RESEARCH CORRESPONDENCE

Sustained Remission of Eosinophilic Esophagitis Following Discontinuation of Dietary Elimination in Children

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Eosinophilic esophagitis (EoE), when left untreated, may progress from an inflammatory to a fibrostenotic phenotype. Inflammation generally recurs after treatment withdrawal. Thus, long-term treatment has been recommended. Here, we describe a cohort of children with EoE who achieved clinical and histologic remission with elimination diets, and maintained sustained untreated remission (SUR) despite re-introduction of all eliminated food allergens.

Methods

The RetroPEER[1] database, which included retrospective data from pediatric patients in 26 European centers in 13 countries diagnosed with EoE and on stable medical or dietary treatment, was queried for patients in SUR. Patients were considered to be in SUR if they had been induced into remission (defined as the absence of symptoms and <15 eosinophils/high-power field on esophageal biopsy specimens) with an elimination diet, remained in remission despite the re-introduction of all eliminated foods, were symptom-free, and did not have histologic evidence of active EoE (<15 eosinophils/high-power field) at their last follow-up evaluation.

Results

Of 410 patients, 14 (3.4% of the whole cohort, 8.9% of those treated exclusively with elimination diets) were identified with SUR who had not been treated with systemic, topical, or inhaled steroids or other immunomodulatory drugs during or after dietary re-introduction. Patient demographics and presenting symptoms are shown in Figure 1*A* and *B*.

The most common presenting symptoms in SUR patients were vomiting/gastroesophageal reflux disease (50%) and failure to thrive (FTT) or poor weight gain (26.7%), but only FTT was significantly more common in SUR patients compared with the rest of the RetroPEER cohort ($P = .02$). The most common elimination diets used in SUR patients were the 6-food elimination diet (5 of 14; 35.7%) and an elemental diet (4 of 14; 28.5%). The median time from the final re-introduction of all foods eliminated until the last follow-up endoscopy showing sustained histologic remission was 44 weeks (interquartile range, 20.5–107 wk). The longest follow-up period was 204 weeks (Figure 1*C*).

Three of the 14 patients had been exposed to steroids after diagnosis, 1 systemic and 2 with topical steroids; however, none were exposed during food re-introduction or throughout the follow-up evaluation.

An additional patient, not included in the earlier-described cohort, had entered SUR. However, histologic exacerbation was found during a routine semi-annual follow-up endoscopy 15 months after completion of the full re-introduction, while the patient remained asymptomatic.

Discussion

The 14 SUR patients described encompassed 8.9% of patients (n = 157) treated exclusively with elimination diets and 3.4% of the whole cohort (n = 410). SUR in

Abbreviations used in this paper: EoE, eosinophilic esophagitis; FTT, failure to thrive; SUR, sustained untreated remission.

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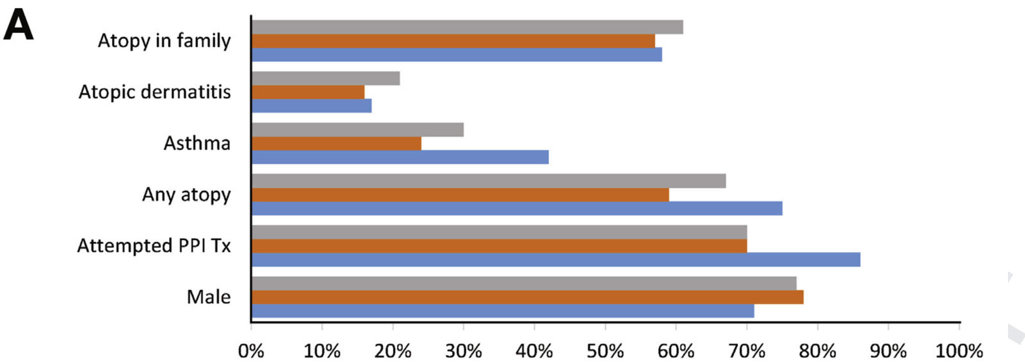

	Age at diagnosis (years)	Symptoms: Onset to diagnosis. (months)	Most common elimination diet
All Non SUR (n=396)	8.9 ±4.8	12 (IQR 4-30) n=375	ATBD (23.2%)
Treated only with elimination diets (n=143)	9.2 ±4.7	12 (IQR 4-25.5) n=132	ATBD (31.4%)
SUR (n=14)	8.6 ±4.8	10.5 (IQR 3.7-27.2)	6FED (37.5%)
P value	NS	NS	

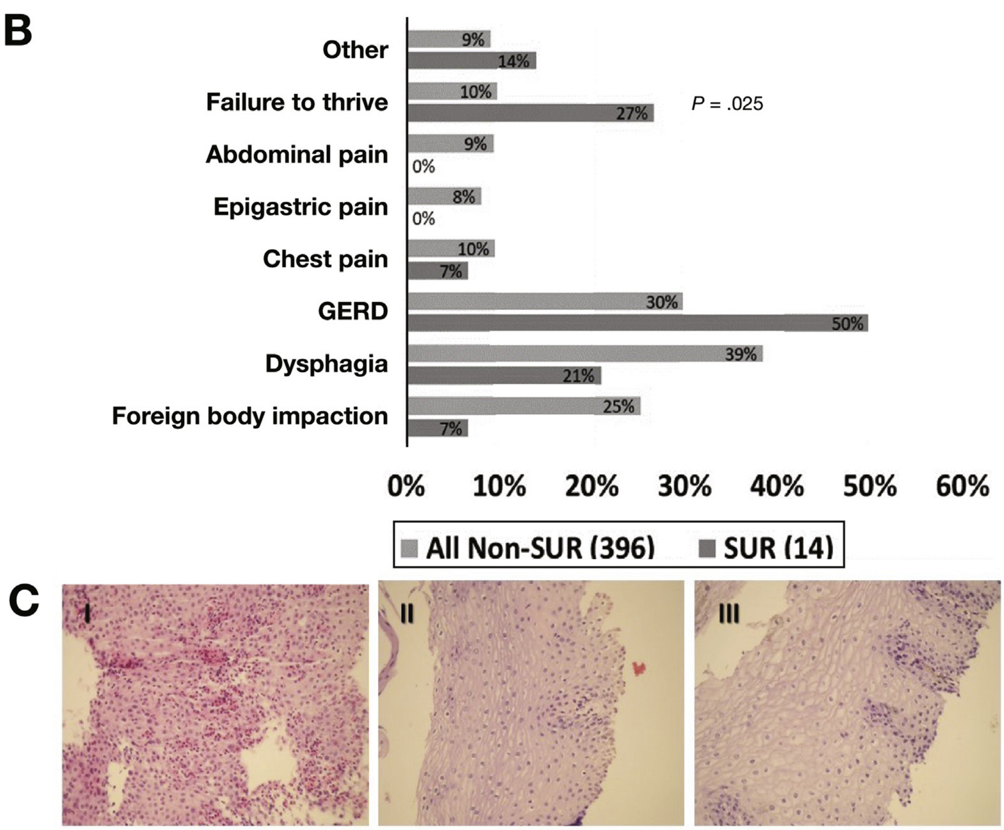

Figure 1. (*A*) Patient characteristics. None of the comparisons differed significantly. (*B*) Presenting symptoms. Statistical significance was found only for failure to thrive. (*C*) Esophageal biopsy specimens of an SUR patient at diagnosis (*I*) at age 1.3 years, with vomiting on a regular diet. There were more than 100 eosinophils/high-power field (proximal and distal). (*II*) Asymptomatic after 4.5 months of elemental formula 4 eosinophils/high-power field. (*III*) In SUR at age 6.8 years. The patient was asymptomatic on a regular diet for 3 years. There were 1 to 2 eosinophils/high-power field. high-power field, 0.2 mm^2. ATBD, allergy testing–based diet; GERD, gastroesophageal reflux disease; IQR, interquartile range; NS, not significant at $P > .05$; PPI Tx, proton pump inhibitor treatment; 6FED, 6-food elimination diet; SUR, sustained untreated remission.

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EoE has been reported infrequently. Spergel et al[2] reported SUR in 1.9% (11 of 562) of patients after stopping medical and/or dietary interventions, while Ruffner et al[3] reported SUR in 0.5% (9 of 1812). Similarly, Doerfler et al[4] showed remission in 7 adult patients 8 weeks after the final re-introduction after the 6-food elimination diet. Our data, together with these studies, show that there is a subset of patients for whom EoE may not be a progressive and life-long condition.

FTT/poor weight gain was the only factor that differed between patients in SUR and other EoE patients. The clinical significance of this is uncertain. Although Spergel et al[2] found that patients in SUR had fewer food allergies, Ruffner et al[3] reported a high co-occurrence of atopic conditions in SUR patients and neither group found differences in clinical presentations. The presence of known inheritance alleles did not differentiate the groups.

In contrast to the age-associated decrease in food allergy prevalence,[5] no difference in the age of diagnosis between patients in SUR and other EoE patients was identified.

In our cohort, SUR was not assessed in patients on medical treatment. However, it has been described in 1.2% to 9% of adults who discontinued topical steroid treatment for EoE.[6–8]

It is not clear whether patients with SUR will be free of disease throughout their lifetime or if the condition will flare later in life. We reported 1 child who had been in both clinical and histologic remission before having a histologic flare after 15 months.

A limitation of this study inherent to its prolonged retrospective design includes possible differences in management and documentation, which unknowingly may affect the data.

In conclusion, there is a subset of patients with EoE who may enter SUR. Although infrequent, these patients should be identified to minimize unnecessary dietary restrictions that may lead to poor quality of life or nutritional compromise. Future guidelines should address this subset and consider recommendations for withdrawal of treatment and reassessment at chosen time points (Supplementary Table 1). The importance of long-term follow-up evaluation of patients in SUR must be emphasized because such patients do not necessarily have resolved disease, and may relapse after long periods of remission.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2019.03.008.

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Conflicts of interest
The authors disclose the following: Noam Zevit has received consultant fees from ADARE Pharmaceuticals and Dr. Falk Pharma; and Alexandra Papadopoulou has received consultant fees from ADARE Pharmaceuticals and speaker's honorariums or research grants from AbbVie, Nestle, Nutricia, Friesland, United Pharmaceuticals, and BioGaia. The remaining authors disclose no conflicts. Q5

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Supplementary Table 1. Theories for Development of Sustained Untreated Remission

Learned tolerance to food allergens	Age-related tolerance to previously allergenic foods may develop spontaneously
Mild or transient subtype of eosinophilic esophagitis	After lost tolerance to an antigen, induction of remission resets tolerance and sustained untreated remission then is maintained
Molecular mimicry	Proteins on infectious agents may mimic food antigen, stimulating a transient immune response lasting until both the agent and the mimicked antigen are no longer presented for a period of time