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Six-Food Elimination Diet Is Less Effective During Pollen Season in Adults With Eosinophilic Esophagitis Sensitized to Pollens

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INTRODUCTION: **The role of inhaled and swallowed aeroallergens in treatment outcomes of adult patients with eosinophilic esophagitis (EoE) is unclear. We hypothesized that the pollen season contributes to the failure of the 6-food elimination diet (SFED) in EoE.**

METHODS: **We compared outcomes of patients with EoE who underwent SFED during vs outside of the pollen season. Consecutive adult patients with EoE who underwent SFED and skin prick test (SPT) for birch and grass pollen were included. Individual pollen sensitization and pollen count data were analyzed to define whether each patient had been assessed during or outside of the pollen season after SFED. All patients had active EoE (≥15 eosinophils/high-power field) before SFED and adhered to the diet under the supervision of a dietitian.**

RESULTS: **Fifty-eight patients were included, 62.0% had positive SPT for birch and/or grass, whereas 37.9% had negative SPT. Overall, SFED response was 56.9% (95% confidence interval, 44.1%–68.8%). When stratifying response according to whether the assessment had been performed during or outside of the pollen season, patients sensitized to pollens showed significantly lower response to SFED during compared with outside of the pollen season (21.4% vs 77.3%; $P = 0.003$). In addition, during the pollen season, patients with pollen sensitization had significantly lower response to SFED compared with those without sensitization (21.4% vs 77.8%; $P = 0.01$).**

DISCUSSION: **Pollens may have a role in sustaining esophageal eosinophilia in sensitized adults with EoE despite avoidance of trigger foods. The SPT for pollens may identify patients less likely to respond to the diet during the pollen season.**

KEYWORDS: SFED; pollen allergy; skin prick test; eosinophilic esophagitis

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INTRODUCTION

Eosinophilic esophagitis (EoE) is a chronic, immune-mediated, progressive disease of the esophagus triggered by food and possibly inhaled antigens penetrating through a defective esophageal mucosal barrier. This causes an eosinophil-predominant inflammation restricted to the esophagus (1,2). The disease is diagnosed when at least 15 eosinophils/high-power field (eos/HPF) are found on at least 1 esophageal biopsy in patients complaining of symptoms of esophageal dysfunction (1). Typical symptoms in adult patients include dysphagia, episodes of bolus impaction, and chest pain (3). Most patients have concurrent T-helper type 2-mediated disorders including allergic rhinitis, asthma, eczema, and food allergy (1). Accordingly, EoE is believed to be a late manifestation of the atopic march (4).

Several studies have shown that food triggers esophageal eosinophilia in EoE, whereas food avoidance leads to the resolution of the eosinophilic infiltrate in most patients (5–8). Given the precipitating role of food, elimination dietary regimens, together with proton-pump inhibitors (PPI) and topical steroids, are currently considered one of the first-line treatments for EoE

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(9–11). The 6-food elimination diet (SFED), which consists in the avoidance of milk/dairy, wheat, egg, soy, nuts, and seafood/shellfish, represents the most restrictive empiric elimination diet and has been shown to induce remission in up to 72.1% of patients with EoE in meta-analytic studies (12,13).

Although it is established that food antigens trigger and sustain esophageal eosinophilia in patients with EoE, evidence on whether inhaled aeroallergens play a role is conflicting (14–17). In this regard, it has been shown that an EoE-like inflammation can be induced in murine models when exposed to inhaled allergens (18), and several studies have shown that there may be a seasonal variation in the diagnosis and symptom exacerbation in EoE (19–21), suggesting a role of aeroallergens in the pathogenesis.

The contribution of pollen sensitization in SFED outcomes of adults with EoE has not been investigated to date. In this study, we hypothesized that pollens contribute to the failure of the SFED in adult patients with EoE. Accordingly, we compared SFED outcomes during and outside of the pollen season in adult patients with EoE with or without sensitization to pollens on the SPT.

MATERIALS AND METHODS

Study design and patients

This was a cross-sectional retrospective cohort study conducted in 2 EoE tertiary referral centers in London, United Kingdom, and Pisa, Italy. Consecutive adult patients (≥18 years) with histologically active EoE (eos ≥15/HPF) diagnosed according to current guidelines (22) who underwent SFED monotherapy and skin prick test (SPT) for birch and grass pollen between 2017 and 2022 were included. All patients who had previously undergone pharmacologic treatment for EoE initiated the SFED after a minimum of 6 weeks from the cessation of any EoE-directed treatment. The following data were extracted from the electronic patient record of each institution: sex, age at diagnosis, baseline symptoms, EoE endoscopic reference score (EREFS) before and after SFED, duration of the SFED (interval between SFED initiation and histologic assessment while still on SFED), self-reported adherence to the diet, atopy (allergic rhinitis, asthma, and atopic dermatitis), nasal polyposis, autoimmune comorbidities, the exact date of the endoscopy after SFED, response to previous treatment, and SPT results for inhaled and food allergens. Patients with incomplete data or who reported poor adherence to the diet were excluded. The project was considered a review of clinical practice and ethical approval was not required (23).

SFED protocol and outcomes assessment

To be eligible for this study, all patients were required to have histologically active EoE (≥15 eos/HPF in at least 1 esophageal biopsy) before undergoing SFED. All patients subsequently underwent SFED under the supervision of an experienced dietitian at each center. For the SFED protocol, patients were instructed to exclude foods containing milk/dairy, wheat, egg, soy, nuts, and seafood/shellfish from their diet (12). For the assessment of SFED efficacy, each patient underwent upper endoscopy with at least 6 esophageal biopsies. During each endoscopy, the EREFS was also calculated (24). Symptoms were recorded at baseline and, when available, symptom response to SFED was retrospectively assessed based on patients' perception of improvement in severity and/or frequency according to their medical records. The assessment of SFED outcomes was performed after a minimum of 6 weeks of diet. Diet adherence was evaluated before performing the endoscopy for the assessment of SFED efficacy, and only patients reporting strict adherence were included in the study. Histologic response to diet was defined as the presence of <15 eos/HPF in all esophageal biopsies, whereas a failed response was defined as the presence of ≥15 eos/HPF in at least 1 esophageal biopsy.

Skin prick test profiling and definition of pollen season

Skin prick test were performed before undergoing SFED using commercially prepared antigens (Allergy Therapeutics/Diagenics/Alloga UK (ALK)/Biodiagnostics) and standard methodology while off antihistamines for at least 5 days (25). Histamine (10 mg/mL) was used as a positive control, whereas saline was used as a negative control. A positive result was defined as a wheal diameter of 3 mm or more greater than the negative control at 15 minutes. Only patients who had been tested for both birch and grass pollen were eligible. Individual pollen sensitization profiles and historical year and location-specific pollen count data were scrutinized to define whether each patient had been assessed during or outside of the pollen season after SFED. Historical pollen count data for London and Pisa were provided by the Met Office and the Regional Agency for the Environmental Protection (ARPAT), respectively. For grass pollen, the start of the pollen season was defined as the first day of 5 days (of 7 consecutive days) with each of these 5 days ≥3 pollen/m^3 and with a sum of these 5 days of ≥30 pollen/m^3. For birch, the start of the pollen season was defined as the first day of 5 days (of 7 consecutive days) with each of these 5 days ≥10 pollen/m^3 and with a sum of these 5 days of ≥100 pollen/m^3. For both grass and birch pollen, the end of the season was defined as the last days fulfilling the requirements for the start of the season (26). In this study, to accommodate potential latency in the resolution of the esophageal eosinophilia after the drop of pollen counts at the end of each pollen season, patients with positive SPT to pollens were considered to have been assessed on pollen season if the endoscopy for the assessment of the efficacy of the SFED had been performed during or within 2 weeks after the end of the pollen season of each aeroallergen. By contrast, patients were considered to have been assessed outside of the pollen season if the endoscopy had been performed at least 2 weeks after the end of the pollen season of individual aeroallergens. For patients without pollen sensitization, Spring (March, April, or May) was considered as pollen season for comparison purposes.

Statistical analysis

Continuous data were described as median and interquartile range (reported as Q1–Q3), whereas categorical data as counts and percentages. Normality was evaluated using the Shapiro-Wilk test. Homogeneity of the variances was verified with the Fligner-Killeen test. Unless otherwise specified, the continuous variables were found to be non-normal and/or to have a non-uniform variance between the groups, and therefore, non-parametric Kruskal-Wallis rank sum test was used. Categorical variables were analyzed using the Pearson χ^2 test with continuity correction and the Fisher exact test for counts. Receiver operating characteristic curve analyses were used to assess the performance characteristics of predictors of SFED response, including area under the curve (AUC), sensitivity, specificity, positive predictive

Table 1. Baseline characteristics of patients with or without pollen sensitization on the skin prick test

Baseline characteristic	Patients with positive SPT for pollens (n = 36)	Patients with negative SPT for pollens (n = 22)	*P* value
Sex			0.73
Female	11/36 (30.6%)	5/22 (22.7%)	
Male	25/36 (69.4%)	17/22 (77.3%)	
Age at diagnosis	34 (30–41)	35 (30–40)	1
Symptoms			
Dysphagia	36/36 (100%)	20/22 (91.0%)	0.14
Food impaction	19/36 (52.8%)	12/22 (54.5%)	1
Heartburn/ regurgitation	25/36 (22.2%)	11/22 (50.0%)	0.06
Chest pain	2/36 (5.6%)	5/22 (22.7%)	0.09
Nausea/ abdominal pain	2/36 (5.6%)	2/22 (9.1%)	0.63
Comorbidities			
SPT positive for dust mite/cat/ dog	30/35 (85.7%)	7/22 (31.8%)	**<0.001**
SPT positive to any food	22/36 (61.1%)	11/11 (50.0%)	0.58
Rhinitis	29/36 (80.6%)	17/22 (77.3%)	0.75
Asthma	17/36 (47.2%)	9/22 (40.9%)	0.84
Atopic dermatitis	12/36 (33.3%)	6/22 (27.3%)	0.85
Nasal polyposis	2/34 (5.6%)	0/22 (0.0%)	0.52
Endoscopic findings and previous treatment response			
EREFS at baseline	2.00 (1.00–3.00)	2.00 (1.25–3.00)	0.44
PPI refractoriness	25/27 (92.6%)	12/16 (75.0%)	0.17
Steroid refractoriness	9/11 (81.8%)	2/4 (50.0%)	0.52

EREFS, eosinophilic esophagitis endoscopic reference score; PPI, proton-pump inhibitors; SPT, skin prick test.

value, and negative predictive value with bootstrap 95% confidence intervals (CI). A *P* value of <0.05 was considered statistically significant. The statistical analysis was performed using R-studio version 4.1.2.

RESULTS

Baseline characteristics

Fifty-eight patients met the inclusion criteria for this study and were included. Of these, 62.0% (36/58) had positive SPT for birch and/or grass pollen (BG-SPT-positive) and 37.9% (22/58) had negative SPT for birch and grass pollen (BG-SPT-negative). Patients with and without pollen sensitization on the SPT were comparable in sex, age, atopic disorders, baseline symptoms, and history of episodes of bolus impaction requiring endoscopic removal (Table 1).

SPT results for dust mite, cat dander, or dog dander were available for 57 of 58 patients. Significantly more patients with BG-SPT-positive had positive SPT for dust mite, cat dander, or dog dander (85.7% [30/35] vs 31.8% [7/22] in patients with BG-SPT-negative; $P < 0.001$). The 2 groups had similar rates of positive SPT for any food (22/36, 61.1% vs 11/22, 50%, respectively; $P = 0.58$) (Table 1).

Previous treatment with PPI was documented in 27 of 36 of BG-SPT-positive patients and in 16 of 22 of BG-SPT-negative patients. PPI used included esomeprazole, omeprazole, and lansoprazole, at a median dose of 40 mg/d (IQR, 30–40). Among those who underwent previous PPI treatment, 92.5% (25/27) of BG-SPT-positive patients and 75% (12/16) BG-SPT-negative patients had undergone SFED because of PPI failure to induce histologic remission. Similarly, previous treatment with topical steroids was documented in 11 of 36 of BG-SPT-positive patients and in 4 of 22 of BG-SPT-negative patients. Steroids used included nebulized/swallowed fluticasone propionate at a median dose of 625 mcg/day (IQR, 500–970) and nebulized/swallowed budesonide (3 patients, all received 2 mg). Among those who underwent previous topical steroid treatment, 82% (9/11) of BG-SPT-positive patients and 50% (2/4) of BG-SPT-negative patients had undergone SFED because of failure of topical steroids to induce histologic remission. The 2 groups showed comparable rates of PPI and topical steroid failure before SFED ($P = 0.17$ and $P = 0.52$, respectively). Finally, at baseline endoscopy, patients with and without pollen sensitization showed similar EREFS (2.00 [1.00–3.00] vs 2.00 [1.25–3.00]; $P = 0.44$) (Table 1).

SFED outcomes

The overall median duration of the SFED before the assessment of outcomes was 8 weeks (IQR, 7–10.7) and was comparable between BG-SPT-positive and BG-SPT-negative (8.0 [6.0–12.0] vs 8.0 [8.0–10.0]; $P = 0.52$). The overall histologic response to SFED (<15 eos/HPF) regardless of the SPT results and pollen season was 56.9% (95% CI, 44.1%–68.8%). Symptom outcome data were available for 28 of 33 patients who had a histologic response to SFED. Of these, 75.0% (21/28) reported decreased symptom severity and 71.4% (20/28) reported decreased symptom frequency, whereas 25.0% (7/28) did not report symptomatic improvement despite histologic remission.

Effect of pollen season on histologic remission after SFED

In total, 14 of 36 patients (38.9%) sensitized to pollens and 9 of 22 patients (40.9%) without sensitization to pollens were assessed during the pollen season after SFED. When stratifying the histologic response to SFED according to whether the assessment of the efficacy had been performed during or outside of the pollen season, BG-SPT-positive patients showed significantly lower histologic response when the assessment was performed during pollen season compared with outside of the pollen season (21.4% vs 77.3%; $P = 0.003$). By contrast, BG-SPT-negative patients did not show seasonal variations in the histologic response to SFED (77.8% vs 46.1%; $P = 0.20$). In addition, during the pollen season, BG-SPT-positive patients had significantly lower histologic response compared with BG-SPT-negative patients assessed in the same season (21.4% vs 77.8%; $P = 0.01$). By contrast, outside of the pollen season, although there was a trend toward a difference, there was no statistical difference in SFED response between

Table 2. Seasonal variation in the 6-food elimination diet (SFED) response in patients with or without sensitization to pollens

Efficacy of SFED	Histologic response assessed on pollen season	Histologic response assessed off pollen season	*P* value
Patients with positive SPT for pollens	21.4% (3/14)	77.3% (17/22)	0.003
Patients with negative SPT for pollens	77.8% (7/9)	46.1% (6/13)	0.20
P value	0.01	0.08	

SFED, 6-food elimination diet; SPT, skin prick test.

patients with or without pollen sensitization on the SPT (77.3% vs 46.1%, respectively; $P = 0.08$) (Table 2 and Figure 1).

When stratifying response to SFED according to the presence of sensitization to dust mite, cat dander, or dog dander, there was no difference in histologic remission after SFED between patients with or without positive SPT (54.0% [20/37] vs 65% [13/20], respectively; $P = 0.42$).

Endoscopic response after SFED

The EREFS of patients who responded histologically to the diet improved after SFED compared with baseline (0.00 [0.00–1.00] vs 3.00 [2.00–3.00]; $P < 0.001$). Among diet responders, there were no differences in the post-SFED EREFS between BG-SPT-positive vs BG-SPT-negative patients (0.00 [0.00–1.00] vs 0.00 [0.00–1.00]; $P = 0.71$).

Predictors of SFED response

In a *post hoc* analysis, the EREFS at baseline of the overall population was significantly lower in patients who responded histologically to SFED compared with nonresponders (2.00 [1.00–3.00] vs 3.00 [2.00–3.00]; $P = 0.01$) regardless of SPT sensitization to pollens. Accordingly, a receiver operating characteristic curve analysis showed that a baseline EREFS of 2 was associated with a SFED response regardless of SPT results and pollen season (AUC 0.69, 95% CI = 0.55–0.82) with a sensitivity of 70%, specificity of 64%, positive predictive value of 72% (61%–83%), and negative predictive value of 61% (48%–76%) (Figure 2).

DISCUSSION

In this 2-center international study, we hypothesized that inhaled and subsequently swallowed pollen allergens may contribute to the failure of the SFED during pollen season in adult patients with EoE sensitized to grass and/or birch pollen on the SPT. We found that patients sensitized to birch and/or grass pollen had significantly lower response rates to SFED during the pollen season compared with outside of the pollen season (21.4% vs 77.3%; $P < 0.001$). Of particular note, more than a half of the patients with EoE undergoing SFED tested positive for birch and/or grass pollen on the SPT. Accordingly, our results suggest that routine assessment of SPT for pollens could be valuable in the dietary management of EoE, by identifying patients who are less likely to respond to diet and may need alternative treatment during the pollen season.

The strengths of this study include the international 2-center setting, the use of strict criteria for the definition of pollen seasons based on historical year and location-specific pollen count data, and the definition of individual pollen seasons for patients with positive SPT for pollens. This study has limitations that should be mentioned. First, although we only enrolled consecutive patients undergoing SFED who had been tested for pollens on the SPT, this was a retrospective study with a relatively small sample size and selection bias remains possible. In this regard, most patients had previously failed PPI or topical steroid treatment. Although previous treatment was off-label and often used at a low dose, it is not uncommon in routine clinical practice that adult patients undergo dietary treatment after unsuccessful pharmacologic treatment (27). In addition, we collected self-reported baseline and post-SFED symptoms based on patients' perception without validated questionnaires. Nevertheless, symptomatic response to the SFED in this study was similar to what has been reported in another recent retrospective study (28). Second, despite all patients were followed by

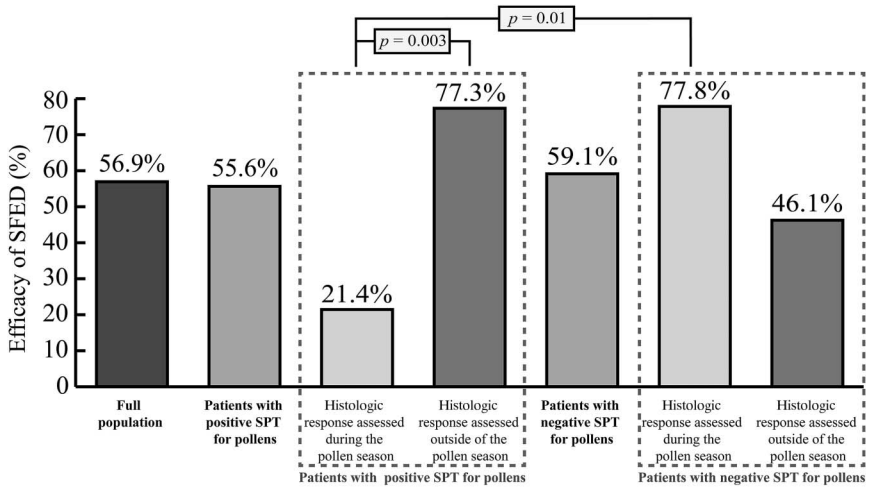

Figure 1. SFED outcomes in patients with or without pollen sensitization on the SPT according to whether the assessment was performed during or outside of the pollen season. SFED, 6-food elimination diet; SPT, skin prick test.

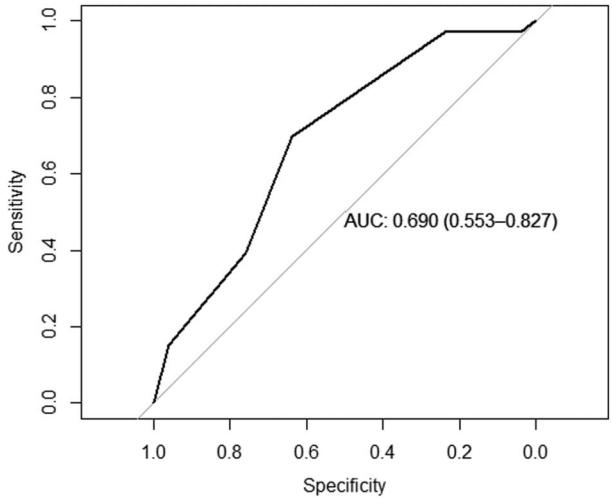

Figure 2. Receiver operating characteristic curve with area under the curve (AUC) of the EREFS at baseline for the prediction of SFED response regardless of pollen season and sensitization. EREFS, eosinophilic esophagitis endoscopic reference score; SFED, 6-food elimination diet.

experienced dietitians during the SFED, the overall efficacy of diet was lower than what it has been reported in older studies (13). However, the efficacy of SFED in this study was comparable to that reported in more recent studies (27,28). In addition, in this study, when patients with pollen sensitization were assessed outside of the pollen season, the efficacy of SFED was higher than that reported in studies that did not consider the pollen season and pollen sensitization as confounding factors (13), corroborating a significant impact of the pollen season on SFED outcomes in sensitized patients. In this regard, assessing the efficacy of SFED during and outside of the pollen season in each patient would have helped strengthening our results. However, this was a retrospective study and individual data both during and outside of the pollen season were not available. Third, only patients tested for birch and grass pollen were included, and we did not investigate the contribution of other pollens. However, grass and birch represent the most common pollinosis in EoE and have been proposed to account for seasonal variation in the diagnosis of EoE (29–31). Fourth, we did not investigate specific SPT and immunoglobulin E food sensitization profiles for each patient. However, patients with or without evidence of pollen sensitization on the SPT had similar SPT sensitization profiles for any food. In addition, food sensitization on the SPT or IgE do not accurately predict histologic response to SFED and are currently not recommended to guide the dietary management of EoE (9,22,32,33).

A recent study conducted on children by Pesek et al (31) reported that patients sensitized to molds on the SPT had lower response to oral corticosteroids and/or elimination diet compared with those without sensitization. The study failed to detect any difference in treatment response based on seasonal variation. However, the authors did not take into account the pollen counts of different seasons in their study. By contrast, in this study, individual sensitization profiles, historical pollen counts by year and location, and the season of the assessment were all considered as confounders, and a season variation in SFED response was detected in patients sensitized to pollens on the SPT. In addition, as already shown by Pesek et al, we found that dust mite and pet dander do not affect treatment response, although we are not aware whether patients did or did not have pets in their house.

We also found that a low EREFS at baseline is associated with histologic response to SFED with an AUC of 0.69. These results are complementary to what has been recently found in a study by Wang et al (27), where a higher pre-SFED EREF score was the only variable associated with dietary nonresponse. However, we acknowledge that the performance of the EREFS in the prediction of the histologic response to the SFED is suboptimal.

Several studies have investigated the use of SPT for food allergens to direct elimination diets in EoE in the past. However, SPT have generally shown low sensitivity for the identification of most trigger foods in patients with EoE (32,33). Therefore, current clinical guidelines discourage the use of targeted elimination diets, in favor of empirical elimination diets in clinical practice (9,22,34). In this study, we showed that SPT for pollens may have a clinical utility in the dietary management of EoE by identifying patients less likely to respond to SFED during pollen season. In addition, together with other studies suggesting a role of pollens in EoE (29,35–38), these findings support that pollens may sustain esophageal eosinophilia in sensitized adults with EoE despite avoidance of trigger foods. Our results suggest that SPT for pollens may help in the identification of the best candidates for elimination diets. In addition, our findings question whether alternative or combined therapies should be undertaken during the pollen season, if elimination diets need to be undertaken outside of the pollen season in patients sensitized to pollens, and if patients with EoE sensitized to pollens should undergo endoscopy with biopsies during the pollen season to assess response to any ongoing treatment. Prospective studies are needed to validate these findings and investigate strategies for improving the outcome of SFED in patients with EoE sensitized to pollens.

CONFLICTS OF INTEREST

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Guarantor of the article: Sebastian Zeki.

Specific author contributions: P.V. and S.Z.: conceived and drafted the study. P.V., G.D.C., F.B.S., and S.Z.: analyzed all data. P.V., E.S., H.H., S.J.T., T.W., N.d.B., and S.Z.: drafted the manuscript. All authors commented the drafts of the paper. All authors approved the final version of the manuscript.

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Potential competing interests: P.V.: none; E.S.: has served as a speaker for AbbVie, AGPharma, Alfasigma, Dr Falk, EG Stada Group, Fresenius Kabi, Grifols, Janssen, Innovamedica, Malesci, Pfizer, Reckitt Benckiser, Sandoz, SILA, Sofar, Takeda, and Unifarco; has served as a consultant for Alfasigma, Amgen, Biogen, Bristol-Myers Squibb, Celltrion, Diadema Farmaceutici, Dr. Falk, Fresenius Kabi, Janssen, Merck & Co, Reckitt Benckiser, Regeneron, Sanofi, Shire, SILA, Sofar, Synformulas GmbH, Takeda, and Unifarco; and he received research support from Pfizer, Reckitt Benckiser, SILA, Sofar, and Unifarco; G.D.C.: None; H.H.: None; F.B.S.: None; S.J.T.: None; T.W.: received grant support from Reckitt Benckiser and Lecture fees from AstraZeneca, and Dr Falk; NdB: Lectures fees from Malesci and Reckitt Benckiser; and S.Z.: has served as a speaker for Dr Falk.

Ethics committee approval: The project was considered a review of clinical practice and ethical approval was not required.

Study Highlights

WHAT IS KNOWN

- ✓ There is a seasonal variation in the diagnosis and symptom exacerbation in eosinophilic esophagitis.
- ✓ The contribution of pollen sensitization to the outcomes of the 6-food elimination diet in adults with eosinophilic esophagitis has not been investigated.

WHAT IS NEW HERE

- ✓ Patients sensitized to birch and/or grass pollen had significantly lower response rates to the 6-food elimination diet during the pollen season compared with outside of the pollen season, implying the contribution of pollens to treatment failure.
- ✓ Skin prick test for pollens may identify patients who are less likely to respond to diet and may need alternative treatment during the pollen season.

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