

A New Hydrolyzed Formula is Well Tolerated in Infants with Suspected Food Protein Allergy or Intolerance

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Abstract: *Background:* Extensively hydrolyzed formulas (eHF) are indicated for infants with food protein allergy. The purpose of the study was to assess the tolerance and compliance of an intended population of infants to a new formulation of a hypoallergenic eHF.

Methods: A non-random, single-group, multicenter study was conducted. Infants with suspected food protein allergy, persistent feeding intolerance, or presenting conditions where an eHF was deemed appropriate were enrolled in a 15-day feeding trial. Intake, stool patterns, weight (wt), length, and questionnaires were collected. The primary outcome was maintenance of wt for age Z-score during the study.

Results: 25 infants (85 ± 8.9 d of age) were enrolled; 7 were ≥ 4 months; 4 were preterm. At entry, 12 had symptoms of allergic colitis or food protein allergy/intolerance, 12 had persistent formula intolerance, 11 had hematochezia/heme positive stools, and 1 was recovering from necrotizing enterocolitis. Mean wt for age Z-score was -0.62 ± 0.19 at entry and -0.41 ± 0.16 at exit. Mean change in wt for age Z-score was 0.21 ± 0.10 . Mean formula intake was 764 ± 48 mL/day. The mean number of stools/day was 1.8 ± 0.4 and the predominant stool consistencies were loose/mushy (48%) or soft (43%).

Conclusion: The results suggest that this eHF was well accepted and tolerated by an intended use population of infants during the first 6 months of life which enabled adequate volume consumption, maintenance of wt for age Z-scores and a high level of parental satisfaction.

Keywords: Cow milk allergy, formula intolerance, hydrolysate formula, infant feeding, infant formula.

INTRODUCTION

Extensively hydrolyzed infant formulas (eHF) are widely available and important tools for pediatricians in the nutritional management of infants. These formulas are often the first choice for infants with documented cow-milk allergy or multiple food protein allergy. They are also used for indications including symptoms of persistent intolerance such as fussiness, diarrhea, vomiting, spit-up, or constipation, when infants are suspected to have milk and/or soy protein sensitivity, when other formulas have been ineffective in managing symptoms, or when other less common conditions may necessitate the need for specific ingredients (e.g. medium-chain triglyceride, lactose-free, extensively hydrolyzed protein) that such formulas can provide.

Although the reported incidence of cow milk allergy in the first year of life is 2.5% [1, 2], a much higher percentage of infants are believed to experience symptoms of feeding intolerance. A recent study from Israel [3] reported that the

type of formula fed was switched in 47% of healthy infants during the first 6 months of life primarily due to parental perceptions of infant feeding intolerance.

The purpose of this study was to assess the tolerance and compliance of an intended population of infants with suspected food protein allergy or persistent feeding intolerance to an extensively hydrolyzed casein-based infant formula reformulated to be compliant with requirements of the European Union (EU). Previous studies have confirmed that the formula supports growth of infants [4] and is safe for feeding children that are documented to be allergic to cow milk and other food allergens [5].

MATERIALS AND METHODOLOGY

The study was a prospective, non-random, single-group, multicenter study. Infants from pediatric practices with suspected food protein allergy, persistent feeding intolerance, or those presenting conditions where an eHF was deemed appropriate were enrolled in a 15 day (d) feeding trial.

Infants enrolled into the study were 0 to 180 d of age, experiencing persistent feeding intolerance symptoms (including but not limited to diarrhea, constipation, vomiting, or spit-up) and had at least 1 formula switch to a

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formula other than an eHF (Group A) OR infant was experiencing or was being managed with an eHF for symptoms of suspected food protein (milk and/or soy) intolerance or allergy (including but not limited to diarrhea, constipation, vomiting, spit-up, eczema, or hematochezia) or other condition where an eHF was deemed appropriate by their healthcare professional (HCP) (Group B). Prescription and over-the-counter medications, home remedies, herbal preparations, rehydration fluids, or vitamin or mineral supplements used by infants at enrollment were discontinued unless recommended by the HCP to continue throughout the study. Infants received the study formula *ad libitum* as the sole source of nutrition. The protocol was conducted in accordance with all applicable regulations, including Good Clinical Practices and the ethical principles originating from the Declaration of Helsinki and registered on ClinicalTrials.gov (Identifier NCT01573871). Written informed consents were provided by parents/guardians prior to enrollment.

The study formula was a clinically labelled hypoallergenic casein-based powdered eHF designed to provide 20 kcal per fl oz at standard dilution (Similac[®] Alimentum[®], Abbott Nutrition, Abbott Laboratories, Columbus, Ohio) and has recently become available in the EU. The formulation was compliant with EU regulations for infant formulae [6] and other than slight differences in some minerals/vitamins varied from the U.S. formulation in that sucrose comprised 20% rather than 30% of the carbohydrate and the emulsifier, diacetyl tartaric acid esters of mono- and diglycerides, was removed and replaced with modified cornstarch as approximately 3% of the carbohydrate.

At Visit 1, eligible infants were enrolled into the 15 ± 5 days feeding trial. Weight and length measurements were collected and plotted against the World Health Organization (WHO) growth standards [7] at Visit 1 and at exit (Visit 2). Intake and stool records were completed by parents daily and an Infant Feeding and Stooling Pattern Questionnaire was completed at Visit 1 to assess the baseline status of infants and at Visit 2 to assess and change in perceived status after feeding the study formula. The primary outcome was maintenance of weight for age Z-score during the study. Secondary variables were average daily formula volume intake and adjusted volume intake (mL/d and mL/kg/d). Supportive variables included percentages of various stool consistencies and color, number of stools/d, percent of feedings with spit-up/vomit associated (within 1 hr) with feeding, number of feedings/d, and parental responses to the Infant Feeding and Stooling Patterns and Formula Satisfaction Questionnaires. Subject demographics (birth weight, birth length, sex, race, ethnicity, and age at enrollment) were collected. For calculation of mean rank stool consistency (MRSC), each stool was ranked by the parents on a scale of 1 to 5 (1=watery, 2=loose/mushy, 3=soft, 4=formed, 5=hard). The MRSC was calculated for each day and the average of these daily means was calculated over the study period reported as the average MRSC. Safety monitoring consisted of the collection of adverse events and serious adverse events during the study.

The change in weight for age Z-score was analyzed using the paired t-test and the Wilcoxon signed rank test. Hypothesis testing was done using a two-sided, 0.05 level test. The study results are shown as mean ± standard error of the mean (SEM) and are for the Protocol Evaluable (PE) group (subjects compliant with the feeding based on *a priori* criteria) unless indicated.

RESULTS

A total of 25 subjects (85 ± 8.9 d of age), 17 males/ 8 females, were enrolled into the study (4 Group A; 21 Group B) and comprised the intent-to-treat group. Seven infants were ≥ 4 mo of age at Visit 1; 4 infants were preterm. The mean birth weight was 3158 ± 118 g and mean birth length was 50.1 ± 0.6 cm. Of the 25 infants, 18 (2 Group A; 16 Group B) comprised the PE group. Of the 7 infants excluded from the PE group, 2 did not satisfy eligibility criteria, 1 consumed a new vitamin supplement after entry, 2 received new medications after entry, 1 (2.8 mo of age) refused the study formula, and 1 was removed from the study by the parent. At entrance, 12 infants had symptoms of allergic colitis or food protein allergy/intolerance; 12 had persistent formula intolerance, 11 had hematochezia/heme positive stools, and 1 was recovering from necrotizing enterocolitis. No safety concerns were identified for the study formula.

Using the WHO reference data [7], weight for age Z-scores of the infants born at term significantly improved from Visit 1 to Visit 2, -0.62 ± 0.19 and -0.41 ± 0.16, respectively ($p < 0.05$). The mean change in weight for age Z-score was 0.21 ± 0.10 (n=15).

The mean study formula volume intake and adjusted volume intake were 764 ± 48 mL/d and 156 ± 12 mL/kg/d, respectively. The mean number of daily study feedings was 7.0 ± 0.4. A mean of 28.9 ± 4.9% of feedings/d had associated spit-up/vomit. The predominant stool consistency was loose/mushy during the trial. The mean % of stools of various consistencies were 43% loose/mushy, 38% soft, 10% watery, 7% formed and 2% hard; no infant had hard as the predominant stool consistency. The average MRSC was 2.49 ± 0.13. The predominant stool color was tied between green and brown. The mean % of stools of various colors were 41% green, 36% brown, 22% yellow, and 1% black. Infants passed an average of 1.8 ± 0.4 stools/d.

Based on questionnaire responses collected at Visits 1 and 2, an overall improvement in gastrointestinal symptoms was observed with the biggest changes in infants perceived as having hard stools, watery stools, too many bowel movements, or constipation at study entry (Table 1). Stool consistency appeared to normalize on the study formula with 34% at Visit 1 versus 67% at Visit 2 always or frequently having stool consistency that was “just right”. All parents responded that they were satisfied with the study formula (50% very satisfied, 50% somewhat satisfied) and 9 of every 10 parents reported that their infant did very well or well on the formula.

Table 1. Percentage of parents responding in the top 3 categories of a 5 point scale for selected questions on an Infant Feeding and Stooling Patterns Questionnaire administered on visits 1 (pre-study formula) and 2 (study formula) and the percent change in symptoms at visit 2 from visit 1. The top 3 categories (always, frequently, some of the time) were in positive agreement with the question asked.

Question	Visit 1 (%)	Visit 2 (%)	Change
My baby fussed or resisted the bottle while being fed the formula	22	11	50% decrease
Stool odor was very bad	78	72	8% decrease
There were days my baby had too many bowel movements	28	11	61% decrease
My baby drank formula within a reasonable period of time	100	100	No change
My baby cried or fussed before or during bowel movements	56	34	39% decrease
My baby had at least one bowel movement per day	94	83	12% decrease
The formula appeared to satisfy my baby's hunger	100	100	No change
My baby had watery stools	34	55	62% increase
My baby was gassy	88	72	18% decrease
My baby spit up with feedings	83	66	20% decrease
My baby had difficulty with bowel movements	39	34	13% decrease
My baby needed to be burped a lot during feedings	83	72	13% decrease
My baby's stool consistency was just right	62	84	35% increase
My baby's stools were too hard	36	0	100% decrease
My baby vomited after feeding	34	34	No change
My baby appeared constipated	44	18	59% decrease

DISCUSSION

The results of this observational study suggest that this new formulation of the study formula is safe for feeding infants and well tolerated by infants with symptoms of suspected food protein allergy and/or persistent formula intolerance. There have been concerns that the poor taste of these formulas will adversely influence formula intake. Mennella and Beauchamp [8] reported that infants younger than 2 mo of age detected a difference between a similar eHF and their regular formulas but drank substantial amounts of the formula; however, almost all 7 to 8 mo old infants rejected the eHF. Formula acceptance was not an issue in the current study. All 7 infants \geq 4 mo of age at enrollment accepted the study formula. The formula was well accepted by infants enabling adequate volume consumption, maintenance of weight for age Z-scores and a high level of parental satisfaction.

CONCLUSION

The results suggest that this eHF was well accepted and tolerated by an intended use population of infants during the first 6 months of life which enabled adequate volume consumption, maintenance of wt for age Z-scores and a high level of parental satisfaction.

CONFLICT OF INTEREST

The authors are employees of Abbott Nutrition, Abbott Laboratories.

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ABBREVIATIONS

eHF	=	Extensively hydrolyzed infant formula
EU	=	European Union
HCP	=	Health Care Professional
MRSC	=	Mean Rank Stool Consistency
PE	=	Protocol Evaluable
SEM	=	Standard Error of the Mean
US	=	United States

WHO = World Health Organization

WT = Weight

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