Disease Burden and Unmet Need in Eosinophilic Esophagitis

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Eosinophilic esophagitis (EoE) is a chronic, progressive, type 2 inflammatory disease of increasing prevalence, characterized by symptoms of dysphagia and reduced quality of life. A dysregulated type 2 immune response to food and aeroallergen leads to barrier dysfunction, chronic esophageal inflammation, remodeling, and fibrosis. Patients with EoE have impaired quality of life because of dysphagia and other symptoms. They may also suffer social and psychological implications of food-related illness and expensive out-of-pocket costs associated with treatment. Disease burden in EoE is often compounded by the presence of comorbid type 2 inflammatory diseases. Current conventional treatments include elimination diet, proton pump inhibitors, and swallowed topical corticosteroids, as well as esophageal dilation in patients who have developed strictures. These treatments demonstrate variable response rates and may not always provide long-term disease control. There is an unmet need for long-term histologic, endoscopic, and symptomatic disease control; for targeted therapies that can normalize the immune response to triggers, reduce chronic inflammation, and limit or prevent remodeling and fibrosis; and for earlier diagnosis, defined treatment outcomes, and a greater understanding of patient perspectives on treatment. In addition, healthcare professionals need a better understanding of the patient perspective on disease burden, the disconnect between symptoms and disease activity, and the progressive nature of EoE and the need for continuous monitoring and maintenance treatment. In this review, we explore the progression of disease over the patient's lifespan, highlight the patient perspective on disease, and discuss the unmet need for effective long-term treatments.

Am J Gastroenterol 2022;117:1231–1241. https://doi.org/10.14309/ajg.0000000000001777

INTRODUCTION

Eosinophilic esophagitis (EoE) is a chronic, progressive, type 2 inflammatory disease characterized by esophageal dysfunction and T-helper type 2 (Th2)-mediated inflammation, believed to be triggered by abnormal type 2 immune responses to food and probably, aeroallergens. Chronic esophageal inflammation, including type 2-associated inflammatory infiltrates, chemokines, and cytokines, leads to barrier dysfunction, remodeling, fibrosis, and stricture formation, with corresponding worsening of dysphagia (1). Patients with EoE have substantially impaired quality of life (QoL) because of EoE symptoms, including dysphagia and food impaction in adults and reflux and failure-to-thrive in children, and the social and psychological implications of food-related illness (2,3). Many adult patients with EoE suffer from mental distress, possibly because of continuous symptoms and acute esophageal food impactions (4–6).

Treatment options for patients with EoE include dietary restriction, proton pump inhibitors (PPIs), swallowed topical corticosteroids (STCs), and dilation of the esophagus. Elimination diets, often very effective, can be problematic to maintain long term, particularly for older children and adults, and may involve financial cost (7). Pharmacological nontargeted daily treatments are limited by adherence and exhibit variable response rates in individual patients. Currently, only one treatment, recommended in professional guidelines (8–10), a budesonide orodispersible tablet, has received European Medicines Agency approval (11), and a budesonide oral suspension was previously under US FDA review (12,13). There is an unmet need for safe and effective treatments offering long-term histologic, endoscopic, and symptomatic disease control in a convenient dosing regimen. Targeted therapies are needed to restore the esophageal barrier, normalize the immune response to triggers, reduce chronic inflammation, and limit or prevent progression of remodeling and fibrosis to restore esophageal function and reduce patient burden. In addition, there is an unmet need for earlier diagnosis, defined treatment outcomes, and a greater understanding of patient perspectives on treatment (14,15).

The objectives of this review are to explore the progression and pathophysiology of EoE over the patient's lifespan and to highlight patient perspectives on disease burden and unmet need for safe and effective long-term treatment.

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Received December 23, 2021; accepted April 4, 2022; published online April 13, 2022

Methodology

Two advisory board meetings (type 2 inflammation and EoE-focused) and discussions with key opinion leaders highlighted a need to educate gastrointestinal specialists on the increasing prevalence, disease burden, unmet need, natural history, and evolving evidence connecting the type 2 immune response, beyond eosinophils, to the progressive signs and symptoms of EoE. The authors of this narrative review were invited by Sanofi and Regeneron Pharmaceuticals, to contribute based on their specific expertise, which was key and relevant to the article. To ensure relevant data and content were included, the authors searched Google Scholar, PubMed, and EBSCO on April 9, 2021, for previous studies and reviews that assessed EoE disease burden and unmet need using multiple search terms including "epidemiology," "natural history," "pathogenesis," "pathophysiology," "disease progression," "phenotype," "endotype," "molecular and cellular mechanisms of disease," "allergic march," "therapy," "treatment response," and "unmet need." Selected references were reviewed and narrowed down by the authors for inclusion. The authors added new references throughout development to reflect advances in the literature and/or changing content. The concept and design of the manuscript was devised by industry representatives and authors and further developed by all authors. Sanofi and Regeneron Pharmaceuticals reviewed the final review article for legal or patent issues; however, the authors had overall control of article content and the decision to submit.

EoE prevalence and etiology

The prevalence and incidence of EoE are rapidly increasing (Figure 1) (16–20). Although improved diagnostics and disease recognition have contributed to this, the increase in EoE cases outpaces increases in biopsy and detection (21,22).

Many factors influence the development of EoE, including environmental factors, such as climate, geography, population density, housing materials, and water and air quality, and prenatal and early life factors, particularly those associated with gut colonization and dysbiosis, and atopic disease in childhood (23–35).

The predominance of white male patients and increased relative risk within families suggests genetic risk; indeed, many genes and associated genetic disorders have been identified (36,37). Four main categories of gene loci associated with EoE have been identified: Th2 signaling, epithelial barrier function, fibrosis, and genetic defects associated with multiple atopic comorbidities (23,36,38). Genetic susceptibilities may interact with environmental factors to contribute to the development of EoE (30).

Atopic diseases are increasing in westernized countries, often concurrently, and sharing common pathophysiologic features, including genetic susceptibility, epithelial barrier dysfunction, and dysregulated type 2 inflammatory responses (39). Comorbid type 2 inflammatory diseases are more common in children than in adolescents or adults (40) with an overall incidence of 6%–70% of patients having allergic rhinitis, asthma, atopic dermatitis, and IgE-mediated food allergy (41). Patients with type 2 inflammatory comorbidities, particularly IgE-mediated food allergy, are at risk of the development of EoE, and EoE has been proposed as a member of atopic march (41,42). These comorbid phenotypes underscore the common dysregulated type 2 immune response as the source of multiple expressions of atopic disease.

EoE pathophysiology

Triggered by food and aeroallergens, the type 2 cytokines IL-4, IL-13, and IL-5 act in concert with Th2 cells, eosinophils, mast cells, basophils, and group 2 innate lymphoid cells weakening the esophageal epithelial barrier, increasing inflammatory cell infiltration, and maintaining a chronic inflammatory environment that over time favors esophageal remodeling and fibrosis; this in turn leads to increasing rates of dysphagia and esophageal food impaction (Figure 2) (56,57).

The natural history of EoE is suggested by studies evaluating the association of disease duration with inflammatory or fibrostenotic phenotypes (Figure 3). Those with inflammatory phenotype tend to be younger with comorbid atopic conditions and food allergies (58); more fibrostenotic complications are observed in older age groups (59,60). Diagnostic delays and lapses in follow-up (61) contribute to a longer duration of untreated EoE and an increase in the likelihood of fibrostenotic complications (62,63). For every 10-year increase in age, the odds of having a fibrostenotic phenotype more than doubles, suggesting a natural history of disease progressing from a largely inflammatory to a more fibrostenotic phenotype over time (58,64–66). However, there is significant diversity in the pattern and rate of disease progression (67), and fibrostenosis has been observed in children.

Clinical manifestations, disease features, and diagnosis

The primary clinical manifestations of EoE in adults and children 10 years and older, as a result of inflammatory damage to the esophageal epithelium and subepithelium (e.g., lamina propria and muscularis layer), are dysphagia and food impaction (10). These symptoms lead to substantially impaired QoL (68–71). Chronic inflammation of the esophagus may also lead to remodeling and fibrosis, highlighting the need for early diagnosis and management. Typical remodeling features in EoE include fixed or transient rings, strictures, mucosal fragility (also known as "crêpe-paper esophagus"), and narrow-caliber esophagus. Inflammatory features include white plaques or exudates, furrows, and edema (Figure 4) (56). Common histological findings of esophageal biopsies in EoE include eosinophil-rich inflammation, basal zone hyperplasia, dilated intercellular spaces, and thickened lamina propria fibers (73), which can persist even if eosinophil counts have returned to normal levels. From a limited number of samples, we know that EoE is a transmural disease. Peak eosinophil counts tend to be highest in the epithelial layer and lowest in the subepithelial layer; however, in one-third of patients, higher eosinophil values are observed in the subepithelial layer compared with the epithelial layer (74). A high-resolution imaging study in children with EoE demonstrated thickening of all layers of the esophagus, including expanded muscular layers, compared with healthy controls (75). The contribution of deeper layers of the esophagus to EoE beyond those evaluated endoscopically and histologically is a key area of active research and likely to substantially contribute to our understanding of EoE progression.

The diagnostic criteria for EoE are symptoms of esophageal dysfunction and the histological presence of eosinophils in the esophagus, with a threshold of 15 eosinophils per high-power field (hpf) (10,22). Research tools for the evaluation of EoE include the Histology Scoring System (HSS) (73), Endoscopic Reference Score (EREFS) (76,77), Dysphagia Symptom Questionnaire (78), EoE Symptom Activity Index (79), Pediatric EoE Symptom Score (v2.0) (80), and EoE diagnostic panel (81);

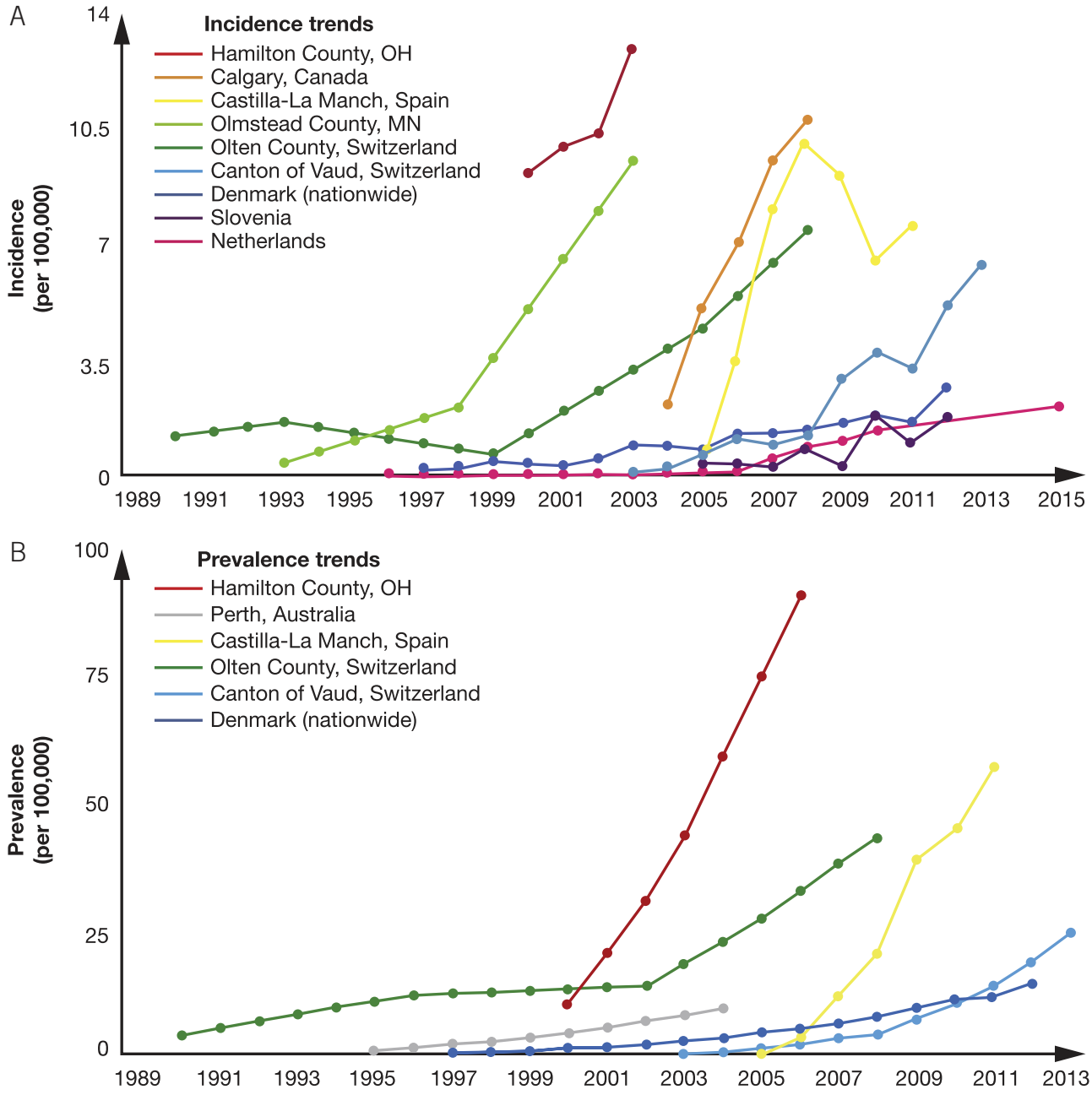

Figure 1. Increasing prevalence of EoE over time. (**a**) Increasing incidence of EoE over time from population-based studies and (**b**) prevalence of EoE over time from population-based studies. EoE, eosinophilic esophagitis (reproduced with permission from Dellon and Hirano, 2018) (16).

(Table 1). Efforts to translate these research tools into clinically applicable practical guidelines are underway. It is likely that diagnosed cases of EoE represent the tip of the iceberg: For each clinically identified case, there are likely many more "beneath the surface" that are misdiagnosed, subclinical, or at a yet-to-be-detected earlier disease stage (Figure 5). Table 2 gives 10 suggestions for better EoE diagnosis and treatment.

Current treatment landscape

First-line therapies First-line therapies for EoE include dietary restriction, STCs, PPIs, and potentially esophageal dilation (Figure 6) (8). Differences in initial choice may reflect evolving clinical guidelines (84) and shared decision-making with patients (8). PPIs fail to induce histologic remission in roughly two-thirds of patients, and STCs, in roughly one-third of patients. However, predictors of therapeutic response are lacking (8). Additional research is needed to understand which therapy is best as initial treatment for patients of different phenotypes and prospective trials designed to evaluate combination therapy are needed. Regardless of first-line therapy choice, shared decision-making with patients is key to securing adherence and optimal outcomes (84).

Lack of long-term disease control, side effects, and adherence limit the effectiveness of available treatments. PPIs are not effective in all patients, with response rates of 33%–75% (85–87). STCs such as fluticasone coat the esophagus, providing symptomatic relief and inflammatory effect (88); they are effective at

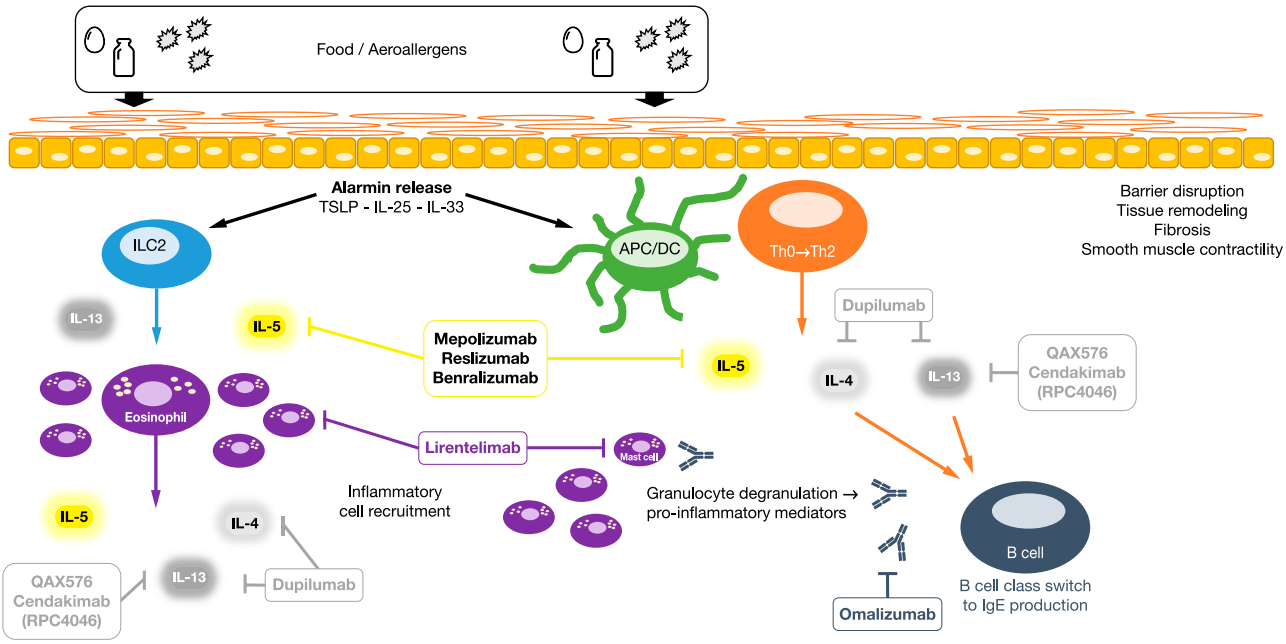

Figure 2. A simplified overview of the type 2 inflammatory processes that drive the pathophysiology of EoE. Aeroallergens and food allergens trigger the esophageal epithelium to the release alarmins from which then polarize downstream pathways toward an aberrant type 2 inflammatory response. Type 2 cytokines, most notably IL-4, IL-5, and IL-13, and other proinflammatory mediators drive localized eosinophilia alongside the recruitment of inflammatory cells to the esophageal epithelium. IgE triggers granulocyte degranulation, releasing additional proinflammatory mediators, which promote a positive feedback loop. The resultant chronic inflammation ultimately leads to tissue remodeling and fibrosis. Several therapies are in development that target specific drivers of these pathways. Most notably, dupilumab (inhibits IL-4 and IL-13 through IL-4 receptor α), QAX576 and RPC4046 (mAb to IL-13), mepolizumab and reslizumab (inhibits IL-5), benralizumab (inhibits IL-5 receptor α), and omalizumab (anti-IgE antibody and lirentelimab) (anti-Siglec8 [sialic acid-binding immunoglobulin-like lectin] mAb) (43–55). APC/DC, antigen presenting cell/dendritic cell; EoE, eosinophilic esophagitis; ILC2, innate lymphoid cell type 2; Th, T-helper cell; TSLP, thymic stromal lymphopoietin.

inducing histologic response in roughly two-thirds of patients and are generally well tolerated in short- and long-term studies (1,9,12,89). However, cumulative side effects of long-term steroid use may be a concern for some patients, and STCs are not approved worldwide. Elimination diets are difficult to maintain long term and can be expensive (7). Several studies have evaluated the 1-food (cow milk protein) elimination diet in children. However, no data are available in adults; methodologic issues limit the interpretation of these studies (90). More recent studies have demonstrated histologic remission in >50% of children and a similar efficacy to the 6-food elimination diet (91,92).

Currently available therapies do not provide the long-term disease control required to alleviate the substantial burden of disease experienced by patients. There is, therefore, a critical need for safe and effective targeted therapies that exert such control.

Emerging targeted therapies Type 2 inflammation-targeted systemic therapies represent an important potential treatment strategy for EoE, given their ability to treat the dysregulated type 2 immune response to environmental triggers (Figure 2). The IL-5-targeting agents mepolizumab and reslizumab, commonly prescribed for severe eosinophilic asthma, showed histologic improvements in EoE but failed to induce symptomatic improvement, although the studies were powered to assess changes in eosinophil counts rather than any clinical outcomes (54,55,93). A phase 3 study of benralizumab in EoE (NCT04543409) is currently ongoing. Omalizumab, a humanized mouse anti-IgE antibody used for severe allergic asthma, caused no improvement in EoE symptoms or reduction in eosinophils in the esophagus (45). Although a study of the anti-IL-13 antibody, QAX576, did not meet the primary endpoint (proportion of patients with a 75% reduction in peak esophageal eosinophil counts), esophageal eosinophil counts were reduced compared with placebo (53). Cendakimab (RPC4046), an anti-IL-13 antibody, reduced eosinophil counts and improved histologic and endoscopic outcomes in a phase 2 study; dysphagia symptoms were not significantly improved. However, the study was underpowered to assess these outcomes (94,95). A phase 3 trial (NCT04753697) is currently in progress. In a phase 2 trial, lirentelimab, a monoclonal antibody (mAb) targeting the eosinophil and mast-cell transmembrane protein Siglec8, was associated with dysphagia improvement in a subset of patients with eosinophilic gastritis and/or duodenitis with concurrent EoE (44). A phase 2/3 trial evaluating lirentelimab in adults and adolescents with EoE (NCT04322708) is currently underway; improvement in symptoms was not achieved, despite meeting the histologic endpoint. Dupilumab, a fully human mAb, blocks the shared receptor component for IL-4 and IL-13. In a phase 2 (NCT02379052) and 3-part (part A/B/C) phase 3 study (NCT03633617) in adolescents/adults with EoE, dupilumab for 12 or 24 weeks (part A) improved peak esophageal intraepithelial eosinophil count, dysphagia, and disease-specific health-related QoL, reduced symptom burden, and was well tolerated; these effects were sustained up to 52 weeks in part C for patients who completed part A (1,96). Part B confirmed the efficacy and safety of dupilumab vs placebo observed in part A,

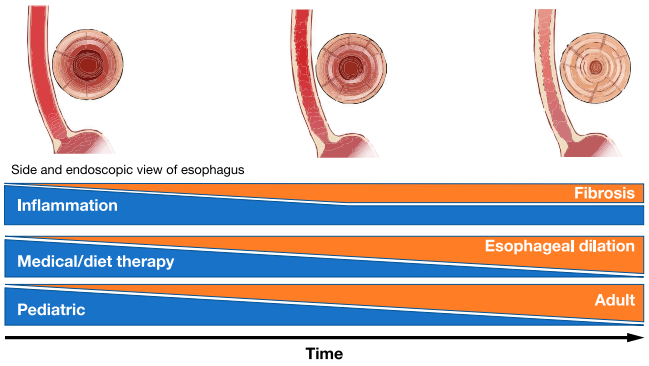

Figure 3. EoE disease progression. EoE disease progresses over time, from an inflammatory phenotype with fewer endoscopic findings, typically treated with medical or diet therapy, to a more fibrotic phenotypes, with evidence of strictures, typically treated with dilation. EoE, eosinophilic esophagitis (reproduced with permission Dellon and Hirano, 2018) (16).

with significant improvements in histologic and symptomatic aspects of EoE at week 24 in a larger sample size of adolescents and adults with EoE. There is also an ongoing phase 3 trial (NCT04394351) in children (≥1 to <12 years) with EoE.

As novel therapies begin to emerge, there is a growing need for the full characterization and standardization of outcomes to better understand treatment responses and to facilitate the optimization and personalization of treatment pathways.

Understanding treatment responses

Treatment responses are yet to be fully defined. Recently, different definitions have been proposed for clinical, endoscopic, and histologic remission, response, and nonresponse, but not yet implemented on a large scale.

Another important question is: "When is a patient with EoE better?" Recent publications, cognizant of the discord between symptomatic, histologic, and endoscopic responses, propose comprehensive assessments across clinical, endoscopic, histologic, and QoL domains, using measures often only evaluated in clinical trials, such as HSS and EREFS, and those more commonly evaluated, including peak eosinophil count and patient-reported dysphagia and QoL measures (Table 1) (82). The following definitions of clinical treatment responses in EoE have been proposed (77): Complete response includes normalization of esophageal biopsies (<1 or <5 eosinophils/hpf), symptom elimination of >90% (or an EoE Symptom Activity Index score <20), and normalization of the esophagus (EREFS score <2); nonresponse includes persistent esophageal eosinophilia (≥15 eosinophils/hpf), persistent symptoms (<30% decrease in a patient-reported outcome), and persistent endoscopic findings (<30% decrease in the EREFS score) (77). It is noted that the middle ground of partial or incomplete response is wide in this framework; it is possible (and often likely) to have discordant responses across these 3 categories.

Because symptoms are not necessarily correlated with histologic or endoscopic disease status, there often exists a disconnect between patient experience of disease and physician perspective (77). This is particularly true in postdilation patients (97). Symptom-masking behaviors such as behavior modification toward food can also contribute to this. Anxiety and depression that impact QoL, particularly mental health, are not uncommon in patients with EoE (2,99). The disparities that exist between patient and physician perspectives emphasize a need for greater physician awareness of the

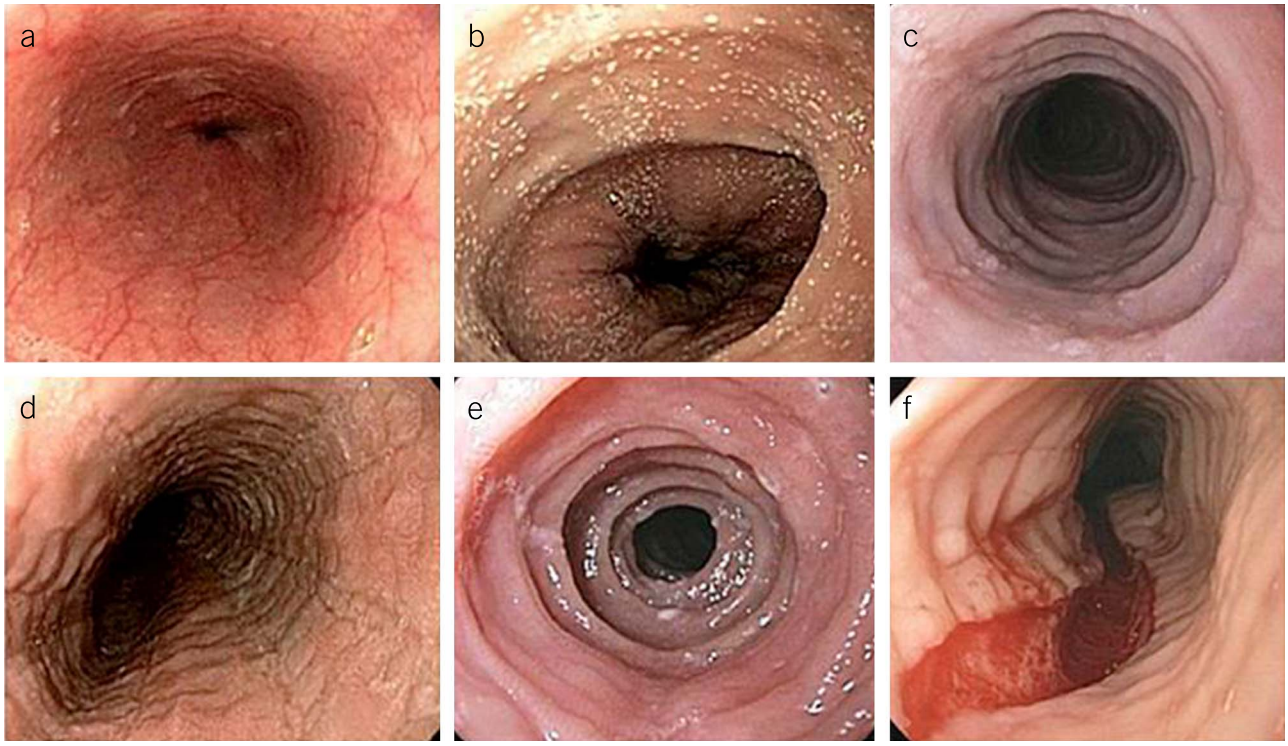

Figure 4. EoE endoscopic features. (**a**) Normal esophagus, (**b**) white pinpoint exudate, (**c**) concentric rings and linear furrows, (**d**) linear furrows, (**e**) concentric rings, and (**f**) longitudinal tear. EoE, eosinophilic esophagitis (reproduced from Lee et al., 2018 [open access]) (72).

Table 1. Tools for the evaluation of EoE

Tools	Description	Scoring	Reference
Eosinophilic esophagitis histology scoring system (HSS)[a]	A validated histologic scoring system to evaluate grade and stage of EoE pathology in esophageal biopsies	8 biopsy features scored separately for grade (severity) or stage (extent) of abnormality using a 4-point scale (0 = normal; 3 = most severe or extensive)	(Collins 2017) (73)
Eosinophilic esophagitis endoscopic reference score (EREFS)[a]	A validated endoscopic scoring system that evaluates the 5 major endoscopic features of EoE: edema, rings, exudates, furrows, and stricture	Edema (0–2), rings (0–3), exudates (0–2), furrows (0–2), and strictures (0–1), with 0 indicating the absence of the feature, and numbers 1, 2, or 3 representing presence or severity.	(Hirano 2013) (76)
Dysphagia symptom questionnaire (DSQ)[a]	A validated, patient-reported, 24-hr recall of dysphagia symptoms	The scoring algorithm is constructed from the responses to questions on presence (0–2) and severity (0–4) of dysphagia; higher scores indicating greater severity	(Dellon 2013) (78)
Eosinophilic esophagitis symptom activity index (EEsAI)[a]	A validated, patient-reported, 7-d symptom recall used in adults	Score range 1–100; includes 7 items that assess frequency and duration of dysphagia, severity of dysphagia, and behavioral adaptations; higher scores indicating greater symptom burden	(Schoepfer 2014) (79)
Pediatric eosinophilic esophagitis symptom score (PEESS v2.0)[a]	A patient-reported, 30-d symptom recall, validated in children 8 yr and older, and caregivers in children 2 yr and older	20 questions on symptoms, scored 0 to 4 scale; higher scores indicating greater symptom burden	(Franciosi 2011) (80)
Eosinophilic esophagitis diagnostic panel (EDP)[b]	An array of 96 genes developed for the identification of EoE	N/A	(Wen 2013) (81)

[a]Measures validated and recommended as a Core Outcome Set for Therapeutic Studies in Eosinophilic Esophagitis (82,83).
[b]Not currently used in clinical practice.

burden experienced by patients (77), alongside an acknowledgement of the discordance between symptomology and disease activity.

Furthermore, with the promise of multiple upcoming EoE treatment options comes an evolving need to understand the phenotypic and endotypic heterogeneity of patients to personalize therapeutic choice. Phenotypic variations in EoE include the age at onset, degree of atopic comorbidity, response to different forms of therapy, and endoscopic or histologic disease severity. Studies to define endotypes that predict/explain the variable response to treatment have been performed. A cross-sectional study using the EoE diagnostic panel along with HSS and EREFS identified 3 distinct endotypes of EoE: (i) the mildest, with biopsies resembling normal tissue; (ii) showing evidence of type 2 inflammation and of being refractory to STC; and (iii) associated with narrow-caliber esophagus and with the greatest endoscopic and histologic disease severity (100). These 3 endotypes are likely representative of the natural history of EoE over time. Endotypes have also been identified based on type 2 inflammatory gene expression, eosinophils and eosinophil chemotaxis, and mast cells. Heterogeneous type 2 gene expression is observed in patients with EoE and is not directly proportional to disease features such as eosinophil levels (64). The stability of these endotypes over time is incompletely understood. More work is needed to correlate genetic endotypes to clinical phenotypes.

Disease burden and healthcare resource utilization

EoE is a lifelong disease requiring invasive monitoring. Patients and caregivers experience chronic, symptom- and QoL-related disease burden besides the economic burden of a disease. In addition, the burden of treatment and disease monitoring can be high, particularly in those on elimination diets requiring avoidance of multiple foods or because of the need for multiple endoscopies.

Healthcare resource utilization (HRU) is particularly high in EoE (84). Contributing factors include diagnostic delays, frequent healthcare visits, increased likelihood of emergency department visits, repeated endoscopy, costly dietary modifications, and lack of approved medications, leading to out-of-pocket payment for expensive, off-label medications (40,88,101,102). In 2010, the estimated median total annual cost of a single EoE case in the United States was $3,304, largely for outpatient visits, pharmacy, and endoscopies, vs $1,001 for controls (103). Total HRU costs attributed to EoE range from $350 to 947 million/yr in the United States (103). Many caregivers identified lack of insurance coverage for elemental formula as a barrier and reported significant stress related to out-of-pocket treatment costs (104).

Disease burden can be further impacted by comorbid type 2 disease, necessitating more medication and potential side effects and greater HRU. In the year before EoE diagnosis, patients were most often treated for other conditions such as gastroesophageal reflux disease (34.6%) with a mean of 12 outpatients visits in the year before diagnosis (40). The effect of multiple atopic comorbidities on EoE patient perspective and the psychological burden of EoE, which can substantially affect patient QoL and treatment adherence (99), have also not been fully explored. Physicians should actively evaluate the impact on mental health and discuss management of anxiety and depression, where required.

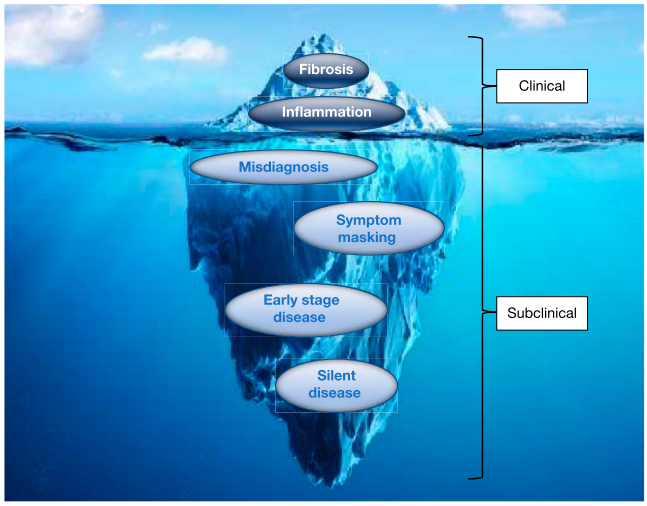

Figure 5. Diagnosed EoE: the tip of the iceberg. Diagnosed cases of EoE represent the tip of the iceberg; for all of the EoE cases that are identified clinically, there are likely many more `beneath the surface' that are misdiagnosed, subclinical, or at an earlier disease stage yet to be detected. EoE, eosinophilic esophagitis.

Unmet need

Patients with EoE have complex unmet needs across medical, social, and emotional domains (Table 3) (103). The observation that many patients switch therapies highlights an unmet need for more optimal long-term management (40). A critical unmet need is for long-term histologic, endoscopic, and symptomatic disease control. Noninvasive biomarkers of disease activity are needed to reduce invasive monitoring using endoscopy and biopsies. There is a need for targeted therapies to normalize esophageal function by regulating the immune response to triggers, restoring the epithelial barrier, reducing chronic inflammation, and limiting or preventing fibrosis. To better tailor treatment, a greater understanding is needed of patient subgroups likely to respond to specific therapies.

In general, symptom response is not a good indication of biological response in EoE (97,104), making treatment adherence a continual challenge in effective management. Almost 50% of gastroenterologists reported spending ≤10 minutes providing patient education at the initial visit (106), highlighting the need for patient and caregiver education. Patients who are well informed are more likely to be adherent to treatment protocols, resulting in better disease control.

Earlier diagnosis, standardized follow-up, and treat-to-target goals are needed with the aim of managing disease symptoms and underlying pathophysiology to prevent progression (107) and reduce complications and consultation with multiple providers before diagnosis. The median delay in EoE diagnosis is reported as 6 years; diagnostic delay is associated with increased fibrotic features and strictures (16,58,60,63) underscoring the critical need for earlier diagnosis. Improved endoscopic recognition may also help with this (108). Follow-up endoscopy and biopsy after food impaction are critical, so that patients are not lost to follow-up. Healthcare professionals also need to be educated on the patient perspective on disease burden, the disconnect between symptoms and disease activity particularly after esophageal dilation (108), as well as the progressive nature of EoE necessitating continuous monitoring and maintenance therapy in many patients.

With most patients with EoE having comorbid atopic conditions, greater awareness is required of the common cause of dysregulated type 2 immune response to dietary and environmental triggers and of the cumulative topical steroid treatment exposure. A better understanding of patient's history will help address comorbidities and evaluate duration of potential subclinical disease before diagnosis, regardless of when the patient presents with EoE symptoms.

CONCLUSIONS

EoE is a complex, heterogenous disease, with increasing prevalence worldwide. There is an emerging understanding of the underlying type 2 inflammation contributing to disease features and progression. Given the discordance between symptoms, histology, and endoscopic features, there is a need for comprehensive treat-to-target goals, individualized therapy, and continuous monitoring of treatment response. Current treatment options can be effective but may not provide long-term

Table 2. 10 dos and don'ts in diagnosis and treatment of EoE

1. DO investigate disease-causing symptoms and tailor treatments toward inflammation or fibrosis, or both, accordingly
2. DO include questions in medical history to identify adaptive or masking behaviors related to eating to assess impact on delayed diagnosis. Examples include avoiding foods that cause symptoms, eating slowly, taking small bites, chewing foods to mush, lubricating foods, drinking lots of liquids after each bite, food refusal, trouble swallowing pills, and pill impaction.
3. DO provide newly diagnosed patients with thorough medical education on the disconnect between symptoms and disease activity highlighting the need for continuous monitoring and treatment adherence to prevent complications
4. DON'T use symptom improvement in isolation for monitoring of disease activity or treatment decisions
5. DO repeat endoscopy, even in the absence of symptoms, to determine endoscopic and histologic response to treatment
6. DO refer patients to an allergist to evaluate for concomitant allergic disorders, if applicable
7. DO perform an initial endoscopy off PPI, if possible
8. DO perform follow-up endoscopy and biopsy after food impaction, so that patients are not lost to follow-up
9. DO perform a thorough initial medical history assessment to determine whether patient has had other atopic conditions and possible subclinical EoE disease contributing to delayed diagnosis
10. DO discuss the benefits of maintenance therapy with your patients

EoE, eosinophilic esophagitis; PPI, proton pump inhibitor.

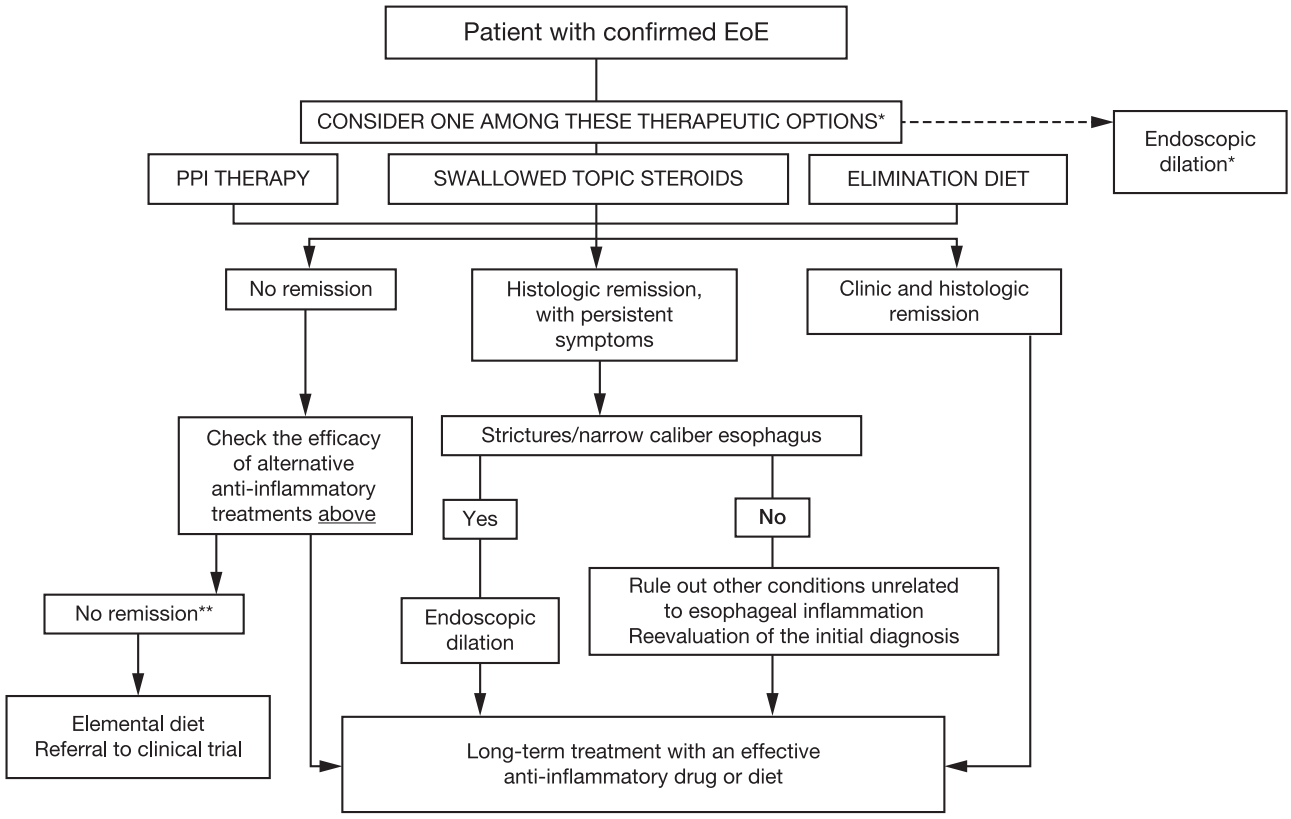

Figure 6. Treatment paradigm in EoE. Treatment for EoE consists of first line therapies PPI, STC, and elimination diet. For patients that do not achieve remission, or achieve incomplete remission, options include endoscopic dilation, elemental diet, and referral to clinical trial. EoE, eosinophilic esophagitis; PPI, proton pump inhibitor; STC, swallowed topical corticosteroids. (Reproduced from Lucendo 2018 [open access]) (2).

comprehensive disease control for all patient phenotypes. The cumulation of side effects and QoL impairment can be a hindrance to adherence. There is an unmet need for targeted systemic therapies that can normalize the immune response to triggers, reduce chronic inflammation, and limit or prevent fibrosis, thereby reducing patient burden.

ACKNOWLEDGEMENTS

We thank Ledia Goga, a former employee at Sanofi, Benjamin Ortiz, former employee at Regeneron Pharmaceuticals, Inc., Danielle Zielinski and Melissa Auclair from Sanofi, and Linda Williams from Regeneron Pharmaceuticals, Inc., for their significant contributions to the development of the manuscript. Editorial assistance following the authors' guidance, incorporating comments according to authors' feedback, and providing support with submission was provided by Alisa L. Willacey MPharm, of Excerpta Medica, and was funded by Sanofi and Regeneron Pharmaceuticals, Inc., according to the Good Publication Practice guideline.

CONFLICTS OF INTEREST

Guarantor of the article: Albert J. Bredenoord, MD, PhD.

Specific author contributions: The concept and design of the manuscript was devised by B.S., K.P., Y.D., P.J.R., and J.A.J.-N. and further developed by A.J.B. (eosinophilic esophagitis, neurogastroenterology, and benign esophageal disorders), A.M.S. (eosinophilic esophagitis), E.S.D. (eosinophilic esophagitis and gastroenterology), M.C. (eosinophilic esophagitis, allergy and immunology, gastroenterology, and pediatric vs adult eosinophilic esophagitis), S.S.A. (eosinophilic esophagitis, pediatric allergy, and immunology), and J.M.S. (eosinophilic esophagitis, pediatric allergy, and immunology). All the authors analyzed and interpreted the literature, drafted and critically reviewed the manuscript drafts for important intellectual content, approved the final version of the manuscript, and agreed to be accountable for all aspects of the work.

Financial support: Medical writing/editorial assistance provided by Alisa L. Willacey, MPharm, of Excerpta Medica was funded by Sanofi and Regeneron Pharmaceuticals, Inc., according to the Good Publication Practice guideline. The authors received honoraria for their participation in the meeting but have not received any funding from Sanofi for writing and reviewing this manuscript.

Potential competing interests: A.J.B. received consulting fees from Arena Pharmaceuticals, AstraZeneca, Calypso Biotech, Dr. Falk Pharma, EsoCap, Gossamer Bio, Laborie, Medtronic, RB Pharma, Regeneron Pharmaceuticals, Inc./Sanofi, and Robarts Clinical Trials; research funding from Bayer, Nutricia, and SST; and holds equity interest in SST. A.M.S. received consulting fees from Adare Pharma Solutions, Bristol Myers Squibb, Dr. Falk Pharma, Ellodi Pharmaceuticals, Gossamer Bio, and Sanofi Genzyme and research funding from AstraZeneca, Aptalis, Dr. Falk Pharma, GlaxoSmithKline, Nestlé, Novartis, Receptos/Bristol Myers Squibb, and Regeneron Pharmaceuticals, Inc. E.S.D. received consulting fees from Abbott,

Table 3. Key unmet needs in EoE

Unmet needs: disease awareness
• There is an overall need to better understand: ○ The correlation between genetic endotypes and clinical phenotypes ○ The phenotypic and endotypic heterogeneity of EoE to guide treatment and management
• There is a need for better physician understanding of: ○ The common dietary and environmental triggers of dysregulated type 2 immune responses ○ The disease burden from a patient perspective ○ The discordance between symptomology and disease activity ○ The progressive nature of EoE
Unmet needs: diagnosis
• There is a need for: ○ Earlier diagnosis of EoE ○ Physicians to better understand a patient's medical history at diagnosis to address comorbidities and establish duration of previous subclinical disease
Unmet needs: treatment
• There is a need to optimize current treatment pathways for each EoE phenotype
• There is a need for safe and effective targeted therapies that: ○ Exert long-term histologic, endoscopic, and symptomatic disease control, including restoration of the esophageal barrier ○ Improve quality of life ○ Normalize the immune response to triggers ○ Reduce chronic inflammation ○ Limit or prevent progression of remodeling and fibrosis ○ Can be administered in a convenient dosing regimen ○ Have minimal side effects
Unmet needs: outcomes
• There is a need for: ○ Predictors of response ○ Defined and standardized outcomes and for these to inform treat-to-target goals
• There is a need to understand patient perspectives toward treatment and associated outcomes
Unmet needs: monitoring and maintenance
• There is a need for: ○ Noninvasive biomarkers of disease activity to reduce invasive monitoring ○ Standardized follow-up with continuous monitoring ○ Maintenance treatment

EoE, eosinophilic esophagitis.

AbbVie, Adare Pharma Solutions/Ellodi Pharmaceuticals, Aimmune Therapeutics, Allakos, Amgen, Arena Pharmaceuticals, AstraZeneca, Avir Pharma, Biorasi, Calypso Biotech, Celldex Therapeutics, Eli Lilly, EsoCap, GlaxoSmithKline, Gossamer Bio, Landos Biopharma, Morphic Therapeutic, Nutricia, Parexel/Calyx, Phathom Pharmaceuticals, Receptos/Bristol Myers Squibb, Regeneron Pharmaceuticals Inc., Revolo Biotherapeutics, Robarts Clinical Trials/Alimentiv, Salix Pharmaceuticals, Sanofi, and Shire/Takeda; research funding from Adare Pharma Solutions/Ellodi Pharmaceuticals, Allakos, Arena Pharmaceuticals, AstraZeneca, GlaxoSmithKline, Meritage Pharma, Miraca Life Sciences, Nutricia, Receptos/Bristol Myers Squibb, Regeneron Pharmaceuticals, Inc., and Shire/Takada; and educational grants from Allakos, Banner Pharmaceuticals, and Holoclara. S.S.A. received consulting fees from AstraZeneca, is an educational speaker for Sanofi-Regeneron Pharmaceuticals, Inc., and Medscape, and is a coinventor of oral viscous budesonide, UCSD patent, Takeda license. M.C. received consulting fees from Adare Pharma Solutions, Allakos, AstraZeneca, Bristol Myers Squibb, Phathom Pharmaceuticals, Regeneron Pharmaceuticals, Inc., Sanofi, and Shire/Takeda and research funding from Adare Pharma Solutions/Ellodi Pharmaceuticals, Allakos, AstraZeneca, Danone, Regeneron Pharmaceuticals Inc., and Shire. J.M.S. received consulting fees from Allakos, DBV Technologies, Novartis, Regeneron Pharmaceuticals, Inc., Shire, and Takeda and grant support from DBV Technologies and Regeneron Pharmaceuticals, Inc. B.S., and Y.D. are employees and shareholders of Regeneron Pharmaceuticals, Inc. J.A.J.-N, P.J.R., and K.P. are employees of Sanofi and may hold stock and/or stock options in the company.

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