on ranks.
‡ Student's *t* test.

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Table 6. Anthropometric data at randomisation and at 6 months
(Mean values and standard deviations)

			Randomisation		6 months		Evolution			
	Treatments	*n*	Mean	SD	Mean	SD	Mean	SD	*P* (intra-group)	*P* (inter-group)
Weight (kg)	eHCF	53	5·9	1·4	8·5	1·2	2·6	1·1	<0·001*	0·467†
	eHCF + probiotics	51	6·0	1·2	8·6	1·1	2·7	0·9	<0·001*	
	Total	104	5·9	1·3	8·6	1·1	2·6	1·0	<0·001*	
Weight-for-age *z* score	eHCF	53	−1·1	1·3	−0·5	1·1	0·6	1·1	<0·001*	0·470†
	eHCF + probiotics	51	−1·2	1·1	−0·4	1·0	0·8	1·2	<0·001‡	
	Total	104	−1·2	1·2	−0·4	1·0	0·7	1·2	<0·001‡	
Length (cm)	eHCF	52	60·2	5·4	70·9	3·4	10·6	3·5	<0·001*	0·995†
	eHCF + probiotics	49	60·8	4·6	71·1	3·1	10·3	3·2	<0·001*	
	Total	101	60·5	5·0	71·0	3·3	10·5	3·3	<0·001*	
Length-for-age *z* score	eHCF	52	−1·3	1·6	−0·8	1·2	0·4	1·3	0·021‡	0·853†
	eHCF + probiotics	49	−1·2	1·4	−0·9	1·2	0·3	1·5	0·104‡	
	Total	101	−1·3	1·5	−0·9	1·2	0·4	1·4	<0·010‡	
Weight-for-length *z* score	eHCF	52	−0·1	0·9	−0·3	1·0	0·1	1·0	0·611‡	0·315†
	eHCF + probiotics	49	0·0	1·0	0·1	0·9	0·4	0·9	0·006‡	
	Total	101	−0·2	1·0	0·0	0·9	0·2	1·0	<0·050‡	
BMI	eHCF	52	16·1	1·5	17·0	1·5	0·9	1·5	<0·001‡	0·510†
	eHCF + probiotics	49	15·9	1·6	17·0	1·3	1·1	1·4	<0·001*	
	Total	101	16·0	1·6	17·0	1·4	1·0	1·5	<0·001‡	
BMI-for-age *z* score	eHCF	52	−0·5	1·0	0·1	1·0	0·6	1·0	<0·001‡	0·398†
	eHCF + probiotics	49	−0·7	1·0	0·1	0·9	0·8	0·9	<0·001‡	
	Total	101	−0·6	1·0	0·1	1·0	0·7	1·0	<0·001‡	

eHCF, extensively hydrolysed casein-based formula.
* Student's *t* test.
† ANCOVA.
‡ Wilcoxon's test.

Compared with healthy infants, infants with allergy can have impaired growth, which is partly attributable to improper food substitutions following allergen elimination[16]. Moreover, CMPA may also increase energy requirements through inflammation (i.e. skin or gastrointestinal) and disrupted sleep, as well as reduce the absorption of major nutrients (i.e. CMPA-induced enteropathy)[17]. However, data on the nutritional adequacy of eHCF are insufficient[4]. Most of the published growth data were obtained in healthy term infants[18–21] or in infants at risk of atopy[22] and very little in allergic infants, despite the fact that this type of formula is particularly targeted to the latter population. Only three previous trials have reported anthropometric indices in allergic infants fed an eHCF.

The *post hoc* analysis of growth data obtained in the CAMEL study[6] provides interesting data on (1) the length and weight deficit affecting infants with CMPA and (2) the potential catch-up for both length and weight using an eHCF, thereby underlining its safe and nutritional adequacy for infants with CMPA.

Savino *et al.*[5] and Agostoni *et al.*[3] showed a decrease in anthropometric indices between birth and inclusion in their study in infants with proved CMPA. In the Savino's study, twenty-six infants fed an eHCF were included at a mean age of 3·33 (SD 2·31) months. The mean weight-for-age *z* scores of these infants were 0·04 (SD 0·79) at birth and decreased to −0·39 (SD 0·55) at 2·5 months of age, showing that CMPA induced a reduction in weight gain. Agostoni *et al.*[3] reported that the mean weight-for-age *z* scores was between −0·13 and

Table 7. Proportions of infants with cows' milk protein allergy and nutritional deficits (*z* scores < −2·0)
(Number of subjects and percentages)

		Randomisation		6 months			
	Treatments	*n*	%	*n*	%	*P** (intra-group)	*P*† (inter-group)
Weight-for-age *z* score	eHCF	10	18·9	5	9·4	0·132	0·455
	eHCF+probiotics	13	25·4	2	3·9	0·004	
	Total	23	22·1	7	6·8	0·002	
Length-for-age *z* score	eHCF	15	28·9	7	13·5	0·032	0·350
	eHCF + probiotics	17	34·7	7	14·3	0·025	
	Total	32	31·7	14	13·9	0·002	
Weight-for-length *z* score	eHCF	1	1·9	0	0·0	0·317	0·350
	eHCF + probiotics	2	4·1	0	0·0	0·157	
	Total	3	3·0	0	0·0	0·083	

eHCF, extensively hydrolysed casein-based formula.
* McNemar's test.
† Fisher's test.

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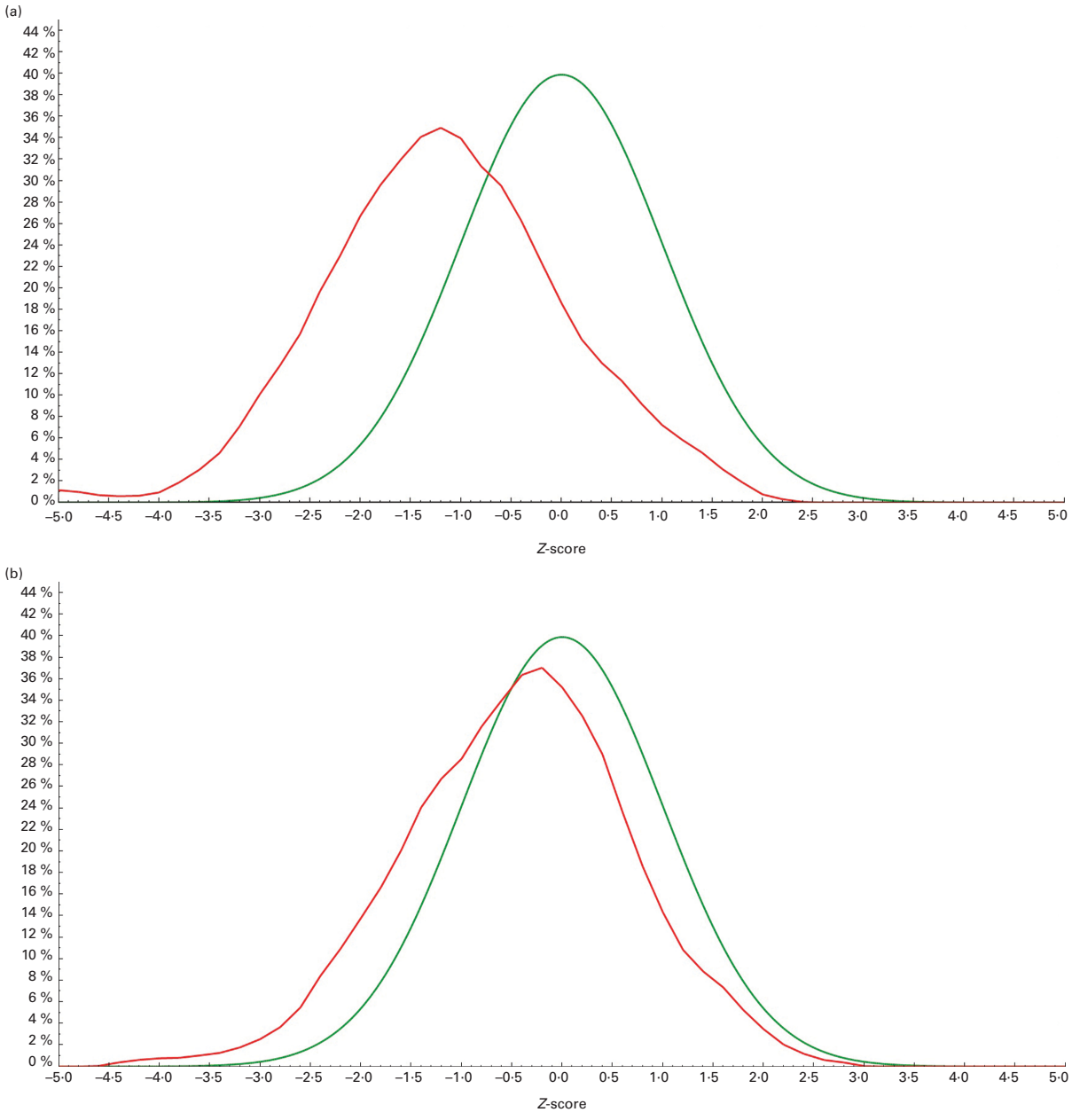

Fig. 2. Distribution of weight-for-age *z* scores of all children (—) compared with normal reference values (—) at (a) randomisation and (b) after 6 months.

0·28 at birth, which decreased to −0·36 to −0·45 at 6 months of age. The same decrease in weight-for-age *z* score between birth and study inclusion was observed in the present study. Because of the delay in diagnosis often seen in clinical practice, children with both immediate and delayed-type CMPA are particularly at risk of being undernourished[14]. Isolauri *et al.*[16] showed that the relative length and weight of infants with CMPA decreased compared with the control group. The decrease in relative length coincided with the onset of the symptoms suggestive of CMPA and the start of the elimination diet. The relative weight of children with CMPA continued to decrease compared with that in the non-allergic control group. In 2000, Agostoni *et al.*[23] compared the growth of 114 healthy infants with that of fifty-five infants with AD in which thirty-eight showed positive reactivity to milk proteins. Subjects affected by AD showed a progressive impairment of growth both in weight-for-age and length-for-age *z* scores. Differences between AD infants and healthy infants were significant from the second month of age onwards, more significantly in the second 6 months of life. More recently, Cho *et al.*[24] showed in 165 subjects with AD, of which seventy-seven were aged less than 12 months, that a higher number of sensitised food allergens was associated with negative effects on the growth and nutritional status of infants and young children with AD. Meyer *et al.*[25] assessed the growth status in ninety-seven food allergic children in the

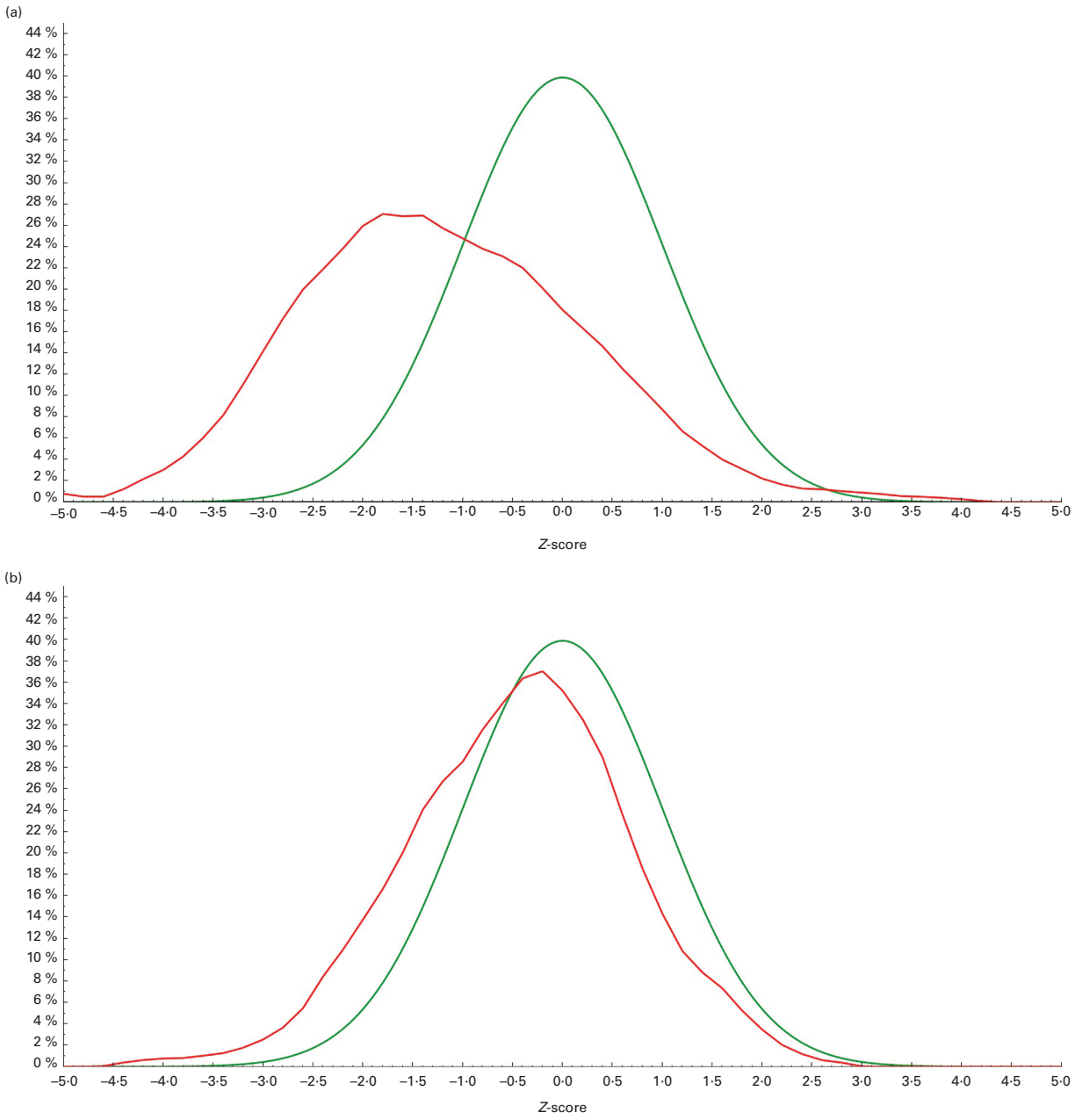

Fig. 3. Distribution of length-for-age *z* scores of all children (—) compared with normal reference values (—) at (a) randomisation and (b) after 6 months.

UK with a median (range) age of 27 (0·5–149) months. They found that elimination of more than three foods significantly affected the weight for age. Several other studies have shown growth deficit in infants with proved CMPA. Studies that have reported exact growth indices have been summarised in Table 8 [3,5,13,26–28]. The growth indices obtained in the present study are similar to the previously published data. Vieira *et al.*[29] reported the prevalence percentages of severe malnutrition in infants with CMPA aged less than 6 months: 16·5% for weight-for-age (underweight), 27·8% for length-for-age (stunting) and 13·9% for weight-for-length *z* scores (wasting)[30]. In the present study, the prevalence of underweight (22·1%) and stunted (31·7%) children was higher, in contrast to wasted children (3·0%), which was low in the CAMEL study.

Recently, the National Institute for Health and Clinical Excellence guidelines[31] for food allergy in children and young people were updated by new evidence concerning the impact of food allergies on growth in babies and infants. The Italian Society of Paediatric Nutrition published a position statement concerning the nutritional management and follow-up of infants and children with food allergy[32], showing an increased implication of scientific bodies in the assessment of physical growth in infants with CMPA.

Savino *et al.*[5] assessed the nutritional adequacy of a rice-based hydrolysed formula, compared with infants fed a soya

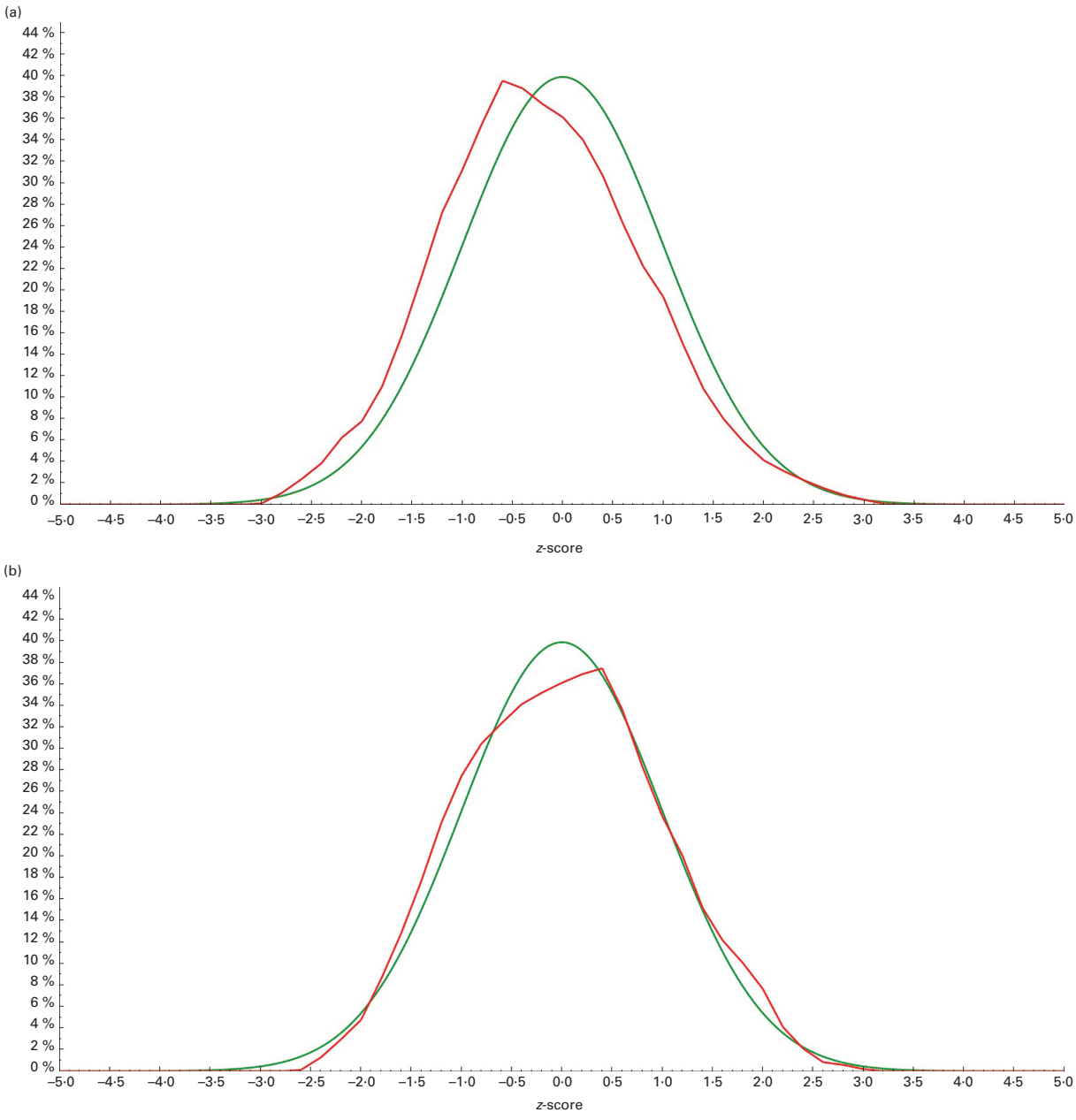

Fig. 4. Distribution of weight-for-length *z* scores of all children (—) compared with normal reference values (—) at (a) randomisation and (b) after 6 months.

formula or an eHCF. The study evaluated the growth of fifty-eight infants with AD and CMPA (confirmed by an open challenge) who were fed either of these formulas during the first 2 years of life. The twenty-six infants fed the eHCF were included at a mean age of 3·33 (SD 2·31) months. Only weight-for-age *z* scores were reported. All *z* scores for infants fed the eHCF were higher than −0·6. They increased between 2·5 and 5 months of age and from 7·5 to 24 months of age. In 2007, Agostoni *et al.*[3] investigated in infants with CMPA whether the type of milk in the complementary feeding period (6–12 months of age) was associated with differences in the evolution of standardised growth indices (i.e. weight-for-age, length-for-age and weight-for-length *z* scores). For this, four feeding groups were compared, including one using a casein hydrolysate formula. Allergic infants (*n* 31), whose diagnosis was confirmed by a positive DBPCFC, were included between 5 and 6 months of age and fed an eHCF for 6 months. All *z* scores increased during this period of time: from −0·44 to −0·27 for the weight-for-age *z* score; from −0·40 to −0·16 for the length-for-age *z* score; from −0·20 to −0·12 for the weight-for-length *z* score. BMI-for-age *z* scores were not reported. Recently, thirty-four allergic infants, aged less than 6 months, fed an eHCF showed a significant improvement in their weight-for-age *z* score as of the first month of dietary treatment[27]. Altogether, these three studies and the present results, which are the largest

Table 8. Summarised data relative to growth parameters in infants with cows' milk protein allergy (CMPA) at inclusion in the study
(Mean values, standard deviations, number of subjects, percentages and 95 % confidence intervals)

	Treatments	Number of infants included	Age of included infants (months)			CMPA diagnosis	Clinical characteristics	Length-for-age *z* scores			Weight-for-age *z* scores			Weight-for-length *z* scores		
			Mean	SD	95 % CI			Mean	SD	95 % CI	Mean	SD	95 % CI	Mean	SD	95 % CI
Isolauri *et al.* (1995)[13]	AAF	23	7	NR	5, 8	Positive reactions to a masked challenge with CM	Mean SCORAD index and total IgE (IU/ml) values: 21 (95 % CI 16, 26) and 35 (95 % CI 11, 115)	−0·3	NR	−0·7, −0·01		NR			NR	
	eHWF	22	6		4, 7		Mean SCORAD index and total IgE (IU/ml) values: 17 (95 % CI 12, 21) and 44 (95 % CI 12, 158)									
De Boissieu & Dupont (2002)[26]	AAF	52	5·3	3·8	NR	Adverse reactions to CM proteins	Type of symptoms: digestive symptoms: *n* 47 (90·4 %), eczema: *n* 23 (44·2 %), failure to thrive: *n* 16 (30·8 %), malaise: *n* 8 (15·4 %), angio-oedema: *n* 6 (11·5 %)	−0·86	1·37	NR	−1·04	1·45	NR		NR	
Savino *et al.* (2005)[5]	eHCF	26	3·33	2·31	NR	RAST, prick-by-prick and patch test and confirmed by food challenge	Presence of atopic dermatitis diagnosed by Hanifin and Rajka criteria (SCORAD index values not reported)		NR		−0·39	0·55	NR		NR	
Agostoni *et al.* (2007)[3]	SF	32	6		NR	Food challenge except in children with a history of anaphylaxis	Symptoms leading to the second-level centres: atopic eczema (78·6 %), urticaria/angio-oedema (23·1 %), asthma and/or rhinitis (11·9 %), gastrointestinal symptoms (8·6 %) and anaphylaxis (5·4 %)	−0·55	NR	−0·81, −0·29	−0·45	NR	−0·71, −0·19	−0·12	NR	−0·45, 0·21
	eHCF	31						−0·40		−0·69, −0·10	−0·44		−0·74, −0·13	−0·20		−0·54, 0·13
	eRHF	30						−0·73		−1·00, −0·46	−0·41		−0·76, −0·06	0·04		−0·34, 0·42
	BF	32						−0·49		−0·75, −0·24	−0·36		−0·63, −0·09	−0·01		−0·29, 0·25
Vandenplas *et al.* (2014)[27]	eHCF	34	86·2*	38·9*	NR	Positive food challenge to CM	Mean SBS: 14·3 (SD 3·3)	−0·5	1·4	NR	−0·6	1·4	NR	−0·2	1·8	NR
Vandenplas *et al.* (2014)[28]	eHRF	40	3·4	1·5	NR	Positive food challenge to CM	Mean SBS: 13·5 (SD 5·2)	−0·1 (*n* 37)	1·0	NR	−0·7 (*n* 38)	1·0	NR	−0·7 (*n* 37)	0·9	NR
Dupont *et al.* (present study)	eHCF	119	4·2	1·4	NR	Positive food challenge to CM	Skin reactions, 54·2 %; gastrointestinal reactions, 33·9 %; subjective symptoms, 44·1 %; airway reactions, 2·5 %	−1·3 (*n* 101)		NR	−1·2 (*n* 104)	1·2	NR	−0·2 (*n* 101)	1·0	NR

AAF, amino acid-based formula; NR, not reported; SCORAD, scoring of atopic dermatitis; eHWF, extensively hydrolysed whey-based formula; CM, cows' milk; eHCF, extensively hydrolysed casein-based formula; RAST, radioallergosorbent test; SF, soya formula; eHRF, extensively hydrolysed rice-based formula; BF, breast-feeding; SBS, symptom-based score[26,27].
*Days.

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reported to date, showed improvement of anthropometric data in allergic infants fed an eHCF. This demonstrates that these formulas are nutritionally adequate for allergic infants. According to paediatric guidelines, food allergic children with severe growth faltering should be fed amino acid-based formulas as first-line dietary treatment[2,33–36]. Results from the present study showed that the eHCF was well tolerated and enabled a growth catch-up in food allergic infants with poor growth at randomisation and favour guidelines recommending amino acid-based formulas mainly in case of intolerance to extensively hydrolysed formulas.

Questions have been raised as to whether the probiotic supplementation could have an effect on weight gain or not[37]. Two recent meta-analyses conducted in healthy term infants have found that probiotics failed to significantly increase gains in weight, length and head circumference compared with the controls[38,39]. Results presented here also showed that the probiotic supplementation had no effect on growth in infants allergic to CM, irrelevant of the nutritional status of the infant at study inclusion.

Conclusion

The randomised, double-blind, placebo-controlled study by the CAMEL study group included 119 infants allergic to CM. All the 119 infants clinically tolerated the formula well during the 4-week period preceding the follow-on study, including the 111 infants fed the eHCF for at least 7 months. In addition, the SCORAD index improved significantly during this period of time.

Standardised growth indices (z scores) were evaluated at randomisation and after 6 months of eHCF feeding. These results show that this eHCF is safe, hypo-allergenic (according to the standards of the American Academy of Paediatrics: tolerance by at least 90% of CMPA infants with a 95% CI) and nutritionally suitable for infants with CMPA.

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