

Letter to the Editor

Evaluation of allergen-microarray-guided dietary intervention as treatment of eosinophilic esophagitis*To the Editor:*

Food allergy is thought to play an important role in the pathophysiology of eosinophilic esophagitis (EoE).^{1,2} Dietary treatment of adults with EoE seems promising, although some diets are very extensive (six food elimination diet [SFED]) while others are considered unpalatable (elemental diet).³ The concept of component-resolved diagnosis (CRD) contains 2 new developments that provide an opportunity for better targeted dietary advice: (1) measurement of specific IgE against single allergen molecules with better defined clinical prognostic value and (2) a microarray assay format allowing the measurement of IgE against 43 allergen molecules from the 16 most important allergenic foods.⁴ The effect of a specific CRD-guided diet on disease activity in patients with EoE is unknown, although preliminary data suggest a beneficial effect.⁵ We aimed to demonstrate that individually tailored CRD-guided dietary treatment decreases the peak eosinophil count in the esophageal mucosa to less than 10 eosinophils per hpf (eos/hpf) in 70% or more of adult patients with EoE. Assuming that a CRD-guided diet would be less invasive and extensive than the SFED, we considered a CRD-guided diet suitable for clinical implementation if its effect would be equivalent to that of the SFED (70% response).³

We prospectively investigated the effect of this diet in adult patients with EoE with active disease (≥ 15 eos/hpf). We aimed to include 40 patients (expecting 10% dropout rate), because with 36 patients, the study would have 80% power to demonstrate a response rate of 70% (95% CI, 55%-85%). The primary outcome was the proportion of patients in histological remission (≤ 10 eos/hpf) after dietary treatment. Secondary parameters were symptoms of dysphagia, quality of life, endoscopic signs of EoE using the endoscopic reference score classification,⁶ serum-IgE level, serum eosinophil count, and histopathological signs (esophageal mast cell infiltration, eosinophilic microabscesses, basal hyperplasia, spongiosis) after dietary treatment. Finally, we compared sensitization patterns found using CRD with results of serum-IgE CAP testing and skin prick test (SPT). Each study subject gave written informed consent. The study protocol was approved by the Academic Medical Center Medical Ethics Committee and registered at Trialregister.nl (NTR4052).

EoE patients underwent vena puncture to obtain serum samples for CRD using ImmunoCAP ISAC testing (Thermo Fisher Scientific, Uppsala, Sweden). Patients with (cross-) sensitization against 1 or more food allergen were then approached for CRD-guided dietary treatment. For dietary instructions, consented patients visited a research dietician with food allergy expertise. Study subjects were instructed to avoid the positive foods, to read labels carefully, and to avoid foods bearing precautionary labeling with the foods to be avoided. Dietary food elimination was guided by CRD results and limited to positive foods. Some additional foods were excluded: in case of cod sensitization, all white fish was excluded; in case of apple, pear; for peach, nectarine; and for cow's milk, all related mammalian milk. However, in case of nut

TABLE I. Baseline characteristics of study participants

Age (y)	40 (27-47)
Sex: male	13 (87)
Age at onset of dysphagia symptoms (y)*	24 (12-33)
Time since start of dysphagia symptoms (y)	14 (7-19)
Time since EoE diagnosis (y)	1 (0-2)
Use of medication during study	
Glucocorticoids	0 (0)
Proton pump inhibitors	3 (20)
Atopic comorbidity*	
Food allergy	14 (93)
Allergic rhinitis	9 (60)
Asthma	6 (40)
Atopic dermatitis	2 (13)
Family history of atopy*	
Food allergy	7 (47)
Allergic rhinitis	7 (47)
Asthma	4 (27)
Atopic dermatitis	3 (20)

Continuous variables are expressed as median (interquartile range). Qualitative variables are expressed as n (%).

*Self-reported.

sensitization (hazelnut, walnut, cashew nut, Brazil nut), only (foods containing) the individual nuts were excluded. After baseline endoscopy, study subjects eliminated positive foods for 6 weeks, and the effect was evaluated by endoscopy with structured biopsies at distal, mid, and proximal esophagus, vena puncture, and questionnaires. Responders (≤ 10 eos/hpf) to the diet were asked to reintroduce all the avoided foods to confirm the observed effect of the diet. Finally, to validate CRD results, patients underwent SPT, and the remaining serum samples were used for serum-IgE CAP testing to assess sensitization to 25 food allergens using the ImmunoCAP 250 system (Thermo Fisher Scientific).⁷ Tested foods are listed in Table E1 in this article's Online Repository at www.jacionline.org. From 8 weeks before the study and until its end, the use of immunosuppressive agents was not allowed. If necessary, continuation of proton pump inhibition in stable dosage was allowed.

Ninety-five patients were tested using CRD, of which 44 (46%) were sensitized to 1 or more food allergen. After inclusion of the first 15 patients (characteristics listed in Table I), interim analysis revealed that 14 patients (93%) failed the CRD-guided diet (Fig 1). Because it would become impossible to meet similar efficacy as the SFED (70% response) after the 40 intended inclusions, the trial was prematurely terminated in consultation with the Medical Ethical Committee. A flow diagram of patient enrolment is shown in Fig E1 in this article's Online Repository at www.jacionline.org. Individual food sensitizations of enrolled patients are presented in Table E2 in this article's Online Repository at www.jacionline.org. The median baseline peak eosinophil count (50 eos/hpf [interquartile range, 35-90 eos/hpf]) was not significantly changed by dietary treatment (70 eos/hpf [IQR, 50-110 eos/hpf] after the diet) ($P = .59$). The diet also had no significant effect on secondary outcomes (Table II). Unfortunately, after good response, the 1 responder to the diet (patient no. 12) was not motivated to reintroduce the avoided foods to confirm their causative role.

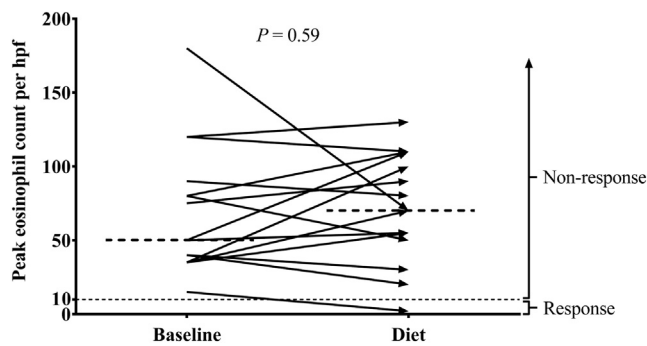


FIG 1. Esophageal peak eosinophil counts in patients with EoE before and after the CRD-guided food elimination diet. One patient histologically responded to the diet. Black dotted bars indicate medians.

TABLE II. Effect of CRD-guided diet on secondary parameters

Parameter	Baseline	After diet	P value
Clinical signs			
Dysphagia score	9.50 (7.25-10.75)	7.00 (5.00-8.75)	.07
Quality of life (SF-36)			
Physical component scale	55.6 (47.5-60.0)	56.3 (50.5-59.0)	.28
Mental component scale	54.8 (38.9-58.0)	50.9 (48.9-56.3)	.70
Endoscopic signs (EREFS)			
Inflammatory signs	4 (3-4)	4 (3-5)	.57
Fibrostenotic signs	2 (1-4)	2 (1-4)	.80
Total EREFS	6 (4-7)	6 (5-7)	.90
Serum markers			
IgE level (kU/L)	170 (90-663)	168 (99-647)	.78
Eosinophil count ($\times 10^9$)	0.39 (0.28-0.55)	0.44 (0.29-0.56)	.44
Histopathological signs			
Peak mast cell count (mcs/hpf)	21 (14-35)	14 (7-26)	.10
Eosinophilic microabscesses	11 (73)	11 (73)	1.00
Spongiosis			
Absent	0 (0)	0 (0)	.55*
Mild	1 (7)	1 (7)	
Moderate	4 (27)	2 (13)	
Severe	10 (67)	12 (73)	
Basal hyperplasia			
Absent	0 (0)	1 (7)	1.00*
Mild	2 (13)	0 (0)	
Moderate	8 (53)	9 (60)	
Severe	5 (33)	5 (33)	

Continuous variables are expressed as median (interquartile range). Qualitative variables are expressed as n (%).

EREFS, Endoscopic reference score; SF-36, short-form 36 health survey.

* χ^2 test for trend.

CRD identified 44 food sensitizations, whereas CAP testing and SPT identified 164 and 54 food sensitizations, respectively. CRD identified at least 1 of the major food triggers of EoE (wheat, n = 0; cow's milk, n = 1; egg white, n = 1; soy, n = 3) in 5 patients (33%). When combined, CAP testing and SPT identified sensitizations to wheat in 6 additional patients, cow's milk in 5 additional patients, egg white in 6 additional patients, and soy in 4 additional patients. In total, 9 patients (60%) were sensitized to 1 of the major food triggers according to combined

results of CAP testing and SPT. Compared with CRD, CAP testing and SPT revealed additional food sensitizations in 14 (93%) and 10 (66%) patients, respectively. When combined, CAP testing and SPT confirmed 36 of 44 sensitizations (82%) found with CRD.

In theory, the disappointing results of this CRD-based food exclusion diet could be influenced by allergy test characteristics. It is possible that food allergies may have been missed, although the chip detects IgE against all common triggers of EoE (wheat, cow's milk, egg white, soy).^{1,3} To test this theory, we compared CRD results with results of CAP testing and SPT. With CAP testing and SPT, additional sensitizations were identified in 93% of the patients. Interestingly, the only responder in our study was the only patient with cow's milk sensitization, a major causative food allergen in pediatric and adult EoE.³ CAP testing confirmed cow's milk sensitization in this patient and demonstrated cow's milk sensitization in 5 additional patients who had not excluded milk. A poor negative-predicting value for milk (44%) has been described for combined SPT and atopy patch testing, but was not anticipated using CRD.⁸ Similarly, CAP testing and SPT identified additional sensitizations to other major food triggers of EoE. Consequently, if the diet would have been guided by CAP testing and SPT, these foods would have been excluded in more patients. The continued intake of these major triggers of EoE might explain the lack of response to the diet.³ It would be of interest to compare the efficacy of a CRD-guided diet with a diet guided by conventional serum-IgE CAP testing to evaluate the power of IgE-based allergy tests in the management of EoE. Another explanation for the lack of response could be that the excluded foods play no role in the pathophysiology of EoE. Furthermore, it has been suggested that the allergic mechanisms underlying EoE are not only IgE-mediated but also cell-mediated.¹

In conclusion, in this prospective study, CRD-based dietary treatment was not effective in adult patients with EoE. The lack of response could be a result of missed sensitizations; however, it may also reflect the limited relevance of IgE in the pathophysiology of EoE.

Bram D. van Rhijn, MD, PhD^a
 Berber J. Vlieg-Boerstra, PhD, RD^b
 Serge A. Versteeg, BSc^c
 Jaap H. Akkerdaas, PhD^c
 Ronald van Ree, PhD^{c,d}
 Ingrid Terreehorst, MD, PhD^d
 Aline B. Sprickelman, MD, PhD^b
 Joanne Verheij, MD, PhD^e
 Andreas J. P. M. Smout, MD, PhD^a
 Albert J. Bredenoord, MD, PhD^a

From the Departments of ^aGastroenterology and Hepatology, ^bRespiratory Medicine and Allergy, Emma Children's Hospital, ^cExperimental Immunology, ^dOtorhinolaryngology, and ^ePathology, Academic Medical Center, Amsterdam, The Netherlands. E-mail: a.j.bredenoord@amc.uva.nl.

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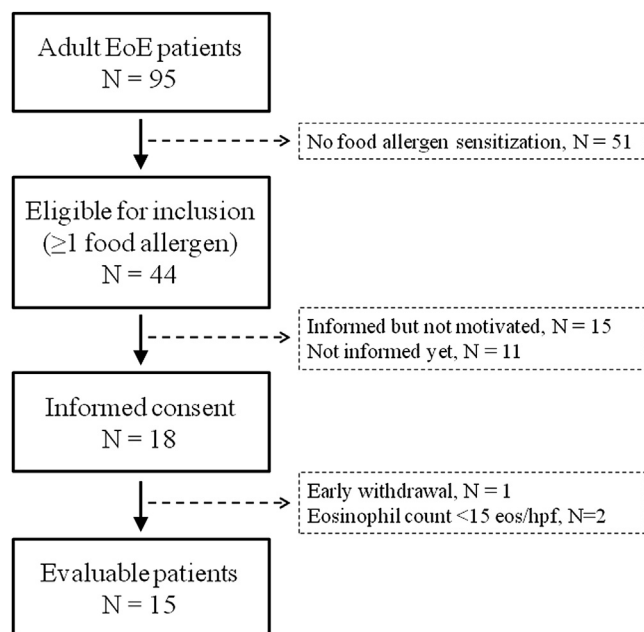


FIG E1. Flow diagram of patient inclusion. Of 95 screened adult EoE patients, 44 patients were eligible for inclusion, of which 15 patients completed the study at interim analysis.

TABLE E1. Food allergens tested with CRD, CAP, and SPT

Foods		CRD (components)	CAP	SPT
Chicken's egg	X	nGal d 1, nGal d 2, nGal d 3, nGal d 5	X	X
Cow's milk	X	nBos d 4, nBos d 5, nBos d 6, nBos d 8, nBos d lactoferrin	X	X
Cod	X	rGad c 1	X	X
Shrimp	X	nPen m 1, nPen m 2, nPen m 4	X	X
Cashew nut	X	rAna o 2		X
Brazil nut	X	rBer e 1		X
Hazelnut	X	rCor a 1.0401, rCor a 8, nCor a 9	X	X
Walnut	X	nJug r 1, nJug r 2, nJug r 3	X	X
Sesame seed	X	nSes i 1	X	x
Peanut	X	rAra h 1, rAra h 2, rAra h 3, nAra h 6, rAra h 8, rAra h 9	X	X
Soy	X	rGly m 4, nGly m 5, nGly m 6	X	X
Buckwheat	X	nFag e 2	X	x
Wheat	X	rTri a 14, rTri a 19.0101, nTri a aA_TI	X	X
Kiwi	X	nAct d 1, nAct d 2, nAct d 5, rAct d 8	X	x
Celery	X	rApi g 1	X	x
Apple	X	rMal d 1	X	x
Peach	X	rPru p 1, rPru p 3	X	x
Corn			X	
Rice			X	
Tomato			X	
Carrot			X	
Poppy seed			X	
Lentil			X	
Mustard			X	
Sunflower			X	
Melon			X	
Banana			X	
Pistachio				X
Almond				X

X, Tested; x, tested only when positive on CRD.

TABLE E2. Food sensitizations found with CRD, CAP testing, and SPT

Patient ID	CRD (component; ISU)	CAP testing (kU/L)	SPT (wheal diameter, mm)
1	Apple (rMal d 1: 0.9), hazelnut (rCor a 1.0401: 0.7)	Hazelnut (1.39)	None
2	Soy (rGly m 4: 1.4)	Hazelnut (1.63), tomato (3.08), carrot (4.34), celery (1.29), walnut (2.00), shrimp (0.40), mustard (1.79), sunflower seed (0.46), apple (4.57), kiwi (0.74), melon (2.37), peach (1.14), egg white (2.79), cow's milk (0.43), wheat (1.96), peanut (3.94), soy (2.23), buckwheat (4.71), sesame seed (4.30), rice (2.28), corn (1.41)	Egg white (8), peanut (6), walnut (3), almond (6), pistachio (4)
3	Hazelnut (rCor a 1.0401: 5.6), apple (rMal d 1: 2.5)	Hazelnut (24.83), tomato (1.60), carrot (0.45), celery (0.56), walnut (1.14), shrimp (1.17), mustard (0.60), sunflower seed (0.49), apple (2.06), kiwi (0.87), melon (2.30), banana (1.20), peach (3.17), egg white (1.91), cow's milk (0.55), cod (0.53), wheat (1.08), peanut (2.14), soy (0.45), buckwheat (0.99), sesame seed (1.15), corn (0.48)	Peanut (4), hazelnut (3), apple (3)
4	Hazelnut (rCor a 1.0401: 3.7), apple (rMal d 1: 1.0), walnut (nJug r 2: 0.9), peach (rPru p 1: 0.6)	Hazelnut (12.60), tomato (5.72), carrot (5.64), celery (4.98), walnut (2.98), mustard (1.42), poppy seed (1.29), lentil (2.39), sunflower seed (3.61), apple (3.20), kiwi (3.31), melon (5.39), banana (5.02), peach (1.50), wheat (4.78), peanut (5.92), soy (4.66), buckwheat (6.30), sesame seed (5.59), rice (5.50), corn (4.03)	Peanut (6), hazelnut (7), apple (8), almond (5), pistachio (4)
5	Shrimp (nPen m 1: 3.4), celery (rApi g 1: 2.4), hazelnut (rCor a 1.0401: 1.8, rCor a 8: 0.6), peanut (rAra h 8: 1.6, rAra h 9: 0.6), peach (rPru p 1: 1.2, rPru p 3: 0.7), cod (rGad c 1: 1.7), apple (rMal d 1: 1.3), soy (rGly m 4: 1.1), walnut (nJug r 3: 0.8)	Hazelnut (5.81), tomato (8.35), carrot (2.89), celery (2.89), walnut (7.44), shrimp (1.91), mustard (4.97), poppy seed (2.78), lentil (0.42), sunflower seed (2.83), apple (8.31), kiwi (10.27), melon (8.45), banana (0.94), peach (2.31), egg white (0.57), cow's milk (6.86), cod (8.62), wheat (4.84), peanut (10.06), soy (1.77), buckwheat (3.47), sesame seed (6.11), rice (5.38), corn (7.12)	Cod (11), shrimp (6), peanut (6), hazelnut (5), soy (7), wheat (9), apple (6), peach (9), celery (6), almond (7), pistachio (7)
6	Buckwheat (nFag e 2: 2.1), kiwi (nAct d 2: 1.0), hazelnut (rCor a 1.0401: 0.8)	Hazelnut (2.13), buckwheat (1.02), sesame seed (0.57)	Cod (3), peanut (6), hazelnut (5), cashew nut (9), almond (4), pistachio (7), buckwheat (9)
7	Apple (rMal d 1: 1.2), peach (rPru p 1: 0.6)	Hazelnut (3.13), carrot (0.68), celery (0.77), apple (0.42), melon (0.54)	Apple (4)
8	Apple (rMal d 1: 6.7), hazelnut (rCor a 1.0401: 3.1), soy (rGly m 4: 1.7), peach (rPru p 1: 1.7)	Hazelnut (12.84), tomato (0.51), carrot (1.75), celery (2.18), apple (3.89), kiwi (0.78), melon (1.68), egg white (4.70), cow's milk (0.76), wheat (0.40), peanut (2.21)	Egg white (8), peanut (10), hazelnut (5), apple (7), almond (4)
9	Apple (rMal d 1: 3.8), hazelnut (rCor a 1.0401: 1.3), peanut (rAra h 8: 0.8)	Hazelnut (7.63), carrot (1.05), celery (1.15), apple (1.39), melon (1.29)	Peanut (6), hazelnut (5), apple (6), almond (5)
10	Apple (rMal d 1: 2.3), hazelnut (rCor a 1.0401: 1.6), peanut (rAra h 8: 1.0), walnut (nJug r 1: 1.0)	Hazelnut (6.13), carrot (0.58), celery (0.60), walnut (0.73), apple (0.72), melon (0.63)	Peanut (11), apple (10), cashew nut (11), almond (5), pistachio (18)
11	Hazelnut (rCor a 1.0401: 0.4)	Egg white (0.47)	None
12	Shrimp (nPen m 1: 2.7), cow's milk (nBos d 4: 2.0, nBos d 5: 0.8, nBos d 8: 0.5)	Hazelnut (0.80), tomato (1.56), celery (0.51), walnut (0.68), shrimp (1.44), egg white (0.35), cow's milk (34.95)	Cow's milk (3)
13	Hazelnut (rCor a 1.0401: 1.6), peach (rPru p 1: 0.5)	Hazelnut (1.87), carrot (0.47), celery (0.35), shrimp (0.41), lentil (0.49), wheat (0.39), peanut (0.46), soy (0.40), sesame seed (1.86), rice (0.64), corn (0.47)	Peanut (3)
14	Walnut (nJug r 2: 1.3, nJug r 3: 0.5), egg white (nGal d 1: 0.4), peach (rPru p 3: 0.4)	Hazelnut (1.01), tomato (2.74), carrot (1.15), celery (1.29), walnut (1.00), shrimp (0.90), mustard (1.20), poppy seed (0.91), lentil (1.44), sunflower seed (3.18), apple (1.65), kiwi (0.84), melon (1.73), banana (0.78), peach (0.81), egg white (3.31), cow's milk (8.57), wheat (4.28), peanut (1.19), soy (1.65), buckwheat (1.25), sesame seed (1.60), rice (2.96), corn (1.13)	Shrimp (5), peanut (4), egg white (5), soy (3), peach (7), Brazil nut (7)
15	Apple (rMal d 1: 0.6)	Hazelnut (0.64)	None
Total (n)	44 food sensitizations	164 food sensitizations	54 food sensitizations

Food sensitizations in boldface confirm the sensitizations identified with CRD.

ISU, ISAC standardized units.