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Tolerance of a cow's milk-based hydrolyzed formula in patients with eosinophilic esophagitis triggered by milk

A. J. Lucendo[1], Á. Arias[2], J. González-Cervera[3], T. Mota-Huertas[4] & J. L. Yagüe-Compadre[4]

[1]Department of Gastroenterology, Hospital General de Tomelloso; [2]Research Support Unit, Complejo Hospitalario La Mancha Centro; [3]Department of Allergy, Hospital General de Tomelloso; [4]Department of Pathology, Complejo Hospitalario La Mancha Centro, Ciudad Real, Spain

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Keywords
eosinophilic esophagitis; food allergy; hydrolyzed formula; milk allergy; milk proteins.

Correspondence
Alfredo J. Lucendo, Department of Gastroenterology, Hospital General de Tomelloso, Vereda de Socuéllamos, s/n, 13700 Tomelloso, Spain.
Tel.: +34 926525927
Fax: +34 926525870
E-mail: alucendo@vodafone.es

Guarantor of the article: Alfredo J. Lucendo, MD, PhD.

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Abstract

Background: Cow's milk protein, a major food trigger for EoE in both children and adults, should be continuously avoided once identified as such. This study evaluates tolerance of a cow's milk-based extensively hydrolyzed formula (eHF) with regard to disease remission maintenance in adult patients with milk-triggered EoE.

Methods: Seventeen adult patients in whom cow's milk was consecutively demonstrated to trigger EoE after an empiric six-food elimination diet-based study protocol and who subsequently maintained disease remission were prospectively recruited. They were given 400 ml of a cow's milk-based eHF daily for 8 weeks. Intraepithelial peak eosinophil and blood eosinophil counts, esophageal-related symptoms, serum total and specific IgE to major milk proteins, and eosinophil cationic protein were monitored before and after eHF intake.

Results: Thirteen male and four female patients aged 17–56 completed the study protocol. 15 patients (88.24%) achieved and maintained EoE remission, while an infiltration of ≥15 eosinophils/hpf reappeared in the remaining two patients. No differences in age, gender, symptoms, and endoscopic appearance at baseline conditions or personal/family allergic background were observed between those patients who tolerated the eHF and those who did not. Symptom scores did not significantly change after eHF intake and were significantly lower than those documented at baseline conditions or after cow's milk challenge. No differences were documented in blood eosinophil counts or serum markers after eHF intake.

Conclusion: Most adult patients with EoE triggered by cow's milk tolerate a cow's milk-based eHF, thus providing them with a safe, economical alternative to cow's milk.

Eosinophilic esophagitis (EoE) is an emerging gastrointestinal disorder characterized by marked esophageal eosinophilia that usually persists from childhood to adulthood (1, 2). The high response rate to food elimination diets, especially amino acid-based elemental diets (3–5), and empiric 6-food elimination diets (6, 7) implies that the disease involves allergic sensitization to commonly consumed foods. In fact, sequential food reintroduction identifies EoE food-triggers in both children and adult patients by documenting disease recurrence (7–9). Cow's milk protein (CMP) has been demonstrated to be the food antigen most frequently linked to EoE in both pediatric (8, 10, 11) and adult patients (7, 9) and is identified as an EoE trigger in approximately 3 of 4 patients. Because EoE is thought to be primarily non-IgE mediated (12, 13), current recommendations call for indefinite restriction of foods proved to trigger EoE (14). This presents a dietary challenge, especially in pediatric patients.

Allergy to CMP is recognized as a frequent disorder, the consequences of which range from anaphylaxis to various skin diseases and gastrointestinal motility disturbances (15), especially in pediatric patients. In fact, the immaturity of the digestive enzymatic system and increased permeability of the mucosa have been related with easy passage of undigested proteins, which can cause a primed immune response (16) through Th2 lymphocyte stimulation, cytokine secretion, and IgE production. In contrast, allergy to CMP is a rare condition among adult patients, in whom lactose intolerance is considered the predominant cause of symptoms related to

milk consumption (17). New evidence is currently broadening the known spectrum of CMP allergy in adulthood, especially regarding non-IgE-mediated reactions (18), and the recognition of milk as a major trigger for EoE among adult patients has contributed to a reconsideration of the relevance of milk as a major cause of food allergies.

Cow's milk-based extensively hydrolyzed formulas (eHFs) are used in the management of CMP allergies because they are known to be well tolerated by most infants and children (19). Still, some cases require elemental amino acid-based formulas (20). For adult patients, restriction of milk and milk-derived products from the diet constitutes the predominant treatment in cases of cow's milk allergies. To date, no data are available on the usefulness of replacing cow's milk with a cow's milk-based eHF in adult patients suffering from EoE triggered by CMP.

The primary goal of this study was to prospectively evaluate the tolerance of a cow's milk-based eHF in terms of disease remission maintenance in adults with milk-induced EoE. Our secondary aim was to evaluate changes in peripheral blood markers as additional proof of tolerance to eHF to provide new insights into the immunopathogenesis of EoE.

Patients and methods

Study design and participants

We recruited EoE patients aged 16 years and more who were consecutively attended to in our gastroenterology clinic for EoE and in whom cow's milk had been demonstrated to be a trigger for the disease. All of the subjects had previously participated in a six-food elimination diet-based study protocol (9). After confirming EoE histopathological remission, specific EoE food-triggers were identified by sequential reintroduction challenge. Wheat was the first food to be reintroduced in all cases, followed by milk and dairy products. The order of reintroduction for the remaining foods varied according to previous results and the patient's preferences to normalize their diet as soon as possible. Disease remission was achieved and maintained in all of the study subjects by avoiding those foods identified as EoE triggers without the aid of medication. The subjects were given the option of receiving a cow's milk-based eHF (Nieda Plus®, Abbott Laboratories, Abbott Park, IL, USA) for an 8-week period.

Baseline symptoms and esophageal eosinophil counts for all participants had been determined prior to starting the empiric six-food elimination diet-based study. Symptom records and peak eosinophil counts after cow's milk reintroduction challenge were also available for every patient. All recruited patients had been continuously avoiding the intake of cow's, goat's, and sheep's milk products and their derivatives for at least a 6-week period. The patients, who were encouraged to consume two glasses (400 ml, corresponding to 7.5 g of protein) a day of a 100% lacto-serum-based eHF-containing peptides with a molecular weight of <3500 Daltons, exhibited no pathological eosinophilic infiltration at the moment of eHF intake.

Physical examinations and endoscopies with esophageal biopsies were performed on each of the recruited patients before and after feeding them with the hydrolyzate. Esophageal symptoms had been structurally assessed with a scoring system validated for achalasia (21) and previously used in adult EoE (9, 22) as there is currently no validated score specifically for EoE. The duration and intensity of dysphagia events along with the frequency and intensity of heartburn and regurgitation were also recorded before and after the 8-week study period.

Prescriptions for eHF for the entire study period were given to patients at the time of recruitment; as the eHF is fully financed by our National Health Service and supplied by pharmacies, patients received it on a regular basis. Written information about foods to be avoided and how the hydrolyzed formula should be prepared and consumed (including taking it with coffee and using it to cook sauces and desserts) was provided to patients by gastroenterologists in our department, to ensure an easy consumption in case of a disliking taste. Additional changes in diet apart from the intake of eHF were avoided. A telephone number and e-mail address were also provided to patients in case of further doubts. Control of eHF consumption was ensured by monitoring the frequency and amount of product delivered to patients from pharmacies and by a final interview before carrying out the control endoscopy.

Treatment with oral, nasal, airway, or swallowed steroids was withdrawn from all patients 8 weeks prior to commencing the study. PPI was allowed if necessary. In cases of exacerbated rhinitis or asthma, anti-H_1 or inhaled β_2-agonists and anticholinergic bronchodilator drugs were allowed together with the eHF under study.

Endoscopy and biopsy procedure

All endoscopic examinations were carried out under conscious sedation by a board-certified gastroenterologist (AJL) and were performed with a flexible 9-mm-caliber Pentax EG-2770K gastroscope (Pentax of America, Inc, Montvale, NJ, USA) with a 2.8-mm work channel. Biopsies were taken with the aid of a standard needle biopsy forceps (Endo Jaw FB-220U; Olympus Medical Systems, Tokyo, Japan) from the upper and lower esophageal thirds, obtaining a minimum of five specimens from each location. These were then fixed in 4% formalin and routinely processed for histopathological analysis.

No specific complications were observed in any of the subjects after the biopsy procedure, despite the high fragility of the esophageal wall described in EoE patients.

Histological study

All digestive mucosa samples fixed in formalin were routinely processed: sections (5-μm thick) were cut from formalin-fixed, paraffin-embedded blocks and then placed on microscope slides and stained with hematoxylin and eosin. The peak number of eosinophils was counted in the most densely inflamed areas with the aid of Nikon Eclipse 50i (Nikon corporation, Tokyo, Japan) light microscopy in three hpf at 400× (the hpf area measured 0.212 mm^2). The mean eosinophil count per hpf

was calculated in the epithelial strata by averaging the eosinophil counts in 3 hpf. All biopsies were analyzed by a pathologist (JLY-C) experienced in studying EoE biopsy samples and blinded to the patient biopsy identity.

Analytical study

Before and after the 8-week study period in which patients were given the eHF, peripheral blood analyses were carried out in which blood eosinophil count, eosinophilic cationic protein (ECP), and total serum IgE were all monitored. Specific IgE against the major allergenic proteins in cow's milk was also determined with the aid of the ImmunoCAP test (Pharmacia Diagnostics AB, Uppsala, Sweden) according to the manufacturer's instructions. Values ranged from 0.0 UI/ml (absent or undetectable allergen-specific IgE) to >100 KU/l (very high level of allergen-specific IgE).

Outcome measures

Primary outcome measures were based on the histopathological response to eHF intake for 8 weeks. Peak eosinophil counts were determined in the area with the highest density, independent of where the biopsy was taken or the biopsy examination site. Maintenance of histological remission was considered to be a peak eosinophil count of <15/hpf in both upper and lower esophageal thirds. Secondary outcome measures were based on documenting changes in blood eosinophilia and serum ECP along with total and specific IgE levels against major CMP. Seasonal variations with regard to the moment of eHF introduction, endoscopic examination, or eosinophil counts were not taken into account.

Statistical analysis

Data are shown as mean ± SD for eosinophils and as a median with an interquartile rank (IQR) for scoring clinical symptoms. Comparisons between groups (tolerant and intolerant) were performed with the Mann–Whitney *U*-test for quantitative variables and the chi-squared test (or the Fisher's exact test, where appropriate) for qualitative variables. The Wilcoxon signed-rank test was used to compare values before and after hydrolyzate consumption. A 0.05 level of significance was used throughout. Statistical analyses were performed with the aid of PASW 18.0 statistical analysis software (SPSS Inc, Chicago, IL, USA).

Ethics

The study was conducted in accordance with the principles of the Declaration of Helsinki and approved by the institutional review board of our hospital. Informed consent was obtained from all patients prior to all endoscopic examinations.

Results

A total of 26 EoE patients, all more than 16 years of age and suffering EoE triggered by cow's milk, were assessed to participate in this study. Eight patients chose not to participate as they had successfully substituted cow's milk with soy-based drinks. One of the 18 patients originally enrolled later abandoned the study citing dislike of the assayed eHF; thus, 17 EoE patients (13 male and four female) completed the study protocol (Figure 1). The mean age of the participants was 32.95 ± 10.9 years (range: 17–56), and the average time of having suffered EoE symptoms prior to diagnosis was 38.41 ± 25.5 months.

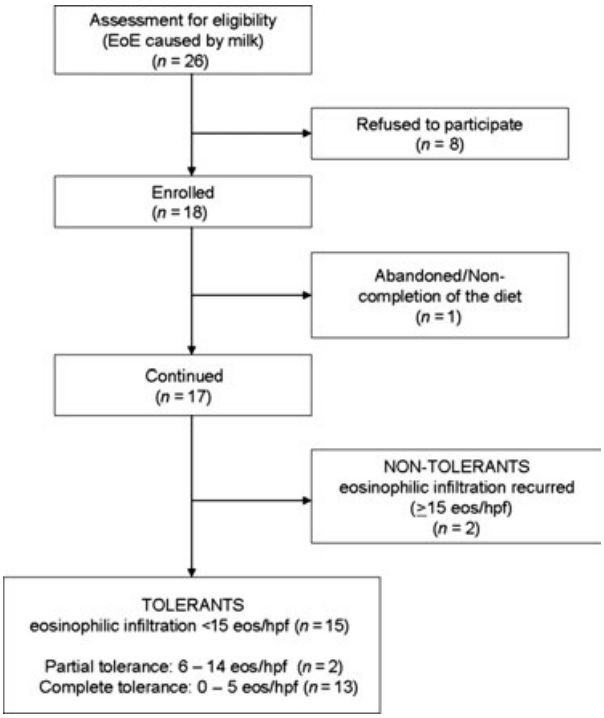

Figure 1 Flowchart of patients included in/completing our cow's milk-based extensively hydrolyzed formula feeding protocol.

No adverse events were described during the 8-week period in which patients were given eHF. Pharmacy records confirmed every patient received the prescribed formula as programmed, and all patients confirmed that they had adhered to the instructions provided concerning daily consumption of eHF. Characteristics of the study participants are shown in Tables 1 and 2.

Histopathological findings and symptoms after eHF feeding

After 8 weeks of daily intake of the prescribed eHF, 15 of the 17 EoE patients (88.24%) had maintained EoE remission, exhibiting <15 eos/hpf in esophageal biopsies from the upper and lower thirds (this value was <5 eos/hpf in 13 study subjects). Recurrence of EoE (peak eosinophil count ≥15/hpf) was documented in the remaining two patients (Figures 1 and 2). No differences in age, gender, symptoms, endoscopic appearance, or personal/family allergic background were observed between those patients who tolerated the hydrolyzate and those who did not (Table 1).

Table 1 Baseline clinical characteristics of adult EoE patients included in our study

Characteristics		Total no. of patients ($N = 17$)	Patients who tolerated eHF ($N = 15$)	Patients with EoE recurrence after eHF ($N = 2$)	$P^{\dagger}$
Mean age (SD; rank)		32.95 (10.9; 17–57)	33.5 (11.2; 17–57)	28.7 (10.4; 21–36)	0.618*
Sex, m/f		13 (76.5%)/4 (23.5%)	11 (73.3%)/4 (26.7%)	2 (100%)/0	1
Time of symptom evolution before EoE diagnosis (months)		38.41 (25.5; 12–120)	38.73 (26.86; 12–120)	36 (16.97; 24–48)	0.941*
Symptoms before EoE diagnosis		13 (76.5%)	11 (73.3%)	2 (100%)	1
		12 (70.6%)	10 (66.7%)	2 (100%)	1
		5 (29.4%)	5 (33.3%)	0	1
		5 (29.4%)	5 (33.3%)	0	1
		1 (5.9%)	1 (6.7%)	0	1
Atopic personal history	Allergic rhinitis	9 (52.9%)	7 (46.7%)	2 (100%)	0.471
	Drug sensitivity	0	0	0	–
	Bronchial asthma	7 (41.2%)	7 (46.7%)	0	0.485
	Dermatitis	1 (5.9%)	1 (6.7%)	0	1
	Food allergy/ sensitization	17 (100%)	15 (100%)	2 (100%)	–
Atopic family history	Allergic rhinitis	6 (35.3%)	4 (26.7%)	2 (100%)	0.110
	Drug sensitivity	3 (17.6%)	3 (20%)	0	1
	Bronchial asthma	5 (29.4%)	4 (26.7%)	1 (50%)	0.515
	Dermatitis	1 (5.9%)	1 (6.7%)	0	1
	Food allergy	1 (5.9%)	1 (6.7%)	0	1
Mean intraepithelial peak eosinophil count at baseline conditions	cells/mm^2 (SD)	221.9 (138.3)	213.8 (141.4)	283 (133.4)	0.441*
	hpf (SD)	47.1 (29.3)	45.33 (30)	60 (28.3)	0.441*
Mean intraepithelial peak eosinophil count after the reintroduction of milk	cells/mm^2 (SD)	242.8 (114.5)	221.7 (101.2)	400.7 (100.4)	0.088*
	hpf (SD)	51.5 (24.3)	47 (21.4)	85 (21.2)	0.088*
Mean intraepithelial peak eosinophil count before reintroduction of CMP hydrolyzate	cells/mm^2 (SD)	7.2 (14.3)	6.6 (14.5)	11.8 (16.7)	0.618*
	hpf (SD)	1.5 (3.1)	1.4 (3.1)	2.5 (3.5)	0.618*
Mean intraepithelial peak eosinophil count after reintroduction of CMP hydrolyzate	cells/mm^2 (SD)	29.1 (51.1)	12.6 (17.5)	153.3 (50)	0.015*
	hpf (SD)	6.2 (10.8)	2.67 (3.7)	32.5 (10.6)	0.015*

eHF, extensively hydrolyzed formula based on cow's milk; SD, standard deviation; hpf, high-power field.
*Mann–Whitney *U*-test.
†Chi-squared test.

At baseline conditions, our subjects presented a mean pathological esophageal infiltrate of 47.1 ± 29.3 eosinophils/hpf, which was not significantly different from that documented after cow's milk reintroduction (51.5 ± 24.3 eos/hpf; $P = 0.61$). Before receiving eHF, the mean esophageal eosinophil count was 1.4 ± 3.1 (Figure 2). In patients who tolerated the eHF, intraepithelial eosinophil values did not significantly change (1.5 ± 3.1 eos/hpf before compared with 6.2 ± 10.8 eos/hpf after eHF intake; $P = 0.15$). Obviously, in patients who did not tolerate the eHF, intraepithelial eosinophils increased significantly after intake (up to 32.5 ± 10.6 eos/hpf; $P = 0.015$).

Symptom scores at baseline conditions and after cow's milk challenge were 8 (IQR: 6–16) and 8 (IQR: 6–13.5) ($P = 0.1$), respectively. These scores decreased to 2 (IQR: 0–3) six weeks after removing milk from the diet ($P < 0.001$). Esophageal symptom scores did not change significantly after intake of cow's milk-based eHF (Figure 3). No differences in symptoms were documented between patients who tolerated the eHF and those who did not.

Analytical changes

No significant differences were documented for any of the parameters analyzed before and after the 8-week period of eHF intake, including serum levels of specific IgE against major CMP (Table 3). The two patients in whom EoE recurred after eHF intake likewise exhibited no significant differences in analytical values before and after the 8-week consumption period.

Table 2 Individual clinical characteristics of adult EoE patients included in our study

Patients	Age	Sex	Time of evolution (months)	Symptoms	Endoscopy		Familiar background of atopy	Personal background of atopy	Identified food triggered	Eosinophils/HPF after eHF diet	EGD Findings after eHF diet
					Caliber	Mucosal appearance					
1	34	M	12	FI, Dy, Ht	N	N	No	AR, FA	Mi, Ri, F&S, Le & Nu	0	N
2	40	M	24	FI, Dy, AP	N	LF, C	Brother: BA, AR, FA	BA, AR, FA	Mi	0	N
3	56	M	60	FI, Dy	N	LF, Rg, C	Mother: BA	FA	Mi	5	N
4	35	M	120	FI, AP	N	Rg	Father: DS	BA, AR, FA	Mi, F&S & Co	5	N
5	17	M	24	AP, V	N	LF, Rg	No	AR, FA	Mi, F&S, Co, Le & Nu	10	N
6	33	M	48	FI, Dy, Ht	R	LF, C, WP	Brother: BA, AR	FA	Mi.	0	N
7	50	F	24	FI, Dy	N	LF, Rg	No	FA	Mi & Le	0	N
8	22	M	25	Ht	N	LF, C	Mother: AR	BA, FA	Mi & Wh	0	N
9	21	M	12	FI, Dy	N	LF, WP	Brother: BA & Father: DS	BA, D, FA	Mi, F&S & Co	5	N
10	40	F	60	FI, Dy	R	Rg, WP	Mother: DS	FA	Mi	0	N
11	24	M	36	Dy	N	LF, Rg, WP	Mother: AR	BA, AR, FA	Mi	10	N
12	37	M	36	Dy	N	LF, Rg, WP	No	BA, AR, FA	Mi, Eg & So	0	N
13	38	M	24	Dy, AP	N	LF, C, R	No	BA, AR, FA	Mi	5	N
14*	36	M	24	FI, Dy	N	LF, C	Brothers: AR, BA	AR, FA	Mi, Nu, Ri & So	40	LF, WP
15	22	F	40	FI, Ht	R	WP	No	FA	Mi.	0	N
16*	21	M	48	FI, Dy	N	LF	Father: AR	AR, FA	Mi & Nu	25	LF, WP
17	29	F	36	FI, Dy, AP, Ht	R	LF, C	Mother: D	FA	Mi & Wh	0	N

M, male; F, female; FI, food impaction; Dy, dysphagia; AP, abdominal pain; V, vomiting; Ht, heartburn; WL, weight loss. Endoscopy: N, normal; R, reduced; Rg, rings; LF, longitudinal furrows; C, crêpe-paper appearance; WP, white plaques; S, stricture. Atopy: BA, bronchial asthma; AR, allergic rhinitis; FA, food allergy; D, dermatitis; DS, drug sensitivity. Mi: milk; Ri: rice; F&S: fish and seafood; Le: legumes; Nu: nuts; Wh: wheat; Co: corn; Eg: eggs; So: soy.

*Patients who did not tolerate cow's milk protein hydrolyzate.

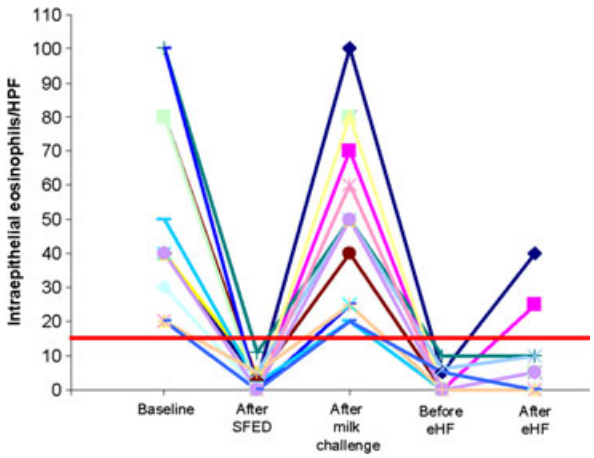

Figure 2 Intraepithelial peak eosinophil counts in 17 adult patients with EoE at baseline conditions, after following an empiric six-food elimination diet for six weeks, after six weeks of cow's milk challenge, and before and after an 8-week feeding period in which they were given a cow's milk-based extensively hydrolyzed formula (eHF). Red horizontal line represents the threshold of 15 eos/hpf.

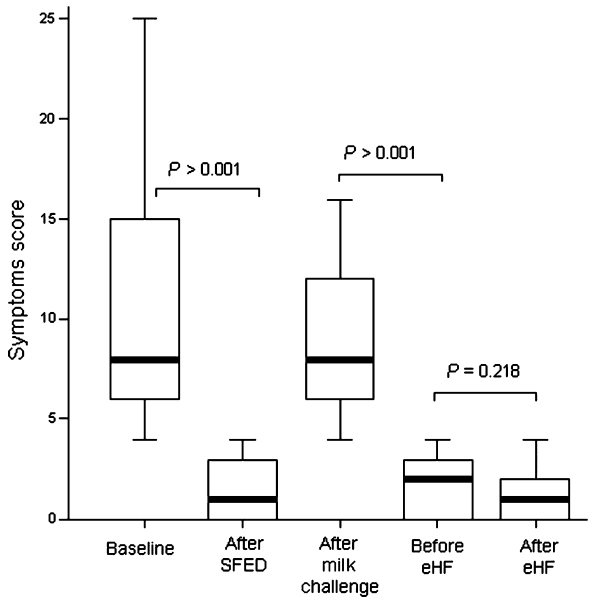

Figure 3 Score of esophageal symptoms in adult eosinophilic esophagitis (EoE): patients at baseline conditions (before starting a six-food elimination diet-based study protocol), after challenge with cow's milk, and before and after intake of a cow's milk-based extensively hydrolyzed formula (eHF). Scores are determined with the method proposed by Zaninotto et al. (21) for achalasia. Median and interquartile range (IQR) are represented in the boxes, with whiskers (vertical lines) extending to a limit of ±1.5 IQRs.

Discussion

This study documents for the first time that most adult patients with EoE triggered by cow's milk, which is the primary food trigger for EoE in children and also a major trigger in adults, correctly tolerate an eHF based entirely on CMP, thus giving them a safe and economical alternative to cow's milk without risk of short-term EoE recurrence. No significant changes were noted in serum-specific IgE against the most common CMP, nor in serum ECP after an eight-week period of consumption. These findings thus indicate that this eHF may constitute an alternative to amino acid-based formula when feeding or supplementing patients with EoE. In fact, the cost of an eHF with reduced antigenic capacity with respect to an amino acid-based elemental formula is significantly lower; indeed, eHF has been recently demonstrated to be a cost-effective first-line treatment option for cow's milk allergy in infants (23). In Spain, the cost of elemental formula exceeds 14.6 times that of the hydrolyzate when considering equivalent volumes, and 4.6 times when considering energy intake.

Taken together, with our previous experience with milk-triggered EoE, the present results provide additional insight into the proposed immunopathological mechanisms involved in EoE as a part of the spectrum of cow's milk allergy (24). Although the exact mechanisms leading to cow's milk allergy have yet to be completely elucidated (16), they seem to include both IgE- and non-IgE reactions, as well as a third group of manifestations that are unpredictably associated with IgE antibodies (IgE-associated/cell-mediated disorders) (25, 26). IgE-mediated allergy to CMP, which seems to predominate in infants and children, is characterized by rapidly evolving symptoms (immediate hypersensitivity) that appear within hours or even minutes after contact with the allergen as a consequence of the rapid release of mediators from mast cells and basophils that occurs when IgE associated with mast cells binds with allergenic epitopes situated on milk proteins. Although anaphylaxis against food constitutes the classic paradigm of IgE-mediated allergy, EoE does not present in this way. Moreover, the limited utility of IgE-based allergy tests in predicting specific IgE triggers has been widely documented in EoE (27), with the results showing little concordance with those of food reintroduction challenges (7–9).

In contrast, non-IgE-mediated CMP allergy is characterized by a delayed setup associated with the onset of symptoms some hours or many days after the ingestion of CMP (delayed hypersensitivity), which is cell-mediated by Th1 lymphocytes. An increasing amount of evidence supports the inclusion of EoE among this last group of disturbances (9, 13). Affected children and adults do not necessarily show circulating IgE specific for CMP and often have negative skin prick tests (28), as has been documented in EoE (9). Assuming that EoE is mediated predominantly by a delayed hypersensitivity reaction, significant changes in Th2-type humoral markers after feeding our patients with eHF should not be expected.

Remarkably, a small proportion of our study subjects did not tolerate the eHF, and its consumption led to a recurrence of EoE. Although disappointing, this finding may provide evidence for cell-mediated reactions in the origin of EoE. In this context, it should be noted that, while the complete allergen must be present to induce immediate IgE-mediated allergic responses, the activation of T lymphocytes requires

Table 3 Analytical values of adult EoE patients before and after intake of a cow's milk-based extensively hydrolyzed formula (eHF)

	Before eHF	After eHF	*P**
Blood eosinophil count (cells /μl)	300 (186.2)	350 (236.6)	0.135
Blood Eosinophils (%)	5.2 (3.2)	5.7 (3.9)	0.280
Total serum IgE levels (Ul/ml)	274.9 (212.8)	287.4 (275.4)	0.754
Specific serum IgE to milk (Ul/mL)	0.597 (1.18)	0.517 (1.2)	0.147
Specific serum IgE to casein (Ul/ml)	0.091 (0.13)	0.082 (0.085)	1
Specific serum IgE to α-lacto-albumin (Ul/ml)	0.041 (0.05)	0.033 (0.05)	0.276
Specific serum IgE to β-lactoglobulin (Ul/ml)	0.387 (1.26)	0.391 (1.50)	0.413
Eosinophilic cationic protein (mcg/l)	45.9 (49.7)	49.7 (49.6)	0.683

*Paired Wilcoxon signed-rank test.

only the presence of specific peptides (29). Peptides that do not contain epitopes for IgE recognition but which preserve those recognized by T cells are generated during the digestive process and may also be contained in cow's milk-based hydrolyzed formulas (30). These peptides seem to be capable of inducing a strong inflammatory response, both local and systemic, mediated exclusively by T cells (31) without any previous IgE-mediated events. When faced with re-exposure to the antigen in the esophageal mucosa, sensitized lymphocytes may trigger the eosinophil inflammatory response without the involvement of IgE (32).

The main limitation of our research is that it only includes adult patients, precisely those in whom CMP allergies are most likely mediated by a delayed hypersensitivity reaction. We thus hypothesize that tolerance to our eHF would have been even higher if younger patients had been included; as the pathogenesis of EoE in children is more likely to involve a potential IgE-mediated component, eliminating whole milk proteins from the diet is more likely to prevent an IgE-mediated reaction. Nevertheless, our study also has the strength of including patients who were consecutively and prospectively recruited in our gastroenterology clinics among whom cow's milk had been demonstrated to trigger EoE after food reintroduction challenge. Therefore, despite the limited size of our series (17 patients), this study constitutes the first demonstration of tolerance to a hydrolyzed food trigger in EoE patients.

In conclusion, we believe that our study has the direct clinical implication of providing a food alternative for EoE patients in whom CMP has been demonstrated to trigger EoE and should thus be restricted indefinitely. It also sheds light on the complex relationship between EoE and food allergies, although this should be elucidated through further research.

Conflict of interest

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in this manuscript apart from those disclosed. No writing assistance was utilized in the production of this manuscript.

Author contributions

Alfredo J Lucendo contributed to study concept and design, patient diagnoses (performance of endoscopic examinations and esophageal biopsies) and follow-up, interpretation of data, drafting of the manuscript, and approval of the final version of the manuscript. Ángel Arias involved in study concept and design; collection, analysis, and interpretation of data; drafting and revision of the manuscript; and approval of the final version of the manuscript. Jesús González-Cervera contributed to allergy studies and follow-up of patients, data collection, critical review of the manuscript with significant contributions, and approval of the final version of the manuscript. Teresa Mota-Huertas involved in performance of histological techniques, analysis of esophageal samples, interpretation of data, and approval of the final version of the manuscript. José Luis Yagüe-Compadre contributed to histological analysis of esophageal samples, interpretation of data, and approval of the final version of the manuscript.

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