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Safety and Usage of an Amino Acid-based Formula for Infants: Results from a Post Market Surveillance Study

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Abstract

Safety and Usage of an Amino Acid-based Formula for Infants: Results from a Post Market Surveillance Study

Background

The primary objective was to assess the frequency and nature of adverse events (AE) in infants fed a hypoallergenic amino acid-based infant formula. Secondary objectives were to describe the demographic and clinical characteristics of participants.

Methods

This prospective, multicenter, post-market surveillance program with Alfamino® Infant formula (HAA) was conducted during 2017-2018. Infants <12 months old were enrolled if the use of HAA was planned per their healthcare provider's (HCP) recommendation, or if the infant was already consuming HAA at enrollment. Infants were followed by their HCP for routine care for four months.

Findings

144 infants were enrolled, 69% (n=100) with a diagnosis of cow's milk protein allergy (CMPA). Six (4%) of the 144 subjects reported a Serious Adverse Event (SAE), though for all the causal relationship to the formula was reported as "Unrelated" or "Unlikely". In total, 156 AE were reported in 58 subjects (40%). Of those, the relationship to the formula was deemed to be "Unrelated" in 122 (78%), "Unlikely" in 14 (9%), "Probable" in 17 (11%), "Definitely" in 1 (1%), and "Unknown" in 2 (1%). Emesis and constipation were the most frequently reported events with a "Probable" association. There were no reports of anaphylaxis during the study. Eighty percent (n=91) of caregivers were satisfied with the formula.

Conclusion

In this study, use of an amino acid infant formula in infants with CMPA, severe CMPA, and malabsorptive conditions does not present with safety concerns and shows a high degree of caregiver satisfaction with the formula.

Keywords: Allergens; CMPA; Food Hypersensitivity; Hypoallergenic; Infant Formula; Infant Nutrition; Malabsorption

Introduction

Infant formulas are often used to supplement breast milk, the gold standard in infant feeding, or used exclusively for infants whose mothers cannot or choose not to breastfeed. About 2.5% of infants require alternative formulas not based on intact cow's milk protein [1-3] Cow's milk protein allergy (CMPA) is one of the major food allergies experienced by infants and children [4,5] Extensively hydrolyzed formulas (EHF) are recommended by the American Academy of Pediatrics (AAP) for the dietary management of infants who are allergic or intolerant to intact cow's milk-based infant formula (CMF); however, a subgroup of these infants cannot tolerate EHFs.6 For these infants or those with multiple food allergies who exhibit poor growth, amino acid-based formulas (AAFs) have been shown to be effective, well-tolerated, and support growth [7-12]. The nitrogen source in AAFs is devoid of intact proteins or peptides, and thus they exhibit a very low level of allergenicity.

According to the AAP,6 an infant formula is considered "hypoallergenic" only after being tested in infants with hypersensitivity to cow's milk or cow's milk-based formula, verified by properly conducted elimination-challenge tests. While severe food allergies, and CMPA in particular, are the primary indication for an AAF, these formulas are also utilized in the management of malabsorption/maldigestion syndromes, short bowel syndrome (SBS)[13] multiple food allergies[9-14] eosinophilic gastrointestinal (GI) disorders[15] such as eosinophilic esophagitis (EoE) [16,17] gastroesophageal reflux

disease (GERD)[18] and food protein induced enterocolitis syndrome (FPIES).19

Infants and children with conditions necessitating an AAF are prone to a wide variety of disease and medication-related symptoms. In some cases, these symptoms may be managed by medical or nutritional interventions, but in other cases, they may continue to present. Some of these symptoms overlap with common conditions experienced by healthy, term infants [20] In all clinical trials, observing the rate and nature of adverse events (AE) is a critical component of compliance with Good Clinical Practice (GCP) guidelines. In this context, also understanding "common" or expected conditions that occur during infancy (e.g., cold and gastrointestinal illnesses), and in particular, symptoms often associated with the high-risk population for which AAFs are frequently prescribed is a critical lens through which to view AE associated with such formulas.

The present study is the first post-market surveillance (PMS) program of a hypoallergenic amino acid-based infant formula. PMS programs provide real-world safety and monitoring data, along with adding to the science of pharmacovigilance. This methodology allows for the assessment of patients who actually receive the therapy, and often includes patients outside the population assessed in early safety and efficacy studies. The primary aim of the PMS program reported here was to further evaluate the safety of a commercialized hypoallergenic AAF in a real-world, routine, clinical practice setting by assessing the frequency and nature of AE in infants fed the formula. The secondary objectives were to describe demographic and clinical characteristics of infants fed the AAF and their complementary food intake, as well as caregiver satisfaction with the formula.

Methods

Study population and design

This prospective, non-randomized, PMS program for the hypoallergenic amino acid-based Alfamino Infant (Nestlé HealthCare Nutrition, Bridgewater, New Jersey, product of Switzerland) formula (HAA) was conducted at 30 sites with wide geographic representation across the United States (US). Eligible infant and caregiver pairs were identified and invited to enroll by their healthcare provider (HCP). Eligibility for enrollment was determined according to the following criteria: 1) infants (≤ 12 months) consuming HAA formula at the time of enrollment or those for whom consumption of the formula was planned, and 2) at least one parent/caregiver to provide prior written informed consent (ICF). Infants who were <37 weeks of corrected gestational age (CGA) at the time of enrollment were excluded from participation in the surveillance program.

Enrolled infants were followed for up to four months or until discontinuation of HAA formula. As the surveillance program was non-interventional, follow-up study clinic visits were not mandated by the study protocol. Each infant was followed by their HCP for routine clinical care. Formula was not provided to the study participants. Enrollment was open from February 2017 to May 2018.

In order to study the use of HAA formula in a real-world setting, enrollment was designed to be non-restrictive, and thus particular diagnoses were not considered as inclusion or exclusion criteria; subject enrollment was based on HCP recommendation. For infants with diagnosed CMPA, allergy was categorized as "severe" if the subject had a history of anaphylactic symptoms, and/or if symptoms did not resolve with the use of an EHF, and/or if CMPA was described as "severe" by a physician assessment. When available, any diagnosed allergy was further characterized by whether it was immunoglobulin E (IgE) mediated or non-IgE mediated.

Subjects were not randomized as this was a prospective, PMS program. A formal sample size calculation was not applied in alignment with the Food and Drug Administration's (FDA) Post-market Surveillance Guidance.21 The intent of this study was to enroll infants consuming HAA formula in the US, with no limit to the number of infants who could contribute data.

Product description

Subjects included in the program consumed HAA, an amino acid-based, hypoallergenic, nutritionally complete infant formula designed for the nutritional management of infants with CMPA, multiple food allergies, eosinophilic GI disorders, FPIES, or malabsorptive conditions. The formula is intended to serve as the sole source of nutrition for infants aged 0 to 6 months and then to be utilized as part of a complementary diet to 12 months of age. HAA formula provides 20 kcal per ounce when mixed as directed. Nutrient information is described in (Table 1).

Table 1: Macronutrient Composition of Hypoallergenic Amino Acid-Based (Alfamino) Infant Formula

Nutrient	Source/Per 100 kcal
Protein source	Amino acids
Protein (g/100 kcal, % kcal)	2.8 / 11%
Fat source	Medium chain triglycerides, soybean oil, high oleic sunflower oil, esterified palm oil, DHA, ARA
Fat (g/100 kcal, % kcal)	5.0% / 45%
MCT, % of fat	43%
Carbohydrate source	Corn syrup solids, potato starch
Carbohydrate (g/100 kcal, % kcal)	11 / 44%

Data collection

Data sources and management

At the time of enrollment and follow-up visits, relevant data were extracted from the infants' medical records and then entered via a secure internet connection into the electronic data capture (EDC) software system (eCaseLink EDC, DSG, Inc., PA, USA).

Data were collected at enrollment and at any follow-up visit with the primary HCP up to four months thereafter. At enrollment, information on demographics, medical history, feeding history since birth (including breast and/or formula

feeding and complementary foods), birth and enrollment anthropometrics (body weight, length, and head circumference), family history of allergy, and baseline symptom history was obtained from the infants' medical records. The diagnoses for which the infants' healthcare provider recommended the use of HAA formula were documented. Starting at initiation of HAA formula (either prior to study enrollment or after), AE were recorded. Information (see below "Adverse Events Reporting") was collected via infant's medical record and/or caregiver report.

At follow-up visits throughout the study, subjects' consumption of HAA formula and complementary foods, anthropometrics, AE, any change in the symptoms or diagnosis that led to the use of HAA formula, concomitant medications, and caregiver satisfaction were documented. Infants who transitioned from HAA formula to Alfamino Junior (Nestlé HealthCare Nutrition, Bridgewater, New Jersey, product of Switzerland) (HAJ) formula during the study continued to be followed through the four-month post-enrollment period. If HAA formula was discontinued before the end of observation period or if a caregiver withdrew consent for study participation, the date of and reason for discontinuation or withdrawal were documented.

Adverse events reporting

AE were defined as any untoward occurrence, which may or may not have a causal relationship with HAA. AE could have been illness, signs or symptoms (including abnormal laboratory findings) that occurred or worsened during the course of the study. AE were reported as non-serious or serious. Serious adverse events (SAE) were defined as fatal or life-threatening events causing permanent harm or requiring/extending in-patient hospital treatment, or which was considered medically relevant by the physician, which may or may not have had a relationship to treatment. Other non-serious events were documented as an AE. HCPs were required to document and assess AE for relationship to the formula, categorized as "Unrelated," "Unlikely," "Probable," or "Definite." In addition, HCPs recorded the date of onset, description of the event, the occurrence and duration of symptoms, intensity, and any action(s) taken (including use of medication(s) to treat the AE/SAE and discontinuation of formula, if warranted).

A list of known symptoms and events associated with CMPA, malabsorption, eosinophilic GI disorders or gastrointestinal intolerance are available in (Table 2). When identified, these symptoms were reported as AE at enrollment and/or during any routine follow-up contact with the HCP.

Table 2: Symptoms and Events that Commonly Lead to the use of Amino Acid-Based Infant Formula.

Category	Symptom or Event
Digestive	Forceful vomiting (return of larger amounts of food), diarrhea (3 or more loose or liquid stools per day), constipation, blood in stool
Skin	Atopic dermatitis (eczema), angioedema (swelling of lips or eyelids), urticaria
Respiratory	Runny nose, otitis media, chronic cough, wheezing
General	Persistent distress, colic (defined as ongoing crying episodes of a minimum of 3 hours of crying for 3 or more days in a week for at least 3 weeks), anaphylaxis, iron deficiency anemia, failure to thrive, dysphagia, odynophagia (painful swallowing)

Sites were instructed to enter an SAE into the electronic case report form (eCRF) within 24 hours after learning of the event. Entry of an SAE into the EDC automatically and immediately notified the study sponsor.

Ethical Approval and Informed Consent

The surveillance program obtained central Institutional Review Board (IRB) approval from Quorum, Seattle, Washington, USA. If sites required local IRB review/approval, the site coordinator secured local IRB approval prior to initiating the surveillance program. Each study site was accountable for ensuring compliance with the Health Insurance Portability and Accountability Act (HIPPA). The study fulfilled all requirements for human research, including informed consent and the Declaration of Helsinki and Good Clinical Practice. This study was registered with ClinicalTrials.gov (ID# NCT02953223).

Statistical methods

All statistical analyses were performed using StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC. The primary outcome was the frequency and nature of AE in infants fed HAA formula. AE were classified and reported as non-serious AE or SAE. AE occurrences are presented as both counts and rates. Counts presented include a count of the total number of infants experiencing any AE as well as a count of the total number of AE experienced over all patients. AE were also tabulated within groupings of possible relationship to the study product. The incidence of AE is presented as rates using the number of AE as the numerator and the follow-up time as the denominator. Confidence intervals around the observed rates were calculated to provide information regarding precision and statistical power of the rates.

The secondary outcomes included demographics and clinical characteristics of infants who consumed HAA formula, as well as caregiver satisfaction with HAA. Secondary endpoints, including demographic and clinical characteristics were analyzed descriptively. Summary statistics for continuous measures presented include means, standard deviations, medians, minimums, and maximums. For categorical measures, counts and percentages are presented.

All enrolled subjects were included in the statistical analysis. In addition, a subgroup analysis was completed for subjects with a CMPA diagnosis, including those meeting the protocol definition of 'severe' CMPA.

Results

Subject disposition

Caregivers of 144 infants provided consent for their infant to enroll in this PMS program. Of the 144 subjects enrolled, 88 (61%) were followed for the intended four-month surveillance period. Of those subjects followed less than four months (n=56), 18 (32%) were lost to follow-up, 29 (52%) discontinued HAA formula, 8 (14%) experienced an AE, and 1 (2%) relocated their residence. All enrolled subjects (n=144) were included in the analysis.

Overall, the number of days HAA was consumed from enrollment to the end of the program was 94 ± 47 days (n=107 of 144; a program end date was not available for the remaining 37 subjects). Subjects followed for four months (n=88) had an average of two follow-up visits and 85% of these (n=75) consumed HAA for a mean of 122 ± 6.6 days. Subjects followed for less than four months (n=56) averaged one follow-up visit and 57% of these (n=32) averaged 27 ± 31 days of HAA consumption. Overall, six subjects (5%) switched to HAJ formula during surveillance.

Demographics and enrollment data

Thirty sites were contracted for recruitment with 53% of enrollment achieved from 2 sites, and another 17 sites enrolling the remaining 47% of the population. Subject and household demographics are shown in Table 3. Of the 144 infants enrolled, the primary diagnosis leading to the use of HAA formula was CMPA (n=100, 69%), followed by malabsorption/maldigestion in 5 subjects (3%), and other diagnoses were reported in 39 subjects (27%), including milk protein intolerance, failure to thrive (FTT), reflux and GERD. Within the CMPA population, 60 (60%) reported a non IgE-mediated allergy, 3 (3%) reported an IgE-mediated allergy, and 37 (37%) were recorded as “not applicable (NA).” The study did not offer the option to mark “both” or “unknown,” therefore; the NA group may represent allergies with missing or unknown IgE categorization. Fifty-nine percent of enrolled subjects (n=84) met one or more criteria for severe CMPA allergy. The most commonly reported criterion leading to severe allergy categorization was consumption of an extensively hydrolyzed formula without symptom resolution (n=82, 98%).

Table 3: Subject Demographics at Enrollment Among Infants Consuming Amino Acid-Based Infant Formula.

	N (%) Or Mean [std] Median [Min, Max]
Gender	
Male	71 (49%)
Female	73 (51%)
Type of delivery	
Vaginal	89 (62%)
Caesarean section	55 (38%)
Birth type	
Singleton	134 (93%)
Twin	10 (7%)
Gestational age at birth, weeks	
All subjects	37.8 [3.1] 39 [23,41]
Subjects born prematurely (<36 6/7 weeks)	29 (20%) 33 [3.8] 34 [23,36]
Chronological age at enrollment, weeks+	21.0 [12.6] 17.9 [3,51]
Ethnicity	
Asian	4 (3%)
Black	42 (29%)
Caucasian	57 (40%)
Hispanic	38 (26%)
Other	3 (2%)

Anthropometric measurements are reported when available. World Health Organization (WHO) growth charts were used to calculate weight, length, head circumference percentiles and weight-for-age, length-for-age, and head circumference-for-age z-scores.22 Mean (± standard deviation [SD]) percentiles for birth weight (36.3 ± 31.5), and length (45.9 ± 37.6) reflect that the enrolled population was smaller than average at their respective gestational ages. Mean z-scores at birth reinforce this trend across enrolled subjects, with the birth weight z-score of -0.80 (n=117) and birth length z-score of -0.98 (n=102). Descriptive statistics for WHO percentiles and z-scores for weight, length, and head circumference from birth and enrollment are available in (Table 4).

Table 4: WHO Percentiles and z-scores for Subject Birth Weight, Length, and Head Circumference.

	At Birth		**At Enrollment**	
	WHO Z Score	**WHO Percentile**	**WHO Z Score**	**WHO Percentile**
	N Mean [std] Median [Min, Max]	N Mean [std] Median [Min, Max]	N Mean [std] Median [Min, Max]	N Mean [std] Median [Min, Max]
All				
Weight, g	117 -0.80 [1.8] -0.47	117 36.3 [31.5] 31.8	141 -1.04 [1.5] -1.08	141 27.9 [30.4] 13.9

	[-7.1,4.8]	[0,100]	[-6.5,2.3]	[0,98.9]
Length, cm	102 -0.98 [3.7] -0.20 [-16.3,4.6]	102 45.9 [37.6] 42.0 [0,100]	141 -1.08 [2.0] -1.05 [-10.1,5.1]	141 29.8 [33.0] 14.6 [0,100]
Head circumference, cm	70 -1.08 [2.7] -0.48 [-11.4,2.4]	70 38.8 [35.3] 31.6 [0,99.2]	85 -0.95 [2.0] -0.46 [-7.1,2.7]	85 36.6 [33.9] 32.3 [0,99.7]
Boys				
Weight, g	58 -0.80 [2.0] -0.42 [-7.1,4.8]	58 37.5 [30.7] 33.9 [0,100]	69 -1.08 [1.6] -1.15 [-6.5,2.2]	69 27.7 [31.4] 12.6 [0,98.5]
Length, cm	50 -1.9 [4.6] -0.20 [-16.3,1.8]	50 40.8 [35.8] 42.0 [0,96.4]	71 -1.05 [2.3] -0.88 [-10.1,5.1]	71 30.9 [32.7] 19.0 [0,100]
Head circumference, cm	33 -0.89 [2.8] -0.13 [-11.4,2.4]	33 44.8 [34.9] 44.9 [0,99.2]	40 -0.98 [1.8] -0.55 [-5.8,1.6]	40 34.9 [32.0] 29.1 [0,94.7]
Girls				
Weight, g	59 -0.79 [1.7] -0.61 [-6.7,2.3]	59 35.1 [32.5] 27.1 [0,99.0]	72 -1.00 [1.5] -1.02 [-5.8,2.3]	72 28.2 [29.6] 15.3 [0,98.9]
Length, cm	52 -0.05 [2.4] -0.16 [-9.5,4.6]	52 50.9 [39.0] 43.7 [0,100]	70 -1.10 [1.7] -1.19 [-5.9,2.6]	70 28.7 [33.5] 11.7 [0,99.5]
Head circumference, cm	37 -1.24 [2.6] -0.74 [-10.2,2.2]	37 33.5 [35.2] 22.9 [0,98.7]	45 -0.93 [2.3] -0.45 [-7.1,2.7]	45 38.1 [35.8] 32.6 [0,99.7]

Primary Outcome

Serious Adverse Events (SAE)

Six SAE were reported in six subjects, three of which had severe CMPA. In all of the SAE, the causal relationship to the product was reported as “Unrelated” or “Unlikely” and none were deemed to have a “Probable” or “Definite” relationship to HAA formula. At study completion, infants had either recovered (n=5, 83%) or were improving (n=1, 17%) from their SAE. There were no reports of anaphylaxis during this study.

In four of the six SAE (67%), HAA use continued with no change, which included one SAE in an infant with severe CMPA. HAA use was withdrawn after one SAE (17%), and one SAE (17%) required the infant to transition from consuming HAA orally to via nasogastric tube; the latter two interventions occurred in infants with severe CMPA.

Adverse Events (AE)

Non-serious AE were not reported in 60% (n=86 of 144) of all subjects and in 63% (n=53 of 84) of those with severe CMPA. In all subjects and within the severe CMPA group, 40% and 37%, respectively, reported non-serious AE over the course of surveillance (Table 5). In both groups, the most frequent intensity of AE reported was “Mild” and occurred “Several times” in the largest percentage of subjects. In 78% (n=122) of all subjects, the AE was deemed to be “Unrelated” to HAA usage by the HCP. Similarly, in subjects with severe CMPA, 74% (n=67) of AE were determined to be “Unrelated” to HAA consumption.

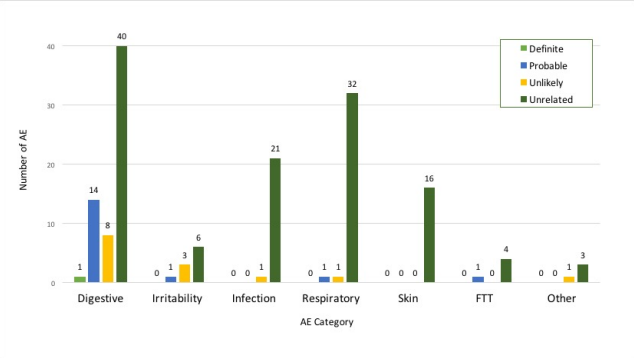
Table 5: Adverse Events (Non-serious and Serious) in Enrolled Subjects.

	All Subjects (N=144)	**Severe CMPA (N=84)**
	N (%)	**N (%)**
Subjects with any Adverse Event?		
Yes	58 (40%)	31 (37%)
No	86 (60%)	53 (63%)
Number of Total Adverse Events	156	90
Relationship to Product		
Unrelated	122 (78%)	67 (74%)
Unlikely	14 (9%)	11 (12%)
Probable	17 (11%)	11 (12%)
Definitely	1 (1%)	1 (1%)
Unknown	2 (1%)	0 (0%)
Subjects with any Serious Adverse Event?		
Yes	6 (4%)	3 (4%)
No	138 (96%)	81 (96%)
Number of Serious Adverse Events†	6	3
Relationship to Product		
Unrelated	5 (83%)	2 (67%)
Unlikely	1 (17%)	1 (33%)
Probable	0 (0%)	0 (0%)
Definitely	0 (0)%	0 (0%)

One subject with CMPA was described as having several occasions of mild emesis. This AE was determined to have a “Definite” relationship to HAA and was attributed to switching to HAA from an extensively hydrolyzed formula; the subject was subsequently switched back to the previous formula. Seventeen AE in 13 subjects (eight with severe CMPA) were categorized as having a “Probable” relationship to HAA; the majority (82%) of these AE was reported as emesis, gastroesophageal reflux,

diarrhea and constipation. Respiratory symptoms were the next most frequent category reported. (Figure 1) illustrates AE by symptom category and their causal relationship to the formula.

Figure 1: Adverse Events (AE), by Symptom Category and Relationship to Hypoallergenic Amino Acid-based Infant formula.



AEs were categorically grouped according to symptom type and their causal relationship to Alfamino HAA as assigned by the subjects' primary HCP.

Seventy-seven percent of AE (n=120) in all subjects and 80% of AE (n=72) in subjects with severe CMPA did not require discontinuation of HAA formula, which is consistent with the rates of AE categorized as "Unrelated" to the product. The product was discontinued in 12% (n=19) of AE in all subjects and in 11% (n=10) of AE in severe CMPA subjects; data on continuation of product was not available in 11% (n=17) of all subjects and 9% (n=8) with severe CMPA. HAA was reintroduced in two subjects; one tolerated the reintroduction, and in the other, symptoms returned.

Secondary Outcomes

Symptom history and family history of allergy

The presence of malabsorptive conditions, SBS, EoE, and GI intolerance, and symptoms associated with CMPA that lead to an indication for use of HAA formula were obtained at enrollment. The most common symptoms prior to enrollment were vomiting and constipation, each reported in 36% of subjects, followed by diarrhea and colic, each reported in 33% of subjects. (Table 6) provides the prevalence of all symptoms reported at enrollment.

Table 6: Symptom History at Enrollment, N=144.

Symptom History at Enrollment	N (%)
Forceful vomiting (return of larger amounts of food)	52 (36%)
Constipation	52 (36%)
Diarrhea (3 or more loose or liquid stools per day)	47 (33%)
Colic	47 (33%)
Failure to thrive	45 (31%)
Atopic dermatitis (eczema)	35 (24%)
Blood in stool	34 (24%)
Persistent distress	22 (15%)
Runny nose	18 (13%)
Wheezing	16 (11%)
Dysphagia	14 (10%)
Chronic cough	12 (8%)
Iron deficiency anemia	7 (5%)
Otitis media	6 (4%)
Urticaria	4 (3%)
Angioedema (swelling of lips or eyelids)	3 (2%)
Odynophagia (painful swallowing)	3 (2%)

In subjects whose parent(s) had a history of allergy, asthma was most common (17% of mothers and 14% of fathers reported a history of asthma). Seventy-one percent of subjects had one or more siblings, and of those, approximately one in five reported a history of either current asthma or food allergy (Table 7).

Table 7: Family History of Allergy.

Among all subjects (N=144), biological parents have existing or history of:	Mother			Father		
	Yes N (%)	No N (%)	Unknown N (%)	Yes N (%)	No N (%)	Unknown N (%)
Allergic rhinitis (hay fever)	14 (10%)	103 (72%)	27 (19%)	16 (11%)	92 (64%)	36 (25%)
Asthma	25 (17%)	92 (64%)	27 (19%)	20 (14%)	90 (62%)	34 (24%)
Atopic dermatitis	15 (10%)	101 (70%)	28 (19%)	12 (8%)	97 (67%)	35 (24%)
Food allergy	13 (9%)	104 (72%)	27 (19%)	12 (8%)	97 (68%)	35 (24%)
Among subjects with 1+ sibling(s) (N=102), sibling(s) have existing or history of:	**Yes N (%)**		**No N (%)**		**Unknown N (%)**	
Allergic rhinitis	14 (14%)		67 (66%)		21 (21%)	

(hay fever)			
Asthma	21 (21%)	57 (56%)	24 (24%)
Atopic dermatitis	15 (15%)	66 (65%)	21 (21%)
Food allergy	20 (20%)	61 (60%)	21 (21%)

More than one allergy may have been selected per family member. Percentages may not sum to 100 due to rounding.

Breast and formula feeding history

At enrollment, breast and formula feeding history and any requirement for parenteral nutrition (PN) was obtained. Based on data from 143 subjects, 97 (68%) had received human milk for a mean of 62 ± 69 days. Most subjects (n=138; 97%) had previously consumed formula, including standard formulas (n=97; 68%), EHF (n=91; 64%), AAF (n=31; 22%), and premature formulas (n=19; 14%). The most common reported reason for switching from an alternate AAF to HAA Infant formula was GI intolerance (n=21 of 33; 68%). Seventeen (12%) subjects had a history of PN use (mean 33.1 ± 35.2 days). Approximately one of every five enrolled subjects consumed an alternate AAF before participating in this program.

Complementary feeding history

Subjects' food and beverage intake and any associated intolerances were documented at enrollment and follow-up visits. Foods and beverages consumed (other than human milk or formula) were assigned the following categories: cereal, dairy products (yogurt and cheese), single-ingredient fruit or vegetable puree, animal protein (egg, chicken and/or beef), and other. At enrollment, 46% (n=65) of subjects had consumed complementary foods (CF), increasing to 72% (n=103) over the course of the study. Of subjects who consumed CF, cereal was the most commonly consumed, by 92% (n=60) of subjects in whom CF were introduced prior to enrollment and by 97% (n=100) of subjects in whom CF were introduced during the study. Reactions, defined as any negative symptoms associated with CF intake, were reported in all food categories. The mean age at which CF were first consumed was 6.2 ± 3.2 months.

In the CMPA subgroup, 71% of subjects reported CF intake. Cereal intake was reported in 99% of subjects (mean age at introduction: 6 months). Despite the high rate of CMPA diagnoses in enrolled subjects, 20% reported intake of dairy products, with mean age at introduction of 8.9 months. Single-ingredient fruit or vegetable purees were consumed by 75% of the subgroup (mean age at introduction: 7.5 months). Egg, chicken and/or beef were consumed by 30% (mean age at introduction: 9.6 months). Twelve subjects (12%) in the CMPA subgroup had a documented reaction to CF during the study period.

Caregiver satisfaction

At each follow-up visit, caregiver satisfaction with HAA was assessed. Eighty percent (n=91) of caregivers were satisfied with HAA, and 5% of caregivers reported mixed satisfaction, i.e. their degree of satisfaction varied throughout the program. In the CMPA subgroup, 82% (n=69) of caregivers reported they were satisfied with HAA and 5% reported mixed satisfaction.

Discussion

To the author's knowledge, this is the first of its kind post-market prospective surveillance program and adds to the record of safety for the hypoallergenic amino acid-based infant formula HAA, demonstrating the safety of the formula for a subject population that included a high incidence of severe CMPA. The primary aim of this project was to demonstrate safety in a real-world setting via assessment of the frequency and nature of AE. The main benefit of this design lies in its pragmatic approach, which offers the ability to assess the effects of the formula in a real-world setting. This type of study allows for an open enrollment of patients on the formula with a variety of diagnoses and enhances visibility to the types of patients that are prescribed AAFs.

The HAA formula used in this study meets the AAP criteria to be labeled hypoallergenic [23] According to the AAP6 and the FDA, an infant formula can be deemed "hypoallergenic" only after being tested in infants with hypersensitivity to cow's milk or cow's milk-based formula, which verifies findings by properly conducted double-blind placebo-controlled food challenge (DBPCFC) [24]. One of the intended applications of hypoallergenic formulas is for use in infants with existing symptoms of allergy.

The monitoring of SAE addresses a higher degree of safety in this vulnerable population of infants. Of the six SAE reported, only one resulted in discontinuation of the study formula and all were deemed either "Unrelated" or "Unlikely" to be related to the HAA formula. There were no cases of anaphylaxis reported in a subject population overwhelmingly diagnosed with CMPA, adding substantiation of the formula's safety for infants requiring AAF for allergy management.

Secondary outcomes are provided to give context on the patient population and caregiver experience. Breastfeeding rates for subjects in the study were lower than the US average, with 68% having received human milk for an average duration of around two months. The CDC reports 84% of infants born in 2017 started breastfeeding and around 58% were still breastfed at 6 months [25] The AAP recommends exclusive breastfeeding for six months [26] and the European Society of Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) recommends exclusive breastfeeding for four months with exclusive or predominant breastfeeding encouraged for six months [27] The mean age at consumption of any food or beverage other than human milk or formula was 6 months, which closely aligns with the AAP recommendations to introduce solid foods between four to six months [28] and ESPGHAN recommendations for solid foods not be introduced before four or delayed beyond six months [27] Complementary food intake increased from 65 (46%) of subjects at enrollment to 103 (72%) during the study.

Many symptoms recorded in the subjects' symptom history were consistent with AE recorded. In our study, gastrointestinal

symptoms were the most frequently reported AE. This is consistent with findings from a review by Vandenplas, who found that regurgitation, constipation, and crying or distress are events common in infancy [20]. A study that followed 934 healthy infants through 12 months of age found that while the infants were free of known severe infections, complications, disease or disorders from birth to one year, 76.9% experienced at least one functional GI disorder (FGID) [29] In an assessment of functional gastrointestinal disorders in infants from birth to 12 months, authors reported an estimated prevalence of colic at 20%, regurgitation at 30%, and functional constipation at 15% with limited data on functional diarrhea and dyschezia leading to an estimated prevalence of <10% [30].It is not uncommon for the GI symptoms noted here to be accompanied by a change in feeding regimen. In a study of 2,879 healthy, newborn infants followed for six months, it was found that GI symptoms result in formula changes around 60% of the time [31] In the same study, the GI symptoms that presented were generally non-serious and rarely resulted in hospitalization.

We found most AE were deemed "Unrelated" to the formula and did not trigger discontinuation of HAA formula; the formula was discontinued in only 12% of the overall population and in 11% of those with CMPA. In our study, caregivers in both the overall and CMPA subgroup reported high levels of satisfaction with the formula at similar rates of 80% and 82%, respectively. Formula was not provided in this study and, thus, the high rate of caregiver satisfaction and comparatively low rates of formula switching are likely indicative of real-world experience, specifically with AAF.

Beyond CMPA, the American College of Gastroenterology (ACG), ESPGHAN, and the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) recognize the use of AAFs as an effective dietary management strategy for eosinophilic GI disorders, and the American Academy of Allergy, Asthma, and Immunology (AAAAI) notes that AAFs are effective in certain children with FPIES who are unable to tolerate extensively hydrolyzed formulas or those with FTT15. Additionally, AAFs are frequently recommended in other conditions including SBS, GERD, multiple food allergies, and with other malabsorption/maldigestion conditions[34]. The main goal of nutritional therapy for infants and children with food allergy or feeding intolerance related to these conditions is to avoid adverse reactions while promoting growth and development. To that end, the AAF assessed in this study includes a unique lipid blend which includes 43% medium chain triglyceride (MCT) oil to facilitate fat absorption. Since MCTs are directly absorbed into the portal circulation for transport to the liver, they facilitate better utilization of energy from fat for infants and children with gut immaturity, anatomical or functional GI disorders, or intestinal failure resulting in severe fat malabsorption [35,36].

Like all infant formulas, hypoallergenic formulas must demonstrate their nutritional adequacy by supporting normal growth and development [37].When assessing growth, the rate of weight gain is considered the single most valuable component of the clinical evaluation of infant formula. In a previous study, growth and tolerance of HAA formula were demonstrated in infants from 14 to 112 days of age [7] In addition, formula intake, AE, flatulence, spit-up/vomiting, mood, and sleep were similar between the groups fed HAA or control formula.

The infants included in this program were smaller than average with mean z-scores for birth weight, length and head circumference all below the median and mean and WHO percentiles for birth weight, length, and head circumference were all below the 50th percentile. Enrollment z-scores and WHO percentiles for weight, length, and head circumference reflected a negative change from baseline (i.e. birth), indicating a declining growth trajectory for the subject population. This trend is not entirely unexpected with this population, since most subjects were diagnosed with CMPA prior to enrollment and FTT is a symptom of CMPA.10 In addition, 20% of subjects had been born prematurely. While they achieved > 37 weeks CGA prior to enrollment (as per inclusion criteria), growth faltering is not uncommon in infants born prematurely, even after achieving term gestational age.38 A growth trajectory assessment over the four-month study period was not a main outcome of this study, and with no mandated study visits, anthropometric data were not available for all subjects. In addition, the study was not designed to assess growth, and thus, precluded a thorough assessment of growth trajectories in the study population.

There are several limitations to this study, some of which are inherent to the post-market surveillance design. This study provides AE data on only one specific AAF, and since this is the first study of its kind and there was no control or comparison group, we are unable to provide context for the results observed here compared to other AAF. One key drawback is the lack of a structured follow-up visit schedule, which restricts the assessment of growth data over the four-month study since site visits were not required. Expected rates of growth change frequently over the first year of life and study criteria hindered a meaningful assessment of growth trends of the enrolled population since subjects could be enrolled at any age during the first year of life, were followed for differing lengths of time up to four months, and follow-ups were dependent on the infant's routine care needs and not on other set criteria for the study. Data were collected from electronic health records (EHR) as well as caregiver reports to the healthcare professional during the clinic visit. Relying solely on EHR may have resulted in missing data in some cases. For this study, the only criterion required for a subject to be included in the CMPA subgroup was verification of a CMPA diagnosis by the infant's physician. Diagnostic criteria for CMPA were not established as part of the inclusion criteria, which could have resulted in inconsistencies across the subjects classified with CMPA. Finally, while an effort was made to obtain a nationally representative sample by contracting 30 centers for recruitment, 19 centers enrolled infants and two centers provided the majority of participants; this may limit the generalizability of the study findings.

Conclusion

HAA consumption by infants with CMPA, severe CMPA and malabsorptive conditions does not present with safety concerns and is associated with a high degree of caregiver satisfaction. Use of HAA in infants demonstrated no unexpected symptoms in this PMS program. SAE reported were not related to formula use

and 89% of AE were classified as either “Unrelated” or “Unlikely” to be related to the formula. The AE reported in this study are common among infants with the diagnoses represented in this study. AAFs provide a vital source of nutrition for infants who are unable to tolerate extensively hydrolyzed infant formulas. Infants who require AAFs tend to be smaller and experience a variety of symptoms. Future studies could benefit from a longer follow-up duration with mandated scheduled visits to assess growth. Also, larger post-market surveillance studies in this population could enhance efforts to incorporate a more nationally representative sample and should provide well-defined diagnostic criteria. Additional long-term post-market surveillance studies are needed to provide a more comprehensive view of the real-world experience of infants requiring specialized formulas to manage complex diagnoses.

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