



Letters

Subcutaneous immunotherapy in patients with eosinophilic esophagitis



Although the association between eosinophilic esophagitis (EoE) and food allergens is well established, a large proportion of EoE patients have concomitant atopic disease, and growing evidence suggests that aeroallergens may play a role in pathogenesis.^{1–3} However, subcutaneous immunotherapy (SCIT) for treatment of EoE has not been extensively described.^{4–8} The aim of this study was to compare characteristics and treatment outcomes in patients with EoE who were treated with SCIT (EoE+SCIT) with those who were not treated with SCIT (EoE-SCIT).

We conducted a retrospective cohort study using the University of North Carolina (UNC) EoE clinicopathologic database,⁹ focusing on patients of all ages from 2008 (the year that International Classification of Disease, version-9 [ICD-9] released an EoE code)¹⁰ through 2016. To be included, patients met consensus guidelines for an incident diagnosis of EoE as published at the time of this study design.¹ This study was approved by the UNC Institutional Review Board.

To capture all EoE patients as well as all patients treated with SCIT, we queried the Carolina Data Warehouse for Health, a central data repository containing granular patient information with searchable fields derived from the UNC electronic medical record. We used ICD-9/10 codes, as well as Current Procedure Terminology (CPT) codes for the search. Eosinophilic esophagitis was identified with 530.13 and K20.0. The SCIT treatments were identified with CPT codes 95115, 95117, 95120, 95125, and 95165. We cross-referenced confirmed EoE patients and those treated with SCIT to identify EoE+SCIT and EoE-SCIT subjects, and extracted relevant data from the medical record ([Supplemental Methods](#)).

Subcutaneous immunotherapy was based on percutaneous testing or ImmunoCAP allergen-specific immunoglobulin E (IgE) measurement. All allergen extracts were from Greer Laboratories (Lenoir, NC). Histologic response to treatment was defined as a peak esophageal eosinophil count less than 15 eosinophils per high-power field (eos/hpf).^{1,9} Symptom response was defined as the clinically reported patient global response (yes/no). We compared clinical, endoscopic, and histologic characteristics between EoE+SCIT and EoE-SCIT ([Supplemental Methods](#)).

Of 692 patients identified with EoE, 25 (3.6%) had CPT codes for SCIT. Of those 25, 15 did not meet inclusion ([eFig 1](#)). When comparing the EoE-SCIT (n = 667) and EoE+SCIT (n = 10) groups, age, sex, race, and baseline endoscopic and histologic features were similar ([Table 1](#)). The symptom duration before diagnosis of EoE was shorter in EoE-SCIT as compared with EoE+SCIT cohort (7.3 vs 13.8 years; $P = .046$). As expected, the EoE+SCIT group had a higher rate of atopic disease.

For EoE+SCIT patients, immunotherapy dose remained consistent throughout the treatment course. The SCIT administered included dust mites, cat, dog, cockroach, tree, grass, weed, ragweed, English plantain, and *Alternaria* ([eTable 1](#)). Of the 10 cases, 9 were diagnosed with EoE before the administration of SCIT, and none of the patients had started SCIT by the time of their first follow-up endoscopy after diagnosis, so we were able to assess initial treatment response in the absence of SCIT. Median follow-up time was 400 days.

After initial diagnosis, these 10 patients were treated with a topical steroid. At the first follow-up endoscopy, 3 (30%) had histological response, and 6 (60%) had a symptom response. Of the 5 patients who had follow-up data and were concurrently treated with SCIT, 40% had a histological response, and 40% had a symptom response. This did not vary by season of follow-up. These 5 patients had 20% histological response and 40% symptomatic response after initial treatment before SCIT. Compared with the initial EGD, at follow-up in the EoE+SCIT group there was less use of topical steroids (80% vs 40%) and more use of dietary elimination (0% vs 80%) ([eTable 2](#)). No adverse outcomes were identified in the EoE+SCIT cohort.

The data from this study merit discussion. Few differences were seen between the EoE+SCIT and EoE-SCIT groups, and because of the small number of patients treated with SCIT, we are unable to make firm conclusions regarding the impact on treatment outcomes. However, in this selected population, no decrement was seen in histologic response rates or worsening of global symptom responses in the EoE+SCIT cohort.

Few studies explore safety and efficacy of SCIT for EoE treatment.^{4–8} Ramirez and Jacobs⁵ describe a 4-year-old boy with refractory EoE who responded histologically and symptomatically to SCIT to dust mites.⁵ De Swert et al⁴ describe a 10-year-old boy who had symptomatic and histologic improvement after desensitization with SCIT to grass and birch allergens.⁴ Castilano and Zacharias⁷ describe a 30-year-old man who had resolution of symptoms and normalization of esophageal biopsies after SCIT to dust mites, cockroaches, weeds, and trees.⁷ Notably, 1 case reports exacerbation of symptoms after SCIT to grass pollen, implicating a potential risk in treatment of EoE with SCIT.⁸

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Table 1

Demographics and Clinical Characteristics of EoE Patients with and without Subcutaneous Immunotherapy

	EoE-SCIT (n = 667)	EoE+SCIT (n = 10)	P
Age (mean years $\pm$ SD)	26.0 $\pm$ 18.4	29.2 $\pm$ 14.2	.59
Male (n, %)	459 (69)	5 (50)	.20
White (n, %)	532 (81)	9 (90)	.46
Symptoms (n, %)			
Dysphagia	466 (71)	8 (80)	.52
Heartburn	249 (39)	4 (40)	.94
Abdominal pain	143 (22)	1 (10)	.36
Symptom length prior to diagnosis (mean years $\pm$ SD)	7.3 $\pm$ 8.6	13.8 $\pm$ 8.8	.046
Atopy (n, %)			
Rhinitis/sinusitis	253 (40)	10 (100)	.01
Asthma	156 (24)	6 (60)	.01
Food allergy	173 (29)	4 (44)	.32
Baseline EGD findings			
Rings	298 (45)	4 (40)	.75
Stricture	134 (20)	3 (30)	.45
Narrowing	93 (14)	2 (20)	.60
Furrows	376 (57)	5 (50)	.67
Exudates/white plaques	225 (34)	7 (70)	.02
Edema/decreased vascularity	199 (30)	4 (40)	.50
Dilation performed	140 (21)	3 (30)	.50
Baseline eosinophil counts (mean eos/hpf $\pm$ SD)	65.2 $\pm$ 44.7	72.8 $\pm$ 36.5	.62

Abbreviations: EGD, esophagogastroduodenoscopy; EoE, esophageal eosinophilic esophagitis; eos, eosinophils; hpf, high-power field; SCIT, subcutaneous immunotherapy; SD, standard deviation.

Despite our review of a large database of EoE patients and a large data warehouse, we could identify only a small fraction of EoE patients who underwent treatment with SCIT at our center, with even fewer receiving SCIT after the initial diagnosis of EoE. Consequently, we are unable to make definitive conclusions regarding the role of SCIT. The number of cases were limited by a single center study, patients could have been seen by an outside allergy practice to receive SCIT, and some had changes in concomitant EoE treatment that could impact response. Further investigation should include multiple medical centers and community-based practices, as well as limit other treatment changes. Nevertheless, because we only included EoE subjects who we could confirm received SCIT, our data are valid in this small group, and they should form the basis for future prospective studies using validated EoE outcomes and standardized SCIT protocols.

In conclusion, with the exception of increased atopic disease and longer duration of symptoms, few differences were found between EoE+SCIT and EoE-SCIT patients. The EoE+SCIT group had relatively low initial treatment response rates before SCIT. At follow-up, response rates were slightly improved, but in the context of less topical steroids and more dietary elimination. We did not observe any worse outcomes among patients in the

EoE+SCIT cohort, suggesting that SCIT in EoE patients may be safe and is worthy of future study.

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Supplementary Data

Supplementary data associated with this article can be found in the online version at <https://doi.org/10.1016/j.anai.2019.02.022>.

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An institutional review of flying Hymenoptera venom immunotherapy in patients with cutaneous systemic reactions only



The basis of venom immunotherapy (VIT) can be defined as protection against IgE-mediated immunologic mechanisms, such as

anaphylaxis.^{1,2} Most insect stings produce local reactions of swelling, pain, erythema, and pruritus, typically peaking by 24 to 48 hours and resolving within 3 to 10 days.³ Unfortunately, some patients experience systemic reactions that range from cutaneous reactions only (characterized by urticaria and/or angioedema, excluding throat, larynx, and tongue) to life-threatening systemic

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**eSupplement.
Supplemental Methods***Data Extraction*

Patient demographics, symptoms, symptom duration before diagnosis, comorbid atopic diseases, baseline esophagogastroduodenoscopy (EGD) findings, and baseline eosinophil counts were extracted from the electronic health record. Additional data extracted included eosinophilic esophagitis (EoE) treatments, subcutaneous immunotherapy (SCIT) start and stop dates in relation to EoE diagnosis and treatments, type of SCIT received, EGD findings after initial treatment, as well as at the time of the last EGD on record, and treatment response.

Statistical Analysis

We used descriptive statistics to summarize clinical characteristics of patients with EoE. We performed bivariate analysis comparing clinical, endoscopic, and histologic characteristics between the groups receiving SCIT (EoE+SCIT) and those that did not receive SCIT (EoE-SCIT) using χ^2 for categorical variables, and a two-sample *t* test for continuous variable. For small sample sizes or variables with non-normal distributions, nonparametric testing with Fisher's exact test and Wilcoxon rank-sum were performed as appropriate.

eTable 1

Subcutaneous Immunotherapy and Dose Administered in EoE + SCIT Cases

Case #	Subcutaneous immunotherapy
1	DM, cat, 8 tree mix, 7 grass mix, English plantain
2	DM, birch, cedar, maple, timothy, ragweed
3	Ragweed, <i>Alternaria</i>
4	Dog, 7 grass mix, <i>Alternaria</i>
5	Cat, 3 weed mix, <i>Alternaria</i>
6	DM, CR, cat, oak, 7-grass mix, 3-weed mix, Bahia
7	DM, cat, 8 tree mix, Bahia, Mugwort, <i>Alternaria</i>
8	DM, cat, dog, oak, timothy, Bermuda, ragweed
9	DM, cat, dog, 8-tree mix, 7-grass mix, English plantain
10	DM, 7-grass mix

Alternaria, 1:20 w/v using 0.05 mL in 0.5-mL maintenance injection.

Bahia, 1:20 w/v using 0.05 mL in 0.5-mL maintenance injection.

Cat, 10,000 BAU/mL at 5000 BAU in 0.5-mL maintenance injection.

Dog, dog epithelia at 1:20 w/v at 0.1 mL in 0.5-mL maintenance injection.

Cockroach (CR), American and German cockroach mix at 1:20 w/v using 0.1 mL in 0.5-mL maintenance injection.

Dust mite (DM), mix of *Dermatophagoides farinae* (10,000 AU/mL) and *Dermatophagoides pteronyssinus* (10,000 AU/mL) at 1000 AU each in 0.5-mL maintenance injection.

Tree, individually or in Eastern 8-tree mix (American beech, eastern cottonwood, red oak, river birch, shagbark hickory, white ash, American Elm, maple sugar/hard) at 1:20 w/v using 0.05 mL in 0.5-mL maintenance injection.

Grass, individually at 100,000 BAU (except Bermuda at 10,000 BAU) or in 7-grass mix (Kentucky blue/June, meadow fescue, orchard, perennial ryegrass, redtop, sweet vernal, timothy) and used at 1000-2500 BAU in 0.5-mL maintenance injection.

Weed, individually or in 3-weed mix (cocklebur, lamb's quarter, rough/redroot pigweed) at 1:20 w/v using 0.05 mL in a 0.5-mL maintenance injection.

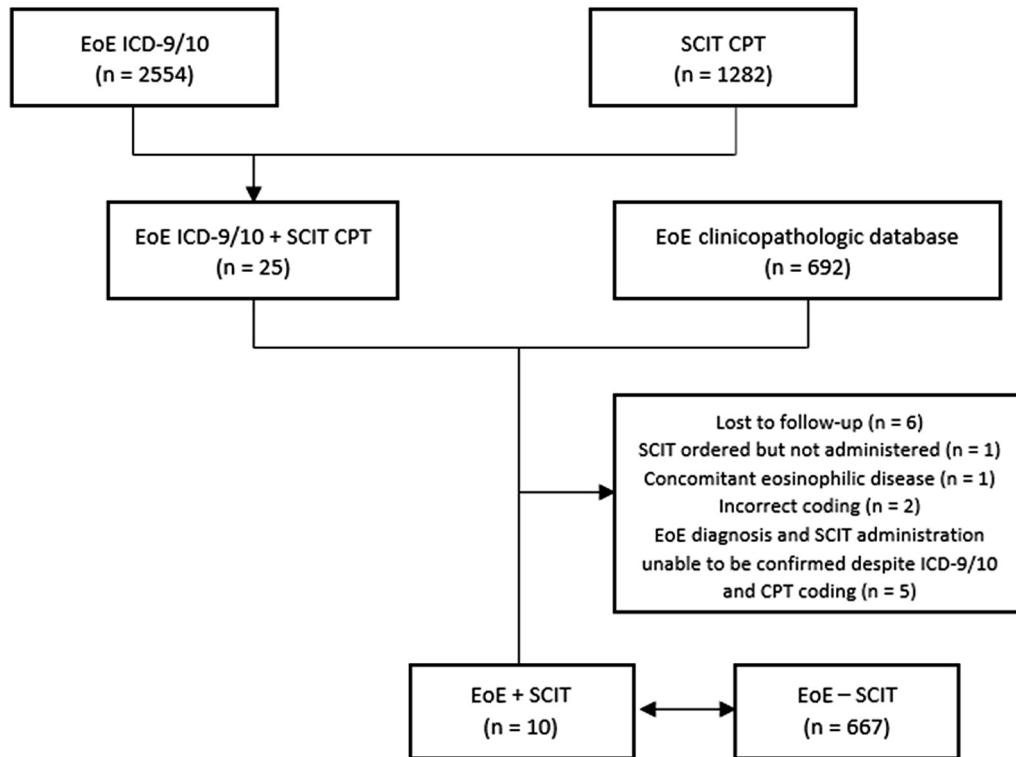
eTable 2

Conventional vs Conventional Treatment + SCIT at the Time of Initial Treatment and Last Endoscopy on Record

	Case 1	Case 2	Case 3	Case 4	Case 5
Conventional treatment					
Steroid type	Budesonide	Fluticasone	Budesonide ^a	Fluticasone	Fluticasone
Steroid dose	0.5 mg BID	440 µg BID	0.5 mg BID	440 µg BID	440 µg BID
Dietary therapy	No	No	No	No	No
Histology (eos/hpf)	0	>30	>100	>60	25
Histologic Response	Yes	No	No	No	No
Symptom response	Yes	Yes	No	No	No
Conventional treatment + SCIT					
Steroid type	Fluticasone	None	None	None	Budesonide
Steroid dose	1 mg	0	0	0	1 mg
Dietary therapy	Yes	Yes	Yes	Yes	No
Histology (eos/hpf)	20	40	3	N/A	3
Histologic response	No	No	Yes	N/A	Yes
Symptom response	No	Yes	No	No	Yes

Abbreviations: eos, eosinophils; hpf, high-power field; SCIT, subcutaneous immunotherapy.

^aQuestionable adherence to the prescribed medication.



eFigure 1. Patient flow using the Carolina Data Warehouse and EoE Clinicopathologic database.