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ORIGINAL RESEARCH ARTICLE

A Thickened Amino-Acid Formula in Infants with Cow's Milk Allergy Failing to Respond to Protein Hydrolysate Formulas: A Randomized Double-Blind Trial

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Abstract

Introduction Amino-acid-based formulas (AAFs) are recommended for children with cow's milk protein allergy (CMPA) failing to respond to extensively hydrolyzed formulas (eHFs).

Objective This study aimed to assess the tolerance/hypoallergenicity and efficacy of a thickened AAF (TAAF) in these infants.

Methods This multicenter, double-blind, randomized controlled trial (NCT01940068) compared 3-month feeding with a pectin-based TAAF (Novalac®, United Pharmaceuticals, Paris, France) and a commercially available "reference" AAF (RAAF; Neocate®, Nutricia, Germany) in infants aged <18 months with CMPA and persistent allergy symptoms with eHF feeding. Reported here are the results of an interim analysis after 1 month of feeding.

Results Of the 86 infants randomized, CMPA with eHF intolerance was confirmed in 75 infants; all of them tolerated the allocated AAFs. The major allergic symptom disappeared within 1 month in 61.9 and 51.5 % and regurgitations disappeared in 66.7 and 42.3 % of infants who received TAAF and RAAF, respectively. Infants had significantly more normal stools (soft or formed consistency) with the TAAF (90.5 vs. 66.7 %; $p = 0.011$). From baseline, daily family life significantly improved with both AAFs: crying time decreased by 97.3 ($p < 0.001$) and 28.6 min ($p = 0.014$) and sleeping time increased by 64.6 ($p = 0.009$) and 29.0 min with TAAF and RAAF, respectively. At day 30, weight and body mass index z-score gains were 0.1 and 0.2 with TAAF and 0.2 and 0.0 with RAAF.

Conclusion Both AAFs were well tolerated by infants with CMPA and eHF intolerance and ensured appropriate growth, with the TAAF providing additional comfort.

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Key Points

Amino-acid-based formulas (AAFs) are well tolerated in infants with cow's milk protein allergy (CMPA) failing to respond to extensively hydrolyzed formula (eHF) treatment.

After 1 month, the majority of infants who received the new AAF thickened with a pectin complex had a complete disappearance of the main allergic symptoms. The thickened AAF (TAAF) ensured appropriate growth and led to an improvement of non-allergic symptoms, including crying and sleeping times, improving the daily family life of infants and their parents as early as the first month of treatment.

The results of this interim analysis suggest that the TAAF may be a good alternative for the management of CMPA and failure to respond to eHF.

1 Introduction

In the past years, several authors and working parties have underlined and reviewed the specific concerns relating to the treatment of allergies to cow's milk proteins in children [1–8]. The overall principle for the treatment of cow's milk protein allergy (CMPA) is allergen avoidance, and guidelines state children with CMPA should be fed extensively hydrolyzed formulas (eHFs) [1–8]. However, extensive enzymatic hydrolysis of high molecular weight proteins does not result in a totally non-allergenic formula [9–11].

Residual allergenicity remains too high for some infants with CMPA who also remain symptomatic while being fed eHFs. A response to this problem was the development of amino-acid-based formulas (AAFs), which have been shown to reduce allergy symptoms in these infants and allow catch-up growth in most infants [12–17]. In 2000, the American Academy of Pediatrics [18], and later on other ad hoc working parties [1, 8, 19], recommended the use of AAFs in infants with persistence of allergic symptoms under eHF feeding.

Previous reviews have highlighted the need to base the use of an infant formula on undisputable data [20]; however, no randomized controlled trials have investigated the use of an AAF in infants with a CMPA not improving with eHF feeding [7]. Published studies of AAF have included retrospective observational studies in a limited number of infants [13, 14, 17] with suspected CMPA. On the other hand, controlled trials showing efficacy, tolerance and safety of AAFs have either been carried out in children with proven CMPA and no intolerance to eHFs [21–27] or in a study where only a few children had documented intolerance to eHFs [16].

The aim of this study was to investigate the tolerance, efficacy and safety of AAFs in infants with both CMPA and intolerance to eHFs. This study compared a standard reference AAF (RAAF) with a new formula thickened with a specific complex, which has been shown to have beneficial effects on gastrointestinal symptoms [28]. Reported here are the results from an interim analysis of this study at 1 month.

2 Methods

2.1 Study Design and Subjects

This was a prospective, multicenter, double-blind, randomized controlled trial comparing a new thickened AAF (TAAF) to a RAAF. Patient selection was performed to reflect real life conditions in hospital outpatient clinics and private practices in France and Belgium. Infants and young children were considered eligible if they were less than 18 months old and had CMPA-like symptoms that persisted for 2 weeks or more on an eviction diet as per guidelines [1–3, 5, 6, 8], i.e., feeding with one or several commercialized eHFs available in France or Belgium, avoidance of any milk and dairy products (recommendations from the Circle of Clinical and Biological Investigations in Food Allergy related to products other than milk to be avoided during an eviction diet were provided) and the postponement of any introduction of new weaning foods. Exclusively breastfed infants were not included.

The diagnosis of CMPA was confirmed by a double-blind, placebo-controlled food challenge (DBPCFC) performed according to current guidelines [29] within 2 months following enrolment (i.e., during blind feeding with one of the study AAFs). The placebo was 200 mL of Neocate® (Nutricia, Erlangen, Germany); the test formula was a blend of standard infant formula (2/3) and Neocate® (1/3) to ensure double-blinding. The DBPCFC was not carried out if already performed within the month prior to inclusion or when the allergy work-up provided a 95 % chance of active CMPA: a skin prick test (SPT) wheal diameter ≥6 mm, specific IgE (sIgE) ≥5 kU/L [4] or the combination of both positive SPT and sIgE [30]. Parents were contacted by phone at the end of the first week of feeding with the study formula, and daily after the DBPCFC in the absence of immediate reaction, to check tolerance to reintroduction of a milk-based formula [1].

2.2 Interventions

Following consent granted by the parents, infants had an allergic work-up including skin testing (SPT) and blood sampling (for allergy and nutritional parameters), and the pediatrician randomly assigned them to be fed for 3 months with one of the two study formulas. Two different codes were attributed to each product, and randomization was performed in blocks of eight in each center to ensure a balanced distribution of patients in each of the two test groups. Code assignment was kept in sealed envelopes until the last patient was included and blind statistical analysis was performed. Blinding was not broken during the study. If accepted by parents, an additional 3-month period of open feeding with the TAAF was offered to families. Parents were instructed to remove from the diet any milk or dairy products.

Visits were carried out at 1, 3 and 6 months following randomization. Parents were asked to report their child's feeding, behavior, sleep and digestive symptoms in a diary covering the 3 days preceding each visit. Formula consumption was recorded.

The RAAF (Neocate®, Nutricia, Erlangen, Germany) was the most documented AAF in children with CMPA and in children with CMPA and failure to respond to eHF feeding [31]. The TAAF (Novalac®, United Pharmaceuticals, Paris, France) had similar nitrogen content (1.9 g/100 mL) and mostly differed by the presence of a patented thickening mixture including fibers (0.5 g/100 mL) mainly composed of pectin and which only thickens in the stomach at gastric pH; therefore, parents and investigators could not determine which product was allocated based on its consistency in the bottle. For the TAAF, fat, carbohydrate and energy contents were 3.2 g, 8.5 g and 71.8 kcal/100 mL, respectively. For the RAAF, these contents were 3.4 g, 7.9 g and 70 kcal/100 ml, respectively.

2.3 Study Measurements

Anthropometric data and CMPA symptoms were carefully evaluated at inclusion and during each visit. CMPA symptoms were itemized by pediatricians according to previous position papers [4, 7, 8] and classified as cutaneous (urticaria, eczema, skin dryness), respiratory (rhinitis, wheezing) and digestive (regurgitations, vomiting, stool consistency). Cutaneous and respiratory symptoms were registered as present or absent; vomiting was described as absent, occasional, frequent or repeated; regurgitations were assessed using the Vandenplas regurgitations scale [32]; and stool consistency was assessed as liquid, soft, formed or hard using the Bekkali's scale [33]. At enrolment, considering the frequent association of multiple symptoms [1, 3, 7, 8], pediatricians were asked to determine the dominant CMPA symptom and described its change as resolved, improved or persistent. Pediatricians assessed eczema at each visit using the SCORing Atopic Dermatitis (SCORAD) index [34].

Regurgitations and stool consistency were assessed during the 3 days preceding each study visit. Both symptoms were of special interest because of a potential modification by the thickening agent [28]. General symptoms, potentially symptomatic of or associated with CMPA [1, 2, 4, 8], such as irritability and crying frequency, crying time, sleep duration and quality (day and night), were also scored at each visit by the pediatrician, through parent questioning. Crying and irritability signs were scored as absent, occasional, frequent or repeated; sleep quality was assessed as very good, fairly good, fairly bad or very bad. Parents filled out the diary (including the daily formula intake) during the 3 days preceding each visit. They were advised at each visit by study investigators on how to complete the diaries, and clear and detailed instructions, as well as examples, were made available on the cover of the diaries. Diaries were available in both French and Dutch to cater for all language groups.

2.4 Outcomes

The primary endpoint of this study was the tolerance/hypoallergenicity of the new AAF in infants with CMPA and intolerance to eHFs at 1 month. It was defined as the absence, for these infants, of allergy symptoms that led to study termination during the first month. The secondary endpoints were (i) resolution of the dominant CMPA symptom, (ii) resolution of other CMPA symptoms, (iii) resolution of general symptoms potentially associated with CMPA and related to daily family life, and (iv) anthropometric variables in accordance with WHO growth curves.

2.5 Sample Size Calculation

The number of subjects to be included was calculated on the basis of the requirement that a hypoallergenic formula must be tolerated by at least 90 % of infants with an overt CMPA (95 % confidence interval). The number of subjects needed was 29 per group [24]. Considering the design of the study, which allowed the CMPA to be confirmed 2 months after inclusion, a 15 % rate for dropouts and inappropriate selection was anticipated; therefore, it was decided to include 35 infants per group.

2.6 Statistics

These results are from an interim analysis performed at 1 month, in an overall study duration of 6 months. The primary endpoint was assessed in the tolerance/

hypoallergenicity population, defined as infants with confirmed CMPA and eHF intolerance. The secondary endpoints were assessed in the full analysis set (FAS) population, which was defined as infants in the tolerance/hypoallergenicity population who had at least one evaluation of the primary efficacy outcome. The intention-to-treat (ITT) population was defined as infants enrolled who took study formula.

For quantitative parameters, changes from baseline were compared between groups by ANCOVA (or non-parametric ANCOVA in the case of non-normality, assessed by Shapiro Wilk's test) using the baseline value as a covariate. Intra-group changes were analyzed using the Student's *t* test or Wilcoxon's test (non-normal data). For qualitative parameters, changes from baseline within treatment groups were analyzed by symmetry test, or by Mac Nemar's test for binary variables. The difference between groups for the changes in qualitative parameters was analyzed using the Chi-2 or the Fisher's test. Weight-for-age, length-for-age, weight-for-length, body mass index (BMI)-for-age and head circumference-for-age *z*-scores were computed for each infant, based on WHO 2006 reference data [35]. Significance was set at $p < 0.05$.

2.7 Ethics

The study design was approved by independent ethic committees: Ile-de-France III, Paris, France, and HUDERF Ethics committee, Brussels, Belgium. This study was conducted in accordance with ethical standards laid down by the Declaration of Helsinki. It was registered at ClinicalTrials.gov under the identifier NCT01940068. Parents or others legally responsible for the infants provided written consent regarding their acceptance to participate and the study procedures.

3 Results

3.1 Study Population

Between March 2011 and July 2013, 46 infants were randomized to receive the TAAF and 40 to receive the RAAF (Fig. 1). Of these, two infants had no confirmed CMPA; one had no characterized history of intolerance to eHF; eight had a negative DBPCFC. The tolerance/hypoallergenicity population was therefore composed of 75 infants (44 % male; mean age 6.2 ± 4.3 months). The median age of infants at inclusion was not different between groups ($p = 0.687$).

Almost one-third of the infants had IgE-mediated CMPA (Table 1). CMPA was confirmed by DBPCFC in 72 % infants, with an immediate reaction observed in 44 % of infants and a delayed reaction observed in the remaining infants. One IgE-negative patient was denied any DBPCFC because of a previous history of iterative, apparently life-threatening events with two different eHFs.

3.2 Tolerance/Hypoallergenicity

Both formulas were well tolerated by all infants included in the tolerance/hypoallergenicity population. No infants in the TAAF group and three infants in the RAAF group discontinued the study. One of these infants had no characterized history of intolerance to eHF, another had a negative DBPCFC, and the last one had no confirmed CMPA, so they did not belong to the tolerance/hypoallergenicity population (Fig. 1).

3.3 Efficacy

In the FAS population, the major CMPA symptom resolved completely during the first month in 26/42 and 17/33 infants in the TAAF and RAAF groups, respectively (ns, Chi-2 test). In the first month, improvement or complete resolution of the major CMPA symptom was observed in 40/42 and 32/33 of infants receiving TAAF and RAAF, respectively (ns, Fisher's test). Whatever the type of the major CMPA symptom (cutaneous, respiratory, digestive or other), there was no significant difference in the symptom resolution percentages between the two groups.

At 1 month, significant improvements in SCORAD index scores, eczema and skin dryness were observed in both AAF groups, while rhinitis and wheezing improved in the TAAF group only (Table 2; Fig. 2; Supplementary Table 1—see Online Resource 1). Urticaria ($n = 8$) did not vary in the total population or in any group (possibly because of a low frequency). Regurgitations disappeared completely in 66.7 % of infants fed the TAAF versus 42.3 % of infants fed the RAAF. Regurgitation scores decreased significantly in both groups (Table 2). In the TAAF group, the proportion of infants with normal stool consistency, defined as soft or formed stools, improved from 47.6 % at baseline to 90.5 % after 1 month of feeding ($p < 0.001$ vs. baseline, Mac Nemar's test). In contrast, in the RAAF group, the proportion of infants with normal stool consistency improved from 51.5 to 66.7 % ($p = 0.132$, Mac Nemar's test). The normalization of stool consistency (from liquid or hard stools to normal stools) was significantly higher with the TAAF (Table 2).

Daily family life improved significantly in both formula groups. In infants who received the TAAF, the general symptoms which could potentially be associated with CMPA (irritability, crying, sleep duration and quality) were significantly improved at 1 month. Significant improvements in crying frequency and sleep quality were also observed in the

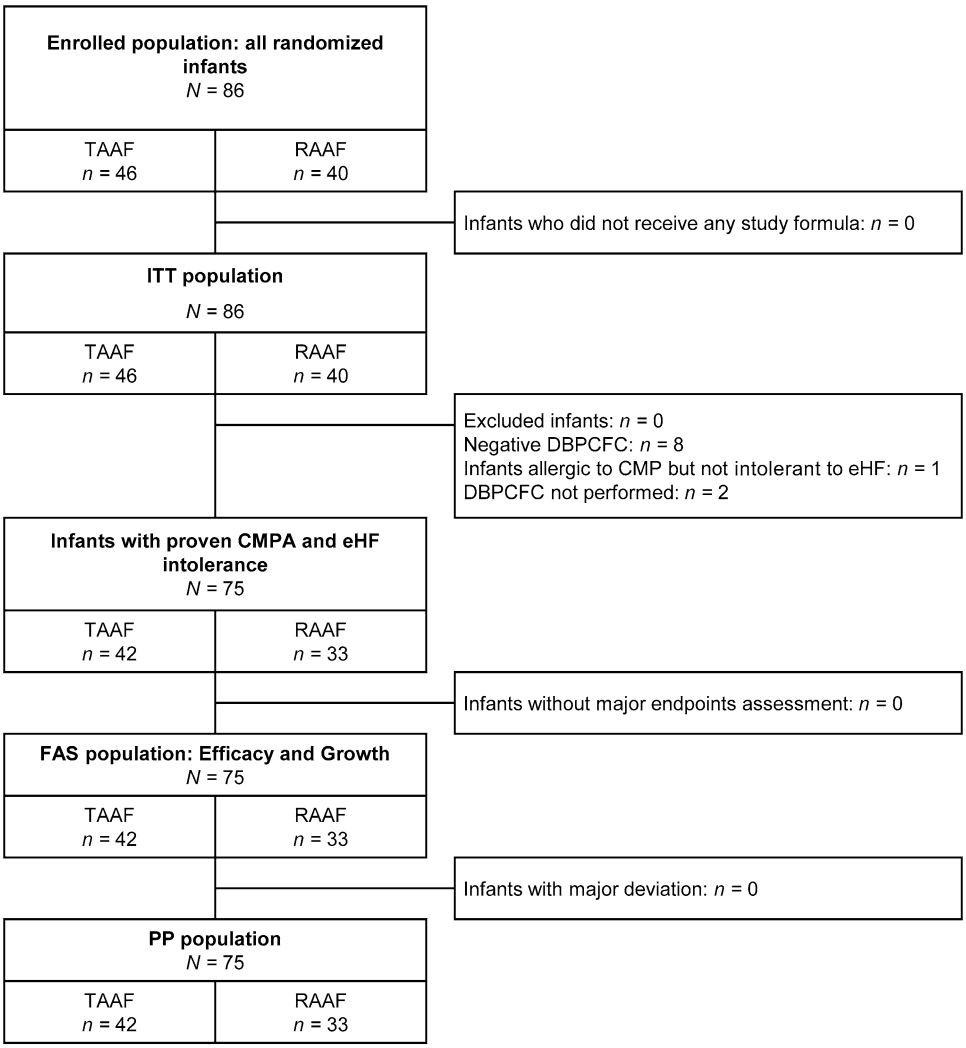

Fig. 1 Study flow of infants enrolled. *CMP* cow's milk proteins, *DBPCFC* double-blind, placebo-controlled food challenge, *eHF* extensively hydrolyzed formula, *FAS* full analysis set, *ITT* intention-to-treat, *N* number of subjects, *PP* per protocol population, *RAAF* reference amino-acid-based formula, *TAAF* thickened amino-acid-based formula

RAAF group (Fig. 3; Supplementary Table 2). Furthermore, infants who received the TAAF had significant reductions in mean crying time and increases in sleep duration, while infants who received the RAAF had only significant improvements in mean crying time (Table 2).

3.4 Safety and Growth

In the ITT population, three infants discontinued the study because of non-serious adverse events (AEs): one case of hemorrhagic rectitis, one case of functional gastrointestinal events including gas, bloating and colic, and one case of gastroesophageal reflux disease. These AEs occurred in the RAAF group, and the first two were considered related to the study formula. Three serious AEs occurred: one case of esophagitis and one case of gastroenteritis in the TAAF group and one case of esophagitis in the RAAF group. None of these serious AEs led to study discontinuation, and none were considered related to the study formula.

At baseline, the consumed daily volume, number of feeding bottles and duration of each bottle did not differ between groups. After 1 month, infants fed the TAAF were drinking significantly more formula than those fed the RAAF (686.4 ± 199.0 vs. 570.7 ± 164.1 mL; $p = 0.010$, Student's t test).

Weight-for-age z-scores were on average −0.8 ± 1.0 at baseline, with values below −2 in eight infants (out of 72). At day 30, the weight-for-age z-score increased significantly in both groups, from −0.7 ± 1.0 to −0.6 ± 1.1 in infants who received the TAAF and from –0.8 ± 1.0 to –0.6 ± 0.8 in infants who received the RAAF ($p = 0.031$ and $p = 0.026$, respectively, Student's t test). No significant increase in BMI z-scores was observed. Changes in weight, weight-for-length, BMI and head circumference z-scores were similar between groups. The only difference between the two groups was noted for length-for-age z-score, with no clinical significance (0.0 ± 0.5 vs. 0.3 ± 0.6 for TAAF and RAAF groups, respectively,

Table 1 Baseline demographic and clinical characteristics of the full analysis set population

	TAAF (*N* = 42)	RAAF (*N* = 33)	Total (*N* = 75)
Demographic			
Male gender, *n* (%)	23 (54.8)	10 (30.3)	33 (44.0)
Age (months), mean ± SD	6.4 ± 4.5	5.9 ± 4.0	6.2 ± 4.3
Weight (kg), mean ± SD	7.0 ± 2.0	6.7 ± 1.6	6.9 ± 1.9
Length (cm), mean ± SD	65.3 ± 7.9	64.7 ± 6.7	65.1 ± 7.3
Family history of allergy, *n* (%)			
Father	17 (41.5)	15 (45.5)	32 (43.2)
Mother	26 (63.4)	24 (72.7)	50 (67.6)
Siblings	25 (69.4)	15 (48.4)	40 (59.7)
Diagnostic of CMPA			
Diagnostic method, *n* (%)			
Biology	11 (26.2)	9 (27.3)	20 (26.7)
Anaphylactic risk	1 (2.4)	0 (0.0)	1 (1.3)
DBPCFC	30 (71.4)	24 (72.7)	54 (72.0)
Type of DBPCFC reaction, *n* (%)			
Immediate	12 (40.0)	12 (50.0)	24 (44.4)
Delayed	18 (60.0)	12 (50.0)	30 (55.5)
IgE-mediated CMPA, *n* (%)	11 (26.2)	12 (36.4)	23 (30.7)
Major symptom of CMPA, *n* (%)			
Cutaneous	16 (38.1)	15 (45.5)	31 (41.3)
Respiratory	4 (9.5)	2 (6.1)	6 (8.0)
Digestive	14 (33.3)	12 (36.4)	26 (34.7)
Other (faltering growth)	8 (19.0)	4 (12.1)	12 (16.0)

CMPA cow's milk proteins allergy, *DBPCFC* double-blind, placebo-controlled food challenge, *N* number of subjects, *RAAF* reference amino-acid-based formula, *SD* standard deviation, *TAAF* thickened amino-acid-based formula

$p = 0.029$, ANCOVA), but weight-for-length *z*-scores did not differ between groups.

4 Discussion

This study assessed the hypoallergenicity of a new TAAF, which was tolerated by 100 % of infants with CMPA and intolerance to eHFs. This clinical trial also compared the efficacy of the new TAAF to the RAAF and demonstrated resolution of the major CMPA symptom in 61.9 and 51.5 % of infants at the end of the first month of feeding. In addition, the study provided an overview of the symptoms associated with eHF intolerance and shed a new light on potential benefits of using an appropriate thickening agent in AAFs.

While 90–95 % of children who are allergic to cow's milk protein respond to eHF [7, 8], 5–10 % of children react to eHFs, with immediate or delayed reactions [21, 36–39]. In children with CMPA who fail to improve on an eHF diet, the use of AAF is recommended [1, 7, 8, 18, 40]. However, although several studies have assessed the tolerance of AAFs in children with CMPA, no prospective trial had ever been published on the use of AAF in this particular medical condition of dual CMPA and no response to eHF treatment [21–27].

The present study was designed to comply with the rules for clinical trials and to recruit a sufficient number of infants with CMPA and an additional failure to respond to eHF feeding during at least 2 weeks [8]. Infants could be enrolled at their first in-hospital consultation, on the basis of a clinical history of failure to control allergic symptoms using eHF, as indicated by CMPA working parties [1, 7, 8]. A DBPCFC could then be organized to prove CMPA within a reasonable delay. During this period of time, infants remained on the allocated AAF.

Tolerance of the TAAF was excellent in this population with CMPA failing to improve under eHF feeding, often considered the most severe form of CMPA. According to recommendations for the feeding of CMPA infants [18], a formula is suitable if it is tolerated by at least 90 % of infants with documented CMPA. In this study, 100 % of infants in the TAAF group and in the RAAF group tolerated the formula. Because tolerance/hypoallergenicity was reported in higher than 90 % of the infants in the TAAF group, application of the criterion to determine suitability of a formula for CMPA infants allows us to state that the new TAAF is suitable for infants with CMPA and intolerance to eHFs.

These results are supported by previous data suggesting that AAFs may be a good alternative to eHFs in patients with CMPA and no response to eHF feeding. In a series of

Table 2 Change from baseline in SCORAD index scores, regurgitations scores, stool consistency, crying and sleep duration at 1 month

	TAAF (*N* = 42)	RAAF (*N* = 33)	Total (*N* = 75)
SCORAD index			
N	25	26	51
Mean ± SD	–19.0 ± 12.0	–23.7 ± 21.2	–21.4 ± 17.3
Median [Min; Max]	−17.5 [−38.7; 8.6]	–18.6 [−64.7; 23.5]	−18.5 [−64.7; 23.5]
p value vs. baseline	<0.001*	<0.001*	<0.001*
p value between groups			0.557†
Regurgitations score			
N	27	26	53
Mean ± SD	−1.8 ± 1.6	−1.6 ± 1.8	−1.7 ± 1.7
Median [Min; Max]	−1 [–6; 1]	−1 [−6; 1]	−1 [−6; 1]
p value vs. baseline	<0.001‡	<0.001*	<0.001‡
p value between groups			0.195§
Stool consistency, *n* (%)			
N	42	33	75
Aggravated or not formed	4 (9.5)	11 (33.3)	15 (20.0)
Improved or formed	38 (90.5)	22 (66.7)	60 (80.0)
p value between groups			0.011‖
Crying duration, min			
N	36	29	65
Mean ± SD	−97.3 ± 185.4	−28.6 ± 62.3	−66.7 ± 147.2
Median [Min; Max]	−35.0 [−780.0; 120.0]	−25.0 [−240.0; 90.0]	−25.0 [−780; 120]
p value vs. baseline	<0.001‡	0.014‡	<0.001‡
p value between groups			0.941§
Sleep duration (min)			
N	39	31	70
Mean ± SD	64.6 ± 146.9	29.0 ± 143.6	48.9 ± 145.5
Median [Min; Max]	0.0 [−300.0; 360.0]	0.0 [−180.0; 600.0]	0.0 [−300.0; 600.0]
p value vs. baseline	0.009*	0.380‡	0.007‡
p value between groups			0.208§

Max maximum, *Min* minimum, *N* number of subjects, *RAAF* reference amino-acid-based formula, *SCORAD* SCORing Atopic Dermatitis, *SD* standard deviation, *TAAF* thickened amino-acid-based formula

* Student's *t* test

† ANCOVA

‡ Wilcoxon's test

§ ANCOVA based on ranks

‖ Chi-2 test

16 children with presumed CMPA and persistent symptoms under eHF feeding, the switch to an AAF resulted in a good response in 13 cases [12]. This was associated with an increase in weight gain and a decrease in intestinal permeability, probably reflecting a decrease in local inflammation [41]. These children relapsed on subsequent challenge with the eHF. In a similar study carried out by Vanderhoof et al. [14], 25 out of 28 children with CMPA who did not respond to an eHF showed symptoms resolution with an AAF. In 31 patients with CMPA, among whom 29 had multiple food allergies, 13 did not tolerate the eHF and responded to the AAF [16].

In addition to showing good tolerance results, the TAAF was associated with complete resolution of the major allergic symptom in 61.9 % of the infants (versus 51.5 % for the RAAF) as early as the first month of treatment. Statistically significant improvement was also observed for most allergic symptoms and general symptoms possibly symptomatic of CMPA. In a previous large series of infants allergic to eHFs [15], digestive symptoms were regurgitations, diarrhea, colicky pain and failure to thrive. Similar symptoms were observed in the present series. The TAAF induced a significant improvement in the regurgitations score after 1 month of treatment; 66.7 % of infants presenting this symptom at inclusion in the TAAF group were symptom free after 1 month versus 42.3 % for the RAAF group. Infants fed the TAAF had a significantly higher proportion of normal stools than those fed the RAAF ($p = 0.011$).

This study shows that beyond treating allergic symptoms, the new TAAF also improved the symptoms potentially related to CMPA, and had thus an impact on patients' daily family life. Results showed a noticeable reduction in crying time and an increase in sleeping time. Irritability and poor quality of daytime sleep seem to prevail as symptoms related to eHF intolerance. As summarized by Heine [42], uncontrolled studies have provided preliminary evidence that AAF may be effective in reducing persistent

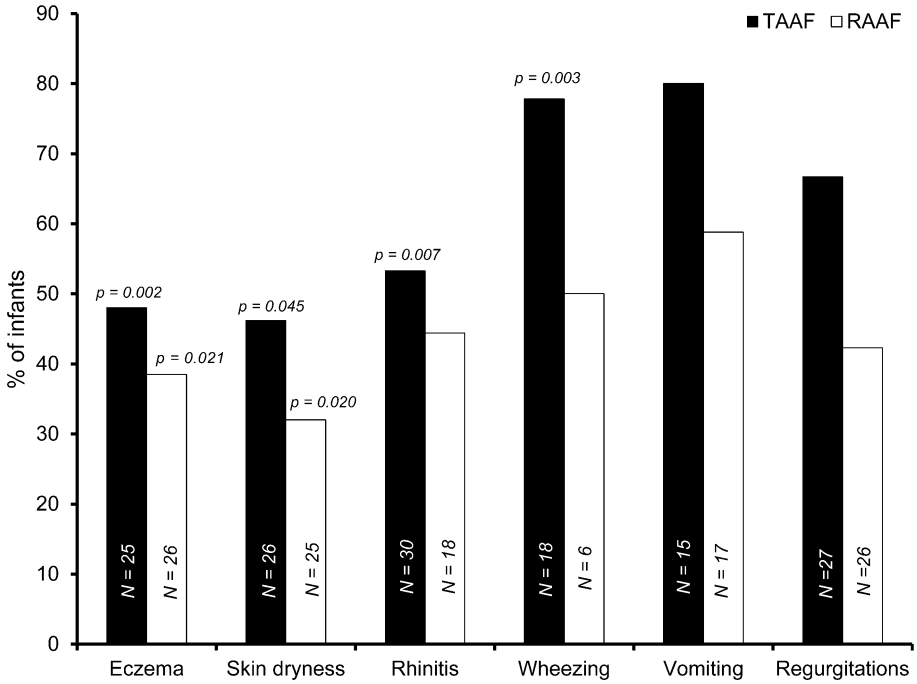

Fig. 2 Proportion of infants with resolution of allergic symptoms at 1 month. All *p* values are versus baseline (Mac Nemar's test). *N* number of subjects, *RAAF* reference amino-acid-based formula, *TAAF* thickened amino-acid-based formula

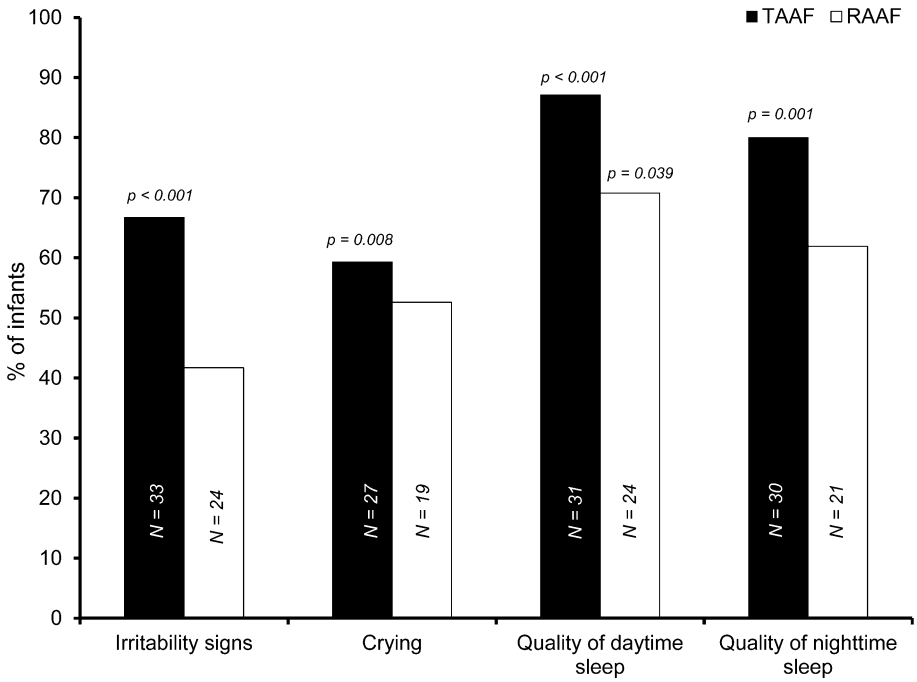

Fig. 3 Proportion of infants with resolution of general symptoms (improvement for sleep quality) at 1 month. All *p* values are versus baseline (symmetry test). *N* number of subjects, *RAAF* reference amino-acid-based formula, *TAAF* thickened amino-acid-based formula

crying [12, 43, 44]. Although it did not particularly focus on infants crying, the present double-blind, placebo-controlled trial further supports the potential role of AAFs with regard to this symptom. Moreover, because the formula was the only change performed in the infant's diet, this result suggests that crying and sleep disturbances are objective symptoms of intolerance to eHFs.

AAF formulas are expected to show tolerance in higher than 90 % of infants and improvement of allergic and non-allergic symptoms, which was observed with the TAAF in this study. Nonetheless, one must keep in mind that an uncontrolled elimination diet may impair the adequate intake of essential nutrients and result in undernutrition [45–48]. Anthropometric measurements showed that both AAFs allowed infants to significantly improve their weight-for-age *z*-score in a period of time as short as 1 month. Moreover, this weight catch-up probably indicates that intolerance to eHF during CMPA impacts weight gain, a trait difficult to recognize in the absence of AAF feeding in these infants.

There are some limitations to this study. No additional DBPCFC with eHF was conducted. This was done for several reasons. Firstly, guidelines consider eHF allergy/intolerance in the case of persistence of allergic symptoms under eHF feeding and recommend an immediate switch to AAF feeding [1–5, 7, 8, 18]. Secondly, asking families to rechallenge with the eHF which infants had already not tolerated before study inclusion would have been too stressful and interventional; all included infants had had allergy symptoms leading to feeding with eHF and had persistence of said symptoms with the eHF during 2 weeks or more before study inclusion.

5 Conclusion

The new TAAF was efficient and well tolerated by all infants with proven CMPA and intolerance to eHF. It ensured appropriate growth, with no significant difference with the reference formula. This new TAAF led to an improvement of allergic symptoms as well as all non-allergic symptoms like crying and sleeping times, improving the daily family life of infants and their parents as early as the first month of treatment. Results of this study suggest that the thickened formula may be a good alternative for the management of CMPA and intolerance to eHF, the most severe cases of CMPA.

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