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ORIGINAL RESEARCH—CLINICAL

Treatment Patterns and Persistent Disease Activity in Patients With Eosinophilic Esophagitis: A Retrospective Cohort Study

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BACKGROUND AND AIMS: Limited real-world nontertiary care evidence on the patient therapeutic journey and disease burden of eosinophilic esophagitis (EoE) exists. The aim was to collect real-world data on the EoE patient journey across different age groups. **METHODS:** This retrospective, real-world, cohort study used electronic medical records and claims data provided by a rural integrated US healthcare system. Eligibility criteria included $\geq$ 2 diagnoses of EoE (2009–2018), $\geq$ 1 endoscopy, and $\geq$ 12 months of data before and after the index date (the first endoscopy date during the 180 days before and the 365 days after the first EoE diagnosis). Clinical findings, all-cause healthcare resource utilization, specialists consulted, therapies, and markers of disease progression were analyzed. **RESULTS:** Overall, 613 patients were enrolled: 0–11 (children, n = 182), 12–17 (adolescents, n = 146), 18–54 (adults, n = 244), and $\geq$ 55 years old (older adults, n = 41). Post index, the prevalence of signs and symptoms increased. At baseline, most endoscopies were abnormal (80.5%) and most peak eosinophil counts were > 15 eosinophils/high-power field (87.9%); post index, all age groups had endoscopic and histologic improvements. However, 3 years post index, abnormal endoscopic appearance (62.3%) and histologic activity (51.2%) were observed. Patients of all ages exhibited considerable all-cause healthcare resource utilization. During follow-up, 86.3% of patients consulted a specialist. Before and after index, proton pump inhibitors and corticosteroids were the most commonly used pharmacological therapies; 44.0% of patients discontinued their first treatment post index. Disease progression occurred in 13.9% of patients post index. **CONCLUSION:** In this setting, patients with EoE irrespective of age face difficult therapeutic journeys with substantial disease burden.

Keywords: Patient Journey; Disease Burden; Esophageal Eosinophilia; Real-World Evidence

Introduction

Eosinophilic esophagitis (EoE) is an immune-mediated inflammatory disease, characterized by symptoms of esophageal dysfunction and eosinophil-predominant inflammation.[1,2] Endoscopic abnormalities can be inflammatory, fibrostenotic, or a mixture of both.[3]

Recent studies have found that patients with EoE experience a complicated journey to diagnosis and a substantial disease burden, which requires significant healthcare resource utilization (HCRU).[4,5] Reasons for this may include delays in diagnosis owing to nonspecific symptoms, adaptive behaviors, progression of silent disease, lack of adequate follow-up or referral, or suboptimal treatment after diagnosis. Management options for patients with EoE include dietary, pharmacological, and endoscopic interventions,[6] and both US and European guidelines[6,7] support the use of pharmacological or dietary therapies for the early-term and long-term management of EoE. To date, only 2 medications have been approved by the US Food and Drug Administration for EoE; dupilumab, a biologic indicated for the treatment of patients aged 1 year and older with EoE[8] and budesonide oral suspension, a swallowed topical corticosteroid indicated for the 12-week treatment of patients aged 11 years and older with EoE.[9] However, biologic therapies may not always be selected as a first-line treatment, and are often associated with high costs.[10] It is therefore important to examine real-world treatment patterns and disease progression in patients with EoE to improve our understanding of these and ultimately to improve the quality of care.[11,12]

EoE is more prevalent in men than women,[13] reported at a ratio of approximately 3:1.[13,14] The prevalence of EoE is

Abbreviations used in this paper: **CI, confidence interval; EoE, eosinophilic esophagitis; eos/hpf, eosinophils per high-power field; EREFS, Endoscopic Reference Score; FDA, US Food and Drug Administration; GERD, gastroesophageal reflux disease; H2RA, histamine-2 receptor antagonist; HCRU, healthcare resource utilization; NA, not applicable; PPI, proton pump inhibitor; Q1, lower quartile; Q3, upper quartile; SD, standard deviation.**

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also higher in White patients than in other racial and ethnic groups,[13] although the prevalence among these groups is thought to be under-reported.[15] Race and sex have been shown to influence the clinical presentation of EoE;[16,17] however, differences by sex to a lesser degree.[14,17] Clinical differences by age are more pronounced;[13,18] children with EoE typically present with an inflammatory-predominant phenotype, which may progress to the fibrostenotic-predominant phenotype that is more commonly reported in adults with EoE.[13] For that reason, differences by age were the main focus of this study.

We aimed to evaluate EoE disease activity, as well as the therapeutic journey and burden of disease experienced by patients with EoE stratified by age in a large-scale, non-tertiary care setting in the United States.

Methods

Study Design and Participants

This retrospective observational cohort study used electronic medical record (EMR) data and linked administrative claims data provided by a rural integrated US healthcare system in Pennsylvania,[19] which cares for more than 1 million patients annually.[20] The study design is shown in Figure A1.

Patients were eligible for inclusion if they had:

- at least 2 diagnoses of EoE (defined as International Classification of Diseases, Ninth Revision,[21] Clinical Modification diagnosis code [ICD-9-CM] 530.13 or International Classification of Diseases, 10th Revision [ICD-10-CM],[22] Clinical Modification diagnosis code K20.0) between August 1, 2009 and June 30, 2018 (2 diagnoses were required to increase the internal validity of the study population) (Table A1)
  - validation of a diagnosis of EoE was conducted based on the supplemental medical record review
- an index endoscopy, which was defined as the first endoscopy that a patient received during the 180 days before the first observed EoE diagnosis and the 365 days after the first observed EoE diagnosis (this was also defined as the index date; other endoscopies could have occurred pre or post index)
- at least 12 months of data before the index date (this was referred to as the 'baseline' or 'preindex' period) and at least 12 months of data after the index date until the earliest date of either death
- discontinuation of medical care through the health system's plan, or database end (ie, June 30, 2019) (this was referred to as the 'follow-up/post-index period' and also represents the end of the study period)
- no evidence of human immunodeficiency virus infection, leukemia, and related malignancies, or other gastrointestinal conditions, such as Crohn's disease, that could contribute to EoE[23] and affect the study findings (these diagnoses were identified using ICD-10-CM [Table A1]).

Follow-up was from index until death, discontinuation of care through the health system's plan, or database end; if no specific month/year post index is reported in the results, the post-index date represents the last follow-up visit after index. Both men and women of all ages with EoE were eligible for inclusion in this study; data were stratified by age: 0–11 years (children), 12–17 years (adolescents), 18–54 years (adults), and $\geq$ 55 years (older adults). Subgroup analyses were conducted in patients with a minimum follow-up period of 24 months.

Study Measures and Variables

Data on procedures, medications, vitals, laboratory test results, and patient demographics were extracted from the EMRs (Table A2), either directly from structured EMR data files or through manual medical record review conducted by research nurses. Data on pharmacy, medical, hospital, and members files were collected from the claims database. Overall HCRU was observed from both the EMRs and claims data; physician specialties were recorded from EMRs only. Patient demographics as of June 30, 2018 were summarized. Outcomes describing EoE disease activity, the therapeutic journey, and disease burden experienced by patients with EoE were assessed during the predefined baseline and follow-up periods. Clinical outcomes evaluated included symptoms of EoE and associated esophageal and atopic conditions; endoscopy findings with or without biopsy (documented through medical records, including the pathology results for endoscopies with biopsy) and results from the biopsy closest to (but before) the study index date (if multiple biopsies were observed in the baseline period). Additionally, the timing of follow-up endoscopy; the proportion of patients with an abnormal esophageal endoscopic appearance (based on the visual endoscopic findings, which may have included inflammatory or fibrostenotic endoscopic features: edema, furrows, esophageal rings, exudates, or strictures); the total EoE Endoscopic Reference Score (EREFS) at each endoscopy, when available, through a supplemental medical record review including each of the major endoscopic features, and was not exclusively based on claims data; and the proportion of patients with a peak eosinophil count ($\leq$ 1, $\leq$ 6, or $\leq$ 15 eosinophils per high-power field [eos/hpf]) were evaluated. Healthcare resource outcomes evaluated included all-cause HCRU before and after index, specialist type consulted, use of pharmacological treatments (for any condition), and food avoidance/elimination practices. For pharmacotherapy incident users, time to treatment, treatment sequence (defined as the first prescription [or ongoing treatment] after index endoscopy, which represents the start of a line of treatment), and duration of therapy were assessed. Complications or events suggestive of disease progression were also evaluated, which were defined as a new incident diagnosis of esophageal stricture, dysphagia, or food impaction, performance of an esophageal dilation, or initiation of pharmacological treatment among untreated patients; time to disease progression calculated from index (the earliest of any of the events was considered as the date of disease progression); and endoscopic and clinical characteristics suggestive of disease remission from index. Patients were followed up for at least 12 months after index; data for up to 3 years after index are presented.

Statistical Analyses

Analyses were descriptive and performed using SAS statistical software (SAS Institute, Inc, Cary, North Carolina; version 9.4). Continuous variables were described using means (standard deviation [SD]); categorical variables were described

Table 1. Baseline Demographics and Characteristics of Patients With EoE Stratified by Age

Demographics	Children, aged 0–11 y (n = 182)	Adolescents, aged 12–17 y (n = 146)	Adults, aged 18–54 y (n = 244)	Older adults, aged ≥ 55 y (n = 41)	All patients (N = 613)
Age, y, mean (SD)	6.6 (3.3)	15.1 (1.6)	36.0 (9.2)	64.4 (8.3)	24.2 (17.8)
Sex, n (%)					
Female	45 (24.7)	46 (31.5)	100 (41.0)	22 (53.7)	213 (34.8)
Male	137 (75.3)	100 (68.5)	144 (59.0)	19 (46.3)	400 (65.3)
Race,[a] n (%)					
Black or African American	12 (6.6)	6 (4.1)	2 (0.8)	1 (2.4)	21 (3.4)
White	168 (92.3)	139 (95.2)	241 (98.8)	40 (97.6)	588 (95.9)
Other	1 (0.6)	1 (0.7)	1 (0.4)	0 (0.0)	3 (0.5)
Ethnicity,[b] n (%)					
Hispanic	20 (11.0)	7 (4.8)	4 (1.6)	0 (0.0)	31 (5.1)
Non-Hispanic	162 (89.0)	139 (95.2)	239 (98.0)	41 (100.0)	581 (94.8)
Primary insurance plan, n (%)					
Health system plan	88 (48.4)	51 (34.9)	99 (40.6)	11 (26.8)	249 (40.6)
Commercial	85 (46.7)	83 (56.9)	120 (49.2)	15 (36.6)	303 (49.4)
Medicare	0 (0.0)	0 (0.0)	9 (3.7)	12 (29.3)	21 (3.4)
Medicaid	1 (0.6)	0 (0.0)	1 (0.4)	0 (0.0)	2 (0.3)
Other	8 (4.4)	12 (8.2)	15 (6.2)	3 (7.3)	38 (6.2)
Follow-up period, mo, mean (SD)	68.9 (29.2)	63.6 (29.0)	56.1 (28.9)	44.4 (23.4)	60.9 (29.4)

EoE, eosinophilic esophagitis; SD, standard deviation.
[a]Unknown, n (%): children, 1 (0.6); adolescents, 0 (0.0); adults, 0 (0.0); older adults, 0 (0.0); all patients, 1 (0.2).
[b]Unknown, n (%): children, 0 (0.0); adolescents, 0 (0.0); adults, 1 (0.4); older adults, 0 (0.0); all patients, 1 (0.2).

using frequency distributions (n [%]). Time to event outcomes were estimated using Kaplan–Meier analyses.

Results

Study Population and Baseline Characteristics

In total, 925 patients were identified who had at least 2 diagnoses of EoE; of whom, 815 had at least 1 endoscopy during the 180 days before the first observed EoE diagnosis and the 365 days after the first observed EoE diagnosis. Of these patients, 678 had at least 12 months of data before the index date (date of first endoscopy during the 180 days before and the 365 days after the first observed EoE diagnosis). A total of 28 patients were then excluded because they had an EoE diagnosis in the 12 months before the start of the patient selection window (August 1, 2009); this was to ensure only newly diagnosed patients were enrolled in this study. Subsequently, 637 patients had at least 12 months of follow-up, but 24 of these patients were excluded owing to evidence of 1 or more of the conditions previously described (see Study Design and Participants section) that may contribute to EoE. Overall, 613 eligible patients were included; of these, 182 were children (aged 0–11 years), 146 were adolescents (aged 12–17 years), 244 were adults (aged 18–54 years), and 41 were older adults (aged ≥ 55 years) (Table 1). Patients' mean (SD) age was 24.2 (17.8) years and most patients were White (95.9%) and male (65.3%) (Table 1). Patients had a mean (SD) total follow-up duration of 60.9 (29.4) months.

Validation of a Diagnosis of EoE

A validation of a diagnosis of EoE was obtained from patient's EMR data, using the medical record review as standard; a positive predictive value (95% confidence interval) of 99.2% (98.1%, 99.7%) was calculated. In addition, a median absolute difference in the date of diagnosis between EMR and chart review of 7.0 days was identified.

Signs, Symptoms, and Associated Esophageal and Atopic Conditions in Patients With EoE

Before and after index, the most common signs and symptoms were dysphagia (before, 34.6%; after, 49.9%), abdominal pain (before, 33.0%; after, 48.1%), and nausea/vomiting (before, 20.1%; after, 31.5%) in the total population. When examined by age, nausea/vomiting was more common in children than in other age groups before and after index, whereas chest or throat pain and dysphagia were more common in adults and older adults than in children and adolescents before and after index (Figure 1A). Patients also exhibited multiple gastro-esophageal and atopic conditions before and after index; gastro-esophageal reflux disease (GERD: before, 38.8%; after, 62.6%), rhinitis (before, 21.4%; after, 52.9%), and asthma (before, 12.6%; after, 35.9%) were the most common in all ages. Before and after index, asthma, allergies (any allergies and food allergies), and failure to thrive were more commonly reported in children than in other age groups; weight loss was more common in adolescents than in other age groups (Figure 1B). Overall, the prevalence of all signs and symptoms and other conditions increased after index (Figure 1A and B).

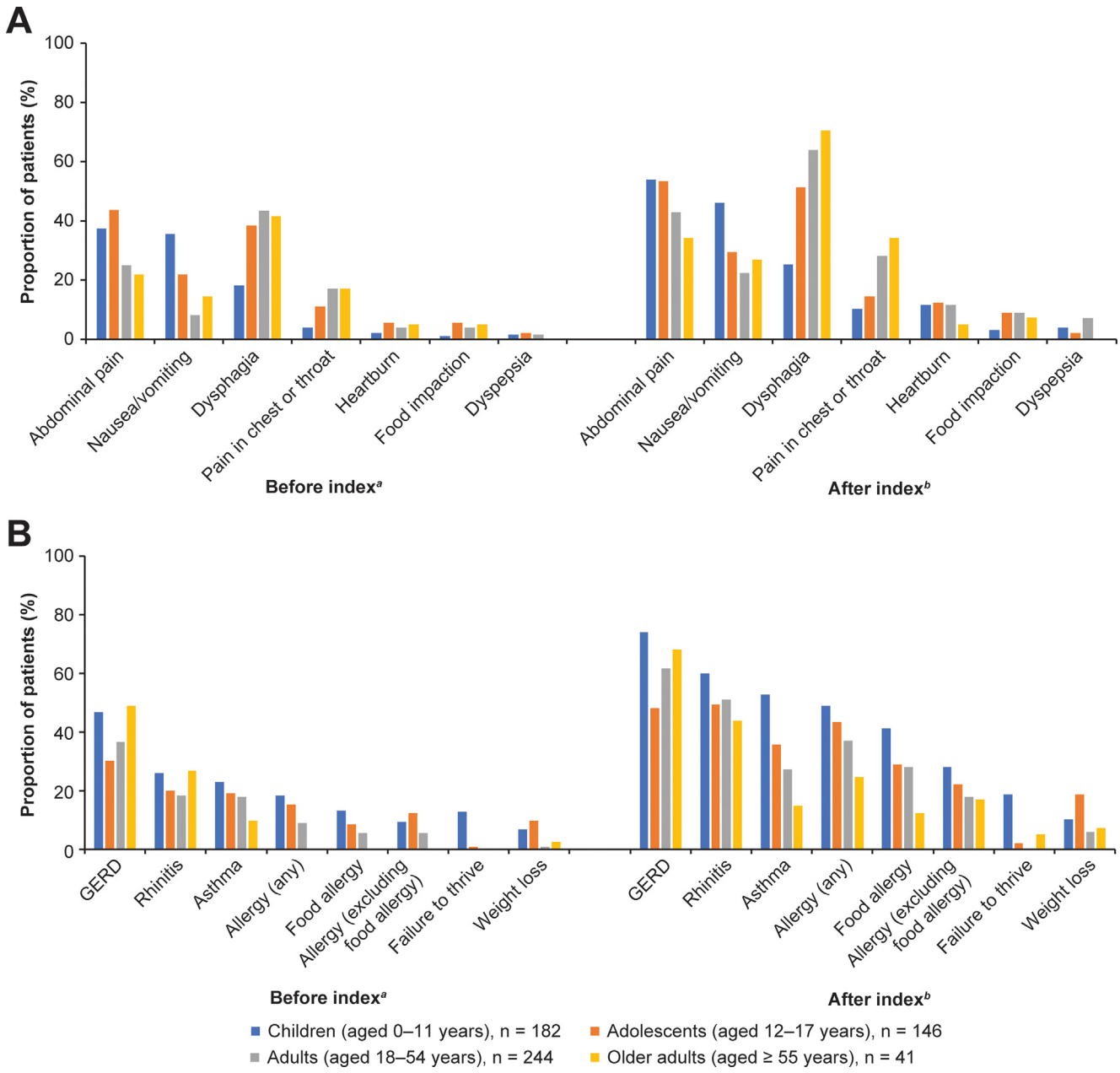

Figure 1. Summary of signs and symptoms (A), and associated gastro-esophageal and atopic conditions (B), in patients with EoE stratified by age group before and after index. [a]Calculated as the period 12 months before index for patients with a first diagnosis of EoE after index, or the time between the index date and 12 months before the first diagnosis of EoE for patients with a first diagnosis of EoE before index. [b]Calculated for patients with a minimum of 12 months of follow-up after index. EoE, eosinophilic esophagitis; GERD, gastro-esophageal reflux disease.

Endoscopic and Histologic Findings

Only 7.5% of patients had undergone an endoscopy before the index endoscopy, and the timing of follow-up endoscopy varied by age. Of 455 patients (74.2%) who had at least 3 years of follow-up, 76.0% underwent a follow-up endoscopy with biopsy within 3 years of index. A follow-up endoscopy within 1 and 2 years of the index date, both with and without biopsy, were significantly more common among patients aged $<$ 18 years and patients who had a preindex gastroenterologist consultation compared with patients aged $\geq$ 18 years and patients without a preindex gastroenterologist consultation, respectively (Table A3; all comparisons, $P < .001$). No significant differences in follow-up endoscopy were observed by sex.

In the total population, most index endoscopies were abnormal in appearance (80.5%). Of these 467 patients with an abnormal esophageal appearance at index, 395 (84.6%) patients had an EREFS score computed (mean [SD]: 1.8 [1.1]). In patients who had at least 3 years of follow-up, 221 patients had an abnormal esophageal

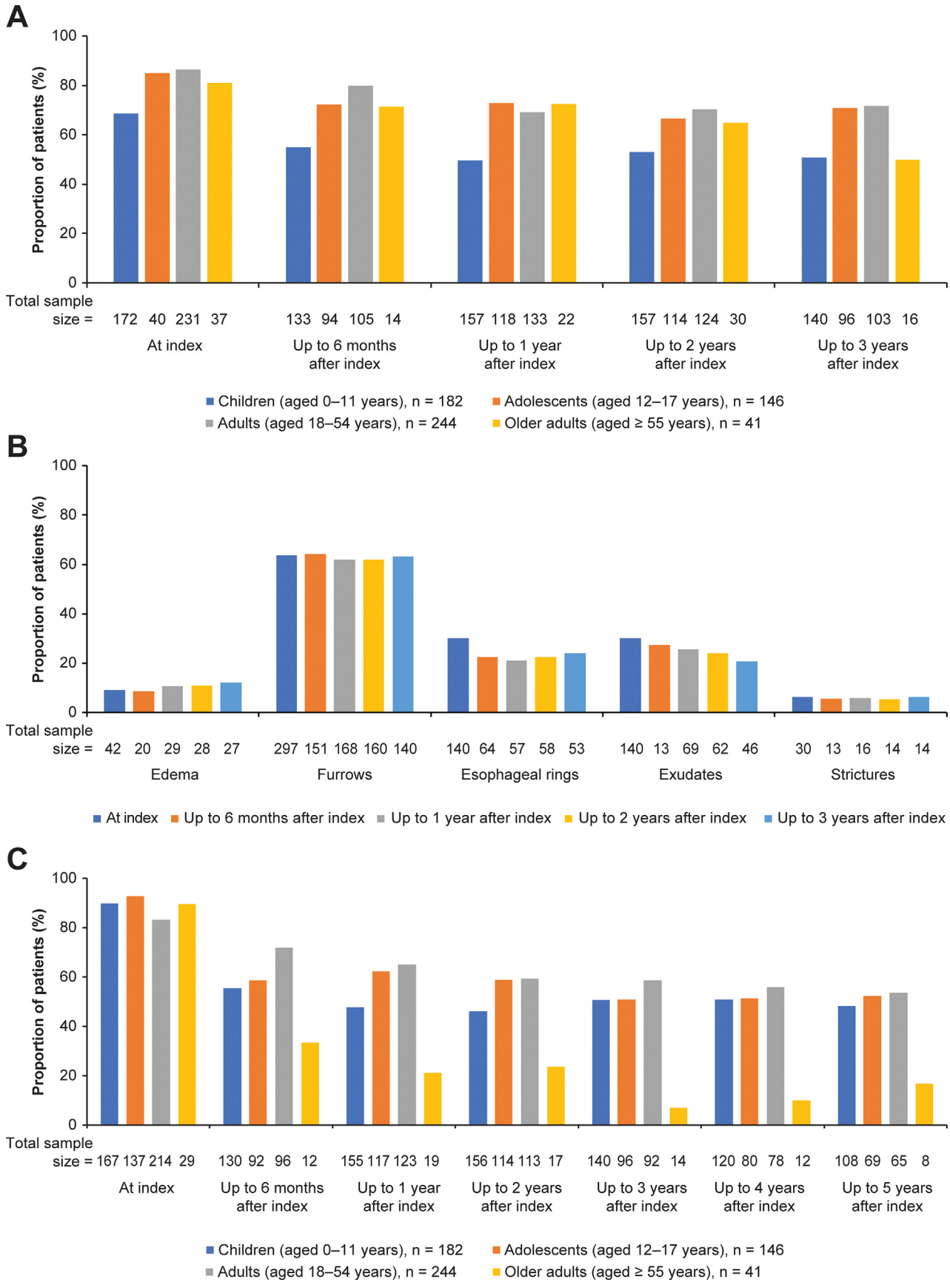

Figure 2. Proportion of patients with EoE, stratified by age group, with an abnormal esophageal endoscopic appearance[a] (A); with inflammatory and fibrostenotic endoscopic esophageal features at index and after index[a] (B); and with a peak eosinophil

Table 2. Summary of the Specialists Consulted by Patients With EoE During Follow-Up, and the Mean Time to Consultation From Index

First specialist consulted after index[a]	n (%)	Time to consultation from index, mo, mean (SD)	Second specialist consulted after index	n (%)	Time to consultation from index, mo, mean (SD)
Gastroenterologist only	347 (56.6)	1.4 (2.4)	None	161 (46.4)	–
			Allergist/immunologist only	137 (39.5)	3.8 (2.9)
			Dietitian/nutritionist only	36 (10.4)	3.2 (2.0)
Allergist/immunologist only	106 (17.3)	2.7 (2.4)	None	50 (47.2)	–
			Gastroenterologist only	30 (28.3)	4.9 (3.3)
			Dietitian/nutritionist only	26 (24.5)	3.9 (2.6)
Dietitian/nutritionist only	50 (8.2)	2.7 (2.6)	None	23 (46.0)	–
			Gastroenterologist only	16 (32.0)	4.0 (2.5)
			Allergist/immunologist only	11 (22.0)	3.6 (3.1)

EoE, eosinophilic esophagitis; SD, standard deviation.
[a]A smaller proportion of patients also consulted either an allergist/immunologist *and* a dietitian/nutritionist (2.3%); both a gastroenterologist *and* a dietitian/nutritionist (1.0%); a gastroenterologist, a dietitian/nutritionist, *and* a psychologist (0.2%); or a psychologist only (0.8%). Overall, 13.7% of patients did not consult with a specialist.

appearance and 177 (80.1%) had an EREFS score computed (mean [SD]: 1.7 [1.0]). At index, more adolescents (85.0%), adults (86.6%), and older adults (81.1%) had an abnormal esophageal appearance than children (68.6%). After index, percentages were lower in all ages, indicating a slight improvement; however, an abnormal appearance was observed in 62.3% of patients 3 years post index (Figure 2A). The most common endoscopic feature at index and after index was furrows in all ages; the proportions of patients presenting with these features did not substantially change after index (Figure 2B). Patients aged $<$ 18 years typically presented more often with inflammatory features (43.6% [103/236]) compared with fibrostenotic features (4.7% [11/236]) up to 3 years after index. Prior to index, only 4 patients (0.7%) had undergone esophageal dilation.

The proportion of all patients with a peak eosinophil count $>$ 15 eos/hpf decreased from index endoscopy to post index; however, 51.2% of patients had high peak eosinophil counts 3 years after index (Figure 2C). Post index, a smaller proportion of children and older adults had a peak eosinophil count $>$ 15 eos/hpf compared with adolescents and adults. The mean (SD) time to histologic response ($\leq$ 15 eos/hpf) was 12.1 (13.6) months in patients aged $<$ 18 years and 17.5 (21.7) months in those aged $\geq$ 18 years. The proportions of patients with peak eosinophil counts of $\leq$ 1, $\leq$ 6, or $\leq$ 15 eos/hpf were mostly similar between age groups, both at index and after index, although a greater proportion of patients met these thresholds after index (Table A4).

All-Cause and EoE-Related HCRU

Patients of all ages exhibited considerable all-cause HCRU, with more than half of patients visiting an emergency department for any reason during the follow-up period (Table A5). Across all ages, the mean number of emergency department visits was approximately 1 visit per patient annually. Most patients were treated as outpatients irrespective of age (99.7% [611/613]). During the follow-up period, only 13.9% of patients had an emergency department visit associated with EoE (Table A6). EoE-related inpatient visits were observed for 5.2% of patients after index. Similar to all-cause utilization, most patients (97.2%) had an EoE-related office or outpatient visit after index. For additional information, see the Supplementary Material.

Specialist Type Consulted

Overall, 529 patients (86.3%) in the total population consulted with a specialist during follow-up: 56.6% consulted with a gastroenterologist, 17.3% with an allergist/immunologist, 8.2% with a dietitian/nutritionist, 2.3% with an allergist/immunologist *and* a dietitian/nutritionist, and 2.0% consulted other types of specialist in the first instance (Table 2). Mean (SD) time, in months, from index to the first consultation with a specialist was 1.4 (2.4) for a gastroenterologist, 2.7 (2.4) for an allergist/immunologist, and 2.7 (2.6) for a dietitian/nutritionist (Table 2). During follow-up, approximately half of all patients who consulted 1 specialist did not go on to consult with a second specialist. Overall, 13.7% of patients did not have a documented consultation

count of $>$ 15 eos/hpf at index and after index (C). Panel C: Reprinted from Gastroenterology, 160, Ayodele O et al., Persistence of abnormal endoscopy and biopsy findings in patients with eosinophilic esophagitis in a real-world setting in the USA, S263–S264, Copyright (2024), with permission of Elsevier.
[a]Abnormal esophageal endoscopic appearance was reported based on the visual endoscopic findings, which may have included inflammatory or fibrostenotic endoscopic features: edema, furrows, esophageal rings, exudates, or strictures. EoE, eosinophilic esophagitis; eos/hpf, eosinophils per high-power field.

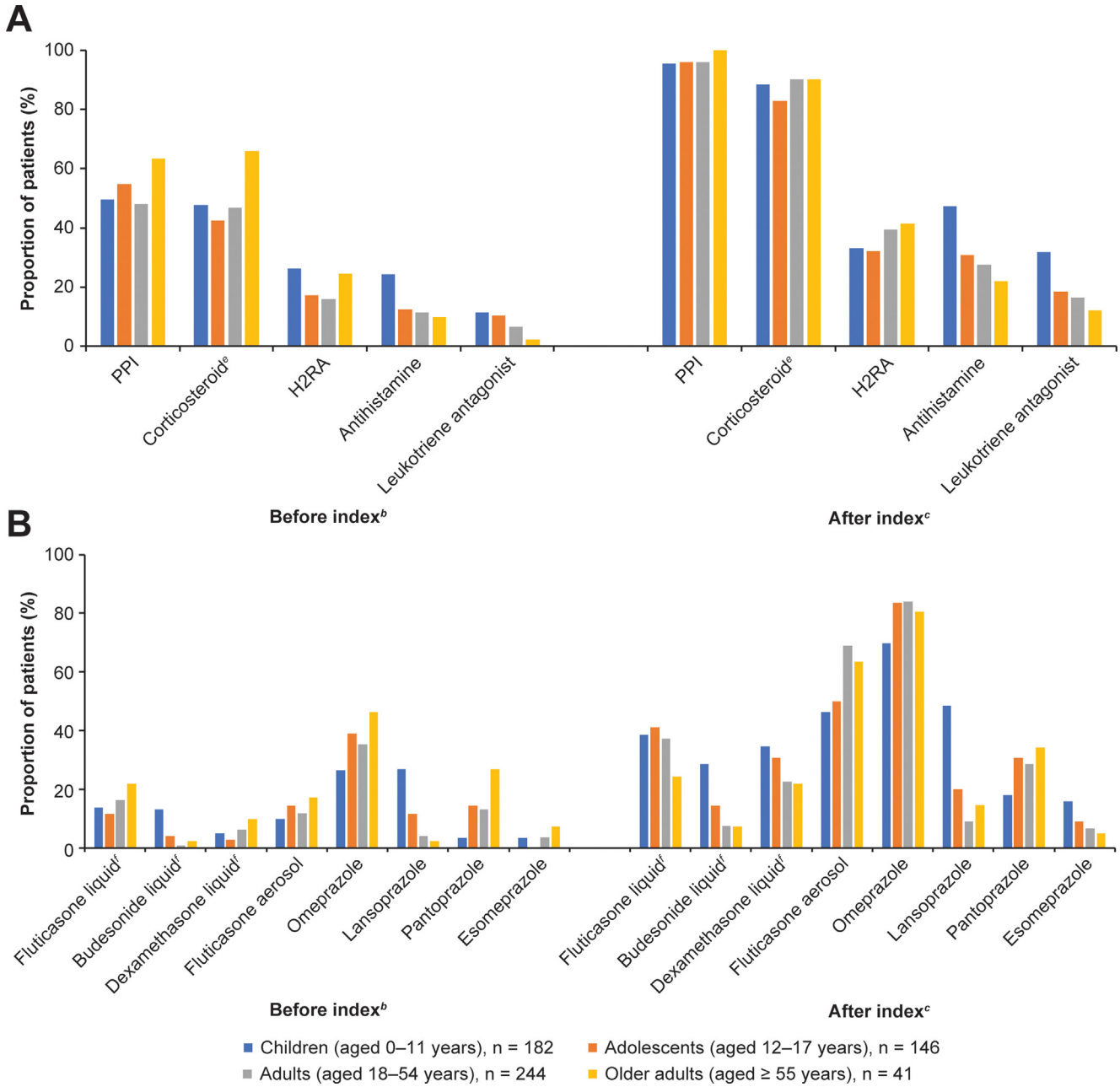

Figure 3. Summary of pharmacological treatments (A) and most commonly used topical (liquid and aerosol) corticosteroids and PPIs[a] (B) used for any condition by patients with EoE stratified by age group before[b] and after[c,d] index. [a]The most commonly used pharmacological treatments were corticosteroids and PPIs. [b]Calculated as the 12-month period before index. [c]Calculated for patients with a minimum of 12 months of follow-up after index. [d]The mean (SD) duration of follow-up was 68.9 (29.2) months among children, 63.6 (29.0) months among adolescents, 56.1 (28.9) months among adults, and 44.4 (23.4) months among older adults. [e]Corticosteroids included tablets, liquids, aerosols, creams, and ointments. [f]Liquid formulations included solutions, concentrates, suspensions, and syrups. EoE, eosinophilic esophagitis; H2RA, histamine-2 receptor antagonist; PPI, proton pump inhibitor; SD, standard deviation.

with a specialist in their medical record post index. During follow-up, more children and adolescents than adults and older adults consulted with a second specialist (Table A7).

Pharmacological Treatment Patterns

Before the index date, the most commonly used pharmacological treatments for any condition were proton pump inhibitors (PPIs) and corticosteroids (irrespective of dosage form); these were prescribed to 51.1% and 47.3% of all patients, respectively. Treatment use increased after index to 96.1% and 87.9% of all patients, respectively. Use of both PPIs and corticosteroids (irrespective of dosage form) was higher in patients aged ≥ 55 years than in other age groups before the index date (Figure 3A); after index, use of both was similar by age group (Figure 3A). In terms of first-line

Table 3. Outcomes that Illustrate the Journey Experienced by Patients With EoE Stratified by Age After Index

Event, n (%)	Children, 0–11 y old (n = 182)	Adolescents, 12–17 y old (n = 146)	Adults, 18–54 y old (n = 244)	Older adults, ≥ 55 y old (n = 41)	All patients (N = 613)	Time from index to event, mo, median (Q1, Q3) (all patients, N = 613)
Outcomes suggestive of plausible disease progression						
Incident diagnosis of esophageal stricture, dysphagia, food impaction, or performance of mechanical dilation[a]	18 (9.9)	22 (15.1)	38 (15.6)	7 (17.1)	85 (13.9)	24.0 (11.8, 42.7)
Initiation of pharmacological treatment,[b] switching or augmentation of PPIs to/with corticosteroids (excluding cream-based and ointment-based corticosteroids)	89 (48.9)	83 (56.9)	124 (50.8)	22 (53.7)	318 (51.9)	14.9 (7.8, 31.3)
Complications or events related to disease progression[c]	99 (54.4)	92 (63.0)	135 (55.3)	25 (61.0)	351 (57.3)	38.3 (12.0, NA)[d]
Outcomes suggestive of plausible disease remission						
Histologic remission during follow-up[e]						
≤ 1 eos/hpf	38 (25.3)	24 (18.9)	12 (6.7)	4 (15.4)	78 (16.2)	9.4 (4.9, 22.4)
≤ 6 eos/hpf	68 (45.3)	39 (30.7)	25 (14.0)	9 (34.6)	141 (29.3)	8.6 (4.4, 19.0)
≤ 15 eos/hpf	85 (56.7)	59 (46.5)	44 (24.7)	12 (46.2)	200 (41.6)	7.1 (3.7, 16.5)
Discontinuation of pharmacological treatment, without switching or augmentation to another EoE-specific treatment or incident diagnosis of esophageal stricture, dysphagia, food impaction, or performance of mechanical dilation[f]	79 (47.3)	55 (39.3)	105 (44.5)	17 (43.6)	256 (44.0)	16.4 (7.4, 31.2)

Calculated for patients with a minimum of 12 mo of follow-up after index and evaluated after 3 mo from the latest of the index date or the first observed diagnosis of EoE. The date of a specific event, consistent with progression, was the earliest of any of these events. Time to event was estimated using Kaplan–Meier analyses (patients who did not have events were censored).

CI, confidence interval; EoE, eosinophilic esophagitis; eos/hpf, eosinophils per high-power field; NA, not available; PPI, proton pump inhibitor; Q1, lower quartile; Q3, upper quartile.

[a]Among patients without a mechanical dilation before index.

[b]Included antihistamines, corticosteroids (excluding cream-based and ointment-based corticosteroids), histamine-2, receptor blockers, leukotriene antagonists, and PPIs.

[c]Complications or events were diagnosis of esophageal stricture, dysphagia, or food impaction; performance of mechanical dilation; or initiation of pharmacological treatment, switching, or augmentation of treatments. The earliest of any of the events was considered as the date of disease progression.

[d]95% CI, 32.9–47.2.

[e]In patients with a peak eosinophil count of > 15 eos/hpf at the index endoscopy with biopsy.

[f]Patients receiving PPIs or corticosteroids within 3 mo at index or after the first observed EoE diagnosis.

medications, PPIs only (50.7% [311/613]), topical corticosteroids plus PPIs (combination therapy; 33.8% [207/613]), and topical corticosteroids only (9.8% [60/613]) were the most used after index. The use of specific PPIs and corticosteroids for any condition before and after index stratified by age is shown in Figure 3B. After index, only 5 patients (0.8%) did not receive any treatment. For patients whose first-line medication was a PPI only, their most common second-line medication was either a topical corticosteroid (34.1% [106/311]) or a topical corticosteroid plus PPI (combination therapy, 18.3% [57/311]). However, 17.0% (53/311) of these patients discontinued their first-line medication and did not initiate a second-line medication. For patients whose first-line medication was a combination therapy of a topical corticosteroid and PPI, second-line treatment was most commonly a tablet corticosteroid (23.7% [49/207]) or a tablet corticosteroid-based combination treatment (18.8% [39/207]). However, 18.4% (38/207) of these patients discontinued their first-line medication and did not initiate a second-line medication. For patients whose first-line medication was a topical corticosteroid only, second-line treatment was most commonly a PPI only (41.7% [25/60]) or another topical corticosteroid (25.0% [15/60]). However, 6.7% (4/60) of these patients discontinued their

first-line medication and did not initiate a second-line medication. Irrespective of whether a patient saw a gastroenterologist only, an allergist/immunologist only, or both, a high proportion of patients were prescribed PPIs by these physicians after index (94.4%, 98.0%, and 97.0%, respectively). This was similar for corticosteroids (irrespective of dosage form; 79.5%, 96.0%, and 93.9%, respectively). The proportion of patients receiving PPIs and corticosteroids (all dosage forms) after index was also found to be similar irrespective of whether a patient had received a dietary modification or not (dietary modification vs no dietary modification: 96.6% vs 96.4% [PPIs]; 90.4% vs 84.2% [corticosteroids – all dosage forms]). Post index, PPIs and corticosteroids (irrespective of the dosage form) were initiated after a median of 3 and 92 days, respectively. For additional information on topical corticosteroids, see the Supplementary Material.

Dietary Modification

After index, food avoidance/elimination was used by 57.9% of all patients. The most common food avoidance/elimination was a 6-food elimination diet; this was used most commonly by adolescents (70.8%) and children (62.3%) (Table A8). A greater proportion of the total population who consulted both a gastroenterologist and an allergist/immunologist (78.8%) or an allergist/immunologist only (66.0%) used food avoidance/elimination than patients who visited a gastroenterologist only (38.5%) after index (Table A8).

Markers of Disease Progression and Remission

Outcomes illustrating the journey experienced by patients with EoE are summarized in Table 3. The incident diagnosis of esophageal stricture (3.9%), dysphagia (7.0%), food impaction (1.6%), or performance of mechanical dilation (4.2%) after index was observed in 13.9% of all patients; the median (Q1, Q3) time to the earliest of these events, suggestive of possible disease progression, was 24.0 (11.8, 42.7) months. Overall, 83.3% (20/24) of patients who did not receive any treatment within 3 months of the index date or first EoE diagnosis initiated pharmacological treatment after index. Of patients who were using PPIs or corticosteroids within 3 months of the index date or first EoE diagnosis, 19.9% (116/582) switched and 31.3% (182/582) augmented their treatment after 3 months, respectively (suggestive of possible disease progression) – 44.0% (256/582) discontinued their first treatment after index; the median (Q1, Q3) time to discontinuation was 16.4 (7.4, 31.2) months (suggestive of possible disease remission). Among patients with a peak eosinophil count of $>$ 15 eos/hpf at the index endoscopy with biopsy, clinical histologic remission ($\leq$ 15 eos/hpf) was observed in 41.6% (200/481) of patients post index; the median (Q1, Q3) time to remission was 7.1 (3.7, 16.5) months. Similar findings were observed for $\leq$ 1 and $\leq$ 6 eos/hpf (Table 3). Histologic remission ($\leq$ 15 and $\leq$ 6 eos/hpf) was more commonly observed in patients aged $<$ 18 years compared with patients aged $\geq$ 18 years ($\leq$ 6 eos/hpf: 38.6% vs 16.7%, respectively; $\leq$ 15 eos/hpf: 52.0% vs 27.5%, respectively; both $P < .001$). Additionally, histologic remission ($\leq$ 15 and $\leq$ 6 eos/hpf) was observed in a higher proportion of patients who had a preindex gastroenterologist consultation compared with patients who did not ($\leq$ 6 eos/hpf: 38.0% vs 17.3%, respectively; $\leq$ 15 eos/hpf: 51.3% vs 28.2%, respectively; both $P < .001$). No differences were observed by sex (Table A3).

Discussion

This retrospective observational cohort study used EMR data and linked claims data from a rural integrated US healthcare system to assess the therapeutic journey and burden of EoE in a real-world setting in the United States. We found that a substantial portion of patients with EoE received variable medical treatments, and did not report undergoing follow-up care, consulting with specialists, or routinely undergoing endoscopy with biopsy after diagnosis; the reasons for this are unknown, but experiences do not appear to be consistent with current guideline recommendations.[6]

As a result, patients may have experienced persistent disease activity and had difficult therapeutic journeys. For example, patients with EoE had multiple EoE-associated symptoms and comorbid gastro-esophageal and atopic conditions, in line with previous studies[3]; these commonly increased after index. Importantly, almost 30% of adults did not undergo repeat endoscopy; patients aged $<$ 18 years and patients who had a preindex consultation with a gastroenterologist were found to be more likely to have a repeat endoscopy. This is supported by a recent claims study which found that approximately 26% of adults did not have a follow-up endoscopy within 12 months,[5] and a survey among gastroenterologists suggested that only 45% would repeat endoscopy to monitor histologic response upon symptom resolution.[24] Nevertheless, this study found that when endoscopy was repeated, an abnormal esophageal endoscopic appearance was observed in more than half of the endoscopies performed up to 3 years post index. Similarly, although patients experienced a decrease in peak eosinophil counts over time, histologic activity was observed in some patients up to 3 years after index, placing them at risk of progressive esophageal dysfunction.[25] This is exemplified by finding that 14% of patients in this study had a new incident diagnosis of esophageal stricture, dysphagia, or food impaction, or performance of mechanical dilation post index. Additional data stratifications by type of treatment could be performed in the future to determine if this correlates with the poor histologic and endoscopic responses observed post index in some patients.

Regardless of age, patients had substantial all-cause HCRU; more than half of the total population had all-cause

emergency department visits and nearly 1 in 5 had an all-cause inpatient admission. This high burden to the healthcare system is consistent with the findings of previous studies, which have also shown higher direct medical costs in patients with EoE vs matched controls.[5,12] Patients with EoE consulted with a range of specialists during follow-up, although 13.7% did not have a consultation with any specialist post index. A recent study (2022), which reported a similar proportion of patients (14%) with a 'gap' in medical contact for EoE, found this correlated with signs of increased disease progression.[26] This highlights the necessity of maintaining a form of medical care with patients following their EoE diagnosis.

Pharmacological treatment use by patients with EoE increased after diagnosis. The most common treatments were PPIs and corticosteroids; similar trends were observed in a recent real-world European study.[27] PPIs (conditionally recommended for symptomatic esophageal eosinophilia)[6] were used earlier and more frequently than corticosteroids, and almost a third of patients were prescribed both concomitantly despite current guidelines strongly recommending topical corticosteroids for patients with EoE.[6] This may be explained by the introduction of the current management guidelines in 2020,[6] prior to which PPIs were strongly recommended to exclude PPI-responsive esophageal eosinophilia.[28] However, it could also be that the diagnosis of GERD increased after index. Additionally, 44% of patients discontinued their first pharmacological treatment after the index date or first EoE diagnosis. Poor treatment adherence among patients with EoE is reported in the literature[29,30]; time to treatment discontinuation in our study was found to be 16.4 months, which may be suggestive of possible disease remission or a lack of treatment adherence. More than half of patients were using food avoidance/elimination and, regardless of age, the most common food avoidance/elimination among patients was a 6-food elimination diet.

Limitations of this study included the potential overutilization or underutilization of specific diagnosis codes, which may have impacted the estimation of the number of patients with EoE (although validation of a diagnosis of EoE was performed); the use of PPIs for a condition other than EoE (eg, GERD); the unlikely but possible contribution of topical corticosteroids for other conditions potentially affecting the EoE disease course; that time to disease progression analyses were exploratory and limited by the study database (eg, markers of disease progression were indirect); and that only patients who were receiving medical care through the healthcare system's plan were examined. This study only reports some comparative analyses; however, potentially useful data stratifications for future consideration include comparing patients with or without disease progression and by other specialist consultation. In addition, the histologic/endoscopic data could be further stratified by the number of concomitant treatments patients received. Although both men and women were eligible for inclusion in this study, the population was predominantly comprised of White men. These demographics reflect the epidemiology of EoE reported in the real world[13]; however, prevalence among other racial and ethnic populations is thought to be under-reported.[15] For these reasons, subgroup analyses by sex or race were not performed for all data as some of the groupings, particularly when further stratifying by age, were small (a subanalysis by sex was performed for the histologic remission and follow-up endoscopy). Additionally, research has shown that differences by race and age are typically more pronounced than differences by sex.[14,17,18] Data for this study were obtained from a rural integrated US healthcare system, and given the known healthcare disparities between rural and urban populations in the United States,[31,32] our findings may not be considered generalizable to the US population as a whole. However, this study represents a large and robust retrospective analysis that used both EMR and claims data to answer important questions surrounding the complicated real-world experience of patients with EoE in the United States. Future research can build on this work to conduct additional comparative analyses using identified covariates; stratifying these data by disease severity, for example, would be of interest. Further research is warranted to explore the reasons patients do not receive care that follows current guideline recommendations, which, in turn, may help improve the management of patients with EoE.

Conclusion

Our findings outline the persistent disease activity and difficult therapeutic journeys faced by patients with EoE irrespective of their age, as well as the substantial disease burden. This is exemplified by the range of signs and symptoms experienced, the presence of abnormal endoscopic and histologic findings despite medical treatment, the high HCRU among all age groups, and disease progression in a proportion of these patients. These data highlight the potential unmet medical need of patients with EoE in the United States.

Supplementary Materials

Material associated with this article can be found in the online version at https://doi.org/10.1016/j.gastha.2024.02.007.

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The authors disclose the following: Olulade Ayodele, Bridgett Goodwin, James Williams, and Nirav K. Desai are employees of Takeda Development Center Americas, Inc, and stockholders of Takeda Pharmaceutical Company Limited. Rohan C. Parikh and Elizabeth Esterberg are employees of RTI Health Solutions and were funded by Shire Human Genetic Therapies, Inc, a Takeda company, to perform this study. Mayank Ajmera was an employee of RTI Health Solutions at the time of this study and was funded by Shire Human Genetic Therapies, Inc, a Takeda company, to perform this study. David A. Katzka has received research funding from Shire, a Takeda company, and a consulting fee from Receptos/Celgene. David A. Katzka is a member of the Board of Editors. Their paper was handled in accordance with our conflicts of interest policy. See https://www.ghadvances.org/content/authorinfo#conflict_of_interest_policy for full details.

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Ethical Statement:
The International Institutional Review Board for RTI reviewed the study protocol and determined that the study did not involve human patients and was therefore exempt from full Institutional Review Board review.

Data Transparency Statement:
Takeda are unable to share data supporting results reported in this article. Sharing of data is restricted as per the license it was acquired under from MedMining to conduct this study.

Reporting Guidelines:
STROBE.