Rationale for an Eosinophilic Esophagitis Treat-to-Target Concept

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Abstract: Eosinophilic esophagitis (EoE) is a chronic T helper 2–mediated inflammatory disorder of the esophagus defined clinically by the presence of symptoms of esophageal dysfunction and histologically by an eosinophil-predominant infiltration. Correspondingly, treatment has aimed at controlling both symptom severity and histologic activity. However, with emerging clinical and pathophysiologic understanding of the disease, it has become increasingly apparent that other disease aspects need to be targeted as well, such as endoscopic severity and quality of life. Moreover, with the role of eosinophils having been questioned lately, histologic changes beyond eosinophil infiltration have come to attention and are captured by newly validated scores. In addition, EoE is being increasingly considered a transmural disease that cannot be assessed by simple endoscopy but needs measurement of esophageal distensibility, a surrogate marker for fibrosis. Finally, novel tools such as measurement of esophageal impedance could make it possible to assess for complete restoration of the esophageal epithelium, potentially corresponding to disease clearance. This article reviews the various outcome parameters in adult EoE management and proposes an algorithm for a treat-to-target concept, in analogy to what has been practiced in inflammatory bowel disease treatment for the last 10 years.

Keywords
Eosinophilic esophagitis, treat-to-target algorithm, validated scores, remission, disease clearance

Eosinophilic esophagitis (EoE) is a chronic inflammatory disorder of the esophagus with a dramatically increasing incidence and prevalence over the last few decades.[1] Originally considered a rare disease,[2,3] EoE currently represents the most frequent cause of solid food dysphagia in the Western hemisphere, with a frequency comparable to that of Crohn's disease.[4] Mechanistically, immunologic studies have revealed a T helper 2 (Th2)-type inflammatory (allergic) response.[5] High efficiency of protein-free diets has further supported the concept of EoE being a food antigen–driven allergic response, at least in the vast majority of patients.[6] Of note, EoE—in contrast to the classic immunoglobulin E

(IgE)-mediated food allergies—is a cell-mediated, delayed allergic reaction,[7] with IgE playing only a subsidiary role in its pathogenesis. Not surprisingly, IgE-based serum and skin tests have shown disappointing correlation with trigger food identification.

It is well accepted that patients with clinically and histologically active EoE require an efficacious anti-inflammatory treatment.[4] Recommendations such as avoidance of stress and changing of eating habits are obsolete, as they affect neither the chronic destructing inflammation nor the risk of unforeseeable food-bolus impactions.[1] The 2 general principles of allergy treatment—avoidance of allergens, if possible, and medical suppression of the chronic destructive inflammation—are valid in EoE management as they are for other allergic conditions. The first consists of a diet eliminating trigger foods, whereas the latter includes topical-acting corticosteroids, proton pump inhibitors, and newer biologics targeting key Th2 cytokines. Both strategies are highly efficacious for controlling symptoms and histologic disease activity. Historically, EoE treatment has aimed at controlling these 2 key aspects of the disease only. However, with emerging clinical and pathophysiologic understanding of the disease, it has become increasingly apparent that other disease aspects need to be targeted as well, ranging from histologic inflammation beyond eosinophil infiltration, endoscopic severity, esophageal distensibility as a surrogate marker for fibrosis, and quality of life. Novel tools such as measurement of esophageal impedance might even allow clinicians to assess for a complete restoration of the esophageal epithelium. Because all these various aspects of EoE should be controlled, a stepwise approach in analogy to what has been done in inflammatory bowel disease (IBD) management appears reasonable, as part of a so-called treat-to-target concept, which is described in this article.

Treat-to-Target Concept

The treat-to-target concept was successfully introduced in the management of IBD almost 10 years ago.[8] IBD and EoE share many similarities.[9] Both are chronic inflammatory disorders of the gastrointestinal tract necessitating long-term treatment. Eosinophilic infiltration can be seen in both Crohn's disease and ulcerative colitis, and even correlates with disease activity.[10-13] Furthermore, ulcerative colitis is characterized by a Th2 immune response.[14] Finally, both entities, IBD and EoE, present with clinical, endoscopic, and histologic disease activity. In 2015, the International Organization for the Study of Inflammatory Bowel Disease (IOIBD) proposed evidence- and consensus-based recommendations for selecting the goals for a treat-to-target strategy in patients with IBD (STRIDE, which stands for Selecting Therapeutic Targets in IBD).[8] The STRIDE recommendations were updated by the IOIBD in 2021 (STRIDE-II).[15] STRIDE-II distinguishes between short-term, intermediate-term, and long-term treatment targets. If targets are not reached, treatment intensification or treatment changes should be considered. The therapeutic targets are as follows: (1) symptomatic response, symptomatic remission, and normalization of C-reactive protein; (2) decrease of fecal calprotectin to an acceptable range, and normal growth in children; and (3) endoscopic healing, normalized quality of life, and absence of disability. Further targets should be considered for Crohn's disease (transmural healing) and ulcerative colitis (histologic healing), although such targets have not been formalized.[15]

As IBD and EoE have considerable overlaps, a treat-to-target concept (as done in IBD) is appealing for the management of EoE patients. In analogy, this would be: (1) symptomatic response and remission; (2) endoscopic healing, normalized quality of life, and absence of disability; and (3) histologic healing and potentially transmural healing (normalization of esophageal distensibility). Historically, only 2 targets have been considered in clinical practice, namely, clinical and histologic response/remission, but in recent years, increasing data have been emerging regarding other disease outcomes.[16-18]

Treatment Targets in Eosinophilic Esophagitis

EoE is a clinicopathologic condition, defined clinically by the presence of symptoms of esophageal dysfunction, and pathologically by the presence of eosinophil-predominant tissue inflammation.[1] As a direct consequence of this definition, the 2 leading goals of EoE treatment are, first, the control of symptoms, and second, the control of inflammation. However, severity of symptoms shows only a modest correlation with the degree of biologic inflammation.[19] Particularly, after endoscopic dilation, long-lasting dissociation between inflammatory activity and symptom severity can be seen.[20] Some treatments have successfully targeted eosinophil infiltration, such as the eosinophil-depleting drugs reslizumab (Cinqair, Teva Respiratory), mepolizumab (Nucala, GlaxoSmithKline), and benralizumab (Fasenra, AstraZeneca), but failed to control clinical symptoms.[21-23] From a disease-modifying perspective, all treatments should aim at preventing the development of complications—in particular tissue remodeling with structural and functional damage of the esophagus resulting in an increased risk of food-bolus impaction.[24] The following section reviews the various outcome parameters that should be assessed in EoE management.

Clinical Response and Remission

Clinically, EoE presents almost exclusively with symptoms of esophageal dysfunction. In order to capture these symptoms, a thorough patient history is key.[4] The leading symptom in adolescent and adult EoE patients is dysphagia for solids ranging from slow passage of food up to long-lasting food-bolus impactions necessitating endoscopic removal. Importantly, dysphagia severity can be underestimated owing to the texture of the ingested food and compensatory eating habits. In order to limit such confounding, several scoring systems have been developed, with the standardized and validated Dysphagia Symptom Questionnaire (DSQ)[25] and Eosinophilic Esophagitis Activity Index patient-reported outcome (EEsAI-PRO) score[26] being most frequently used in clinical trials. Owing to their complexity, these tools are rarely applied in clinical practice. For assessing dysphagia, simpler tools, such as a visual analogue scale (VAS) ranging from 0 to 10 or a Likert scale, are more appealing and probably sufficient. The simplest tool is a dichotomous classification into absence vs presence of symptoms. For this, however, dysphagia including a potential compensatory mechanism has to be specifically asked for. The Index of Severity for EoE (I-SEE, discussed later in this article) is a novel tool to judge disease severity that might be easily applicable in clinical practice as a smartphone application and has been made available lately. All treatments should aim at controlling clinical activity. Clinical response (improvement of symptoms) should be achieved within 2 to 4 weeks, whereas clinical remission should be reached at the end of the introduction phase after 6 to 24 weeks. These timelines are arbitrary, however, and based on prescheduled follow-up visits in clinical trials. In general, drugs act faster than diets, and swallowed topical corticosteroids[27] faster than biologics,[28] although there are no head-to-head comparisons available yet. The difference between clinical response and clinical remission is purely a quantitative one. In clinical trials, these thresholds are predefined in the study protocols, depending on the instrument used for symptom assessment (eg, DSQ, EEsAI-PRO). In clinical practice, response corresponds to a considerable reduction of symptom severity (for instance, a drop in the VAS of at least 2 points), whereas remission refers to a (almost) complete disappearance of any symptoms (VAS 0-1).

Endoscopic Remission

Endoscopic activity had long been graded semi-quantitatively or by using a VAS based on the treating physician's interpretation.[29-31] This measure was somewhat problematic given the absence of universally accepted endoscopic signs for EoE and the fact that, endoscopically, EoE was frequently missed.[32] Endoscopic assessment of EoE has dramatically changed with the development and introduction of the Eosinophilic Esophagitis Endoscopic Reference Score (EREFS), which takes into account both inflammatory (edema, exudates, furrows) and fibrotic (rings and strictures) features.[33] The EREFS represents the first and only standardized and validated endoscopic measurement of EoE activity.[34,35] In fact, these 5 features (3 inflammatory and 2 fibrotic) demonstrate good interobserver agreement, and the EREFS correlates with histologic disease activity and esophageal distensibility.[36,37] Moreover, EREFS is responsive to treatment.[38] Therefore, judgment of endoscopic activity by the EREFS is strongly recommended, and the use of other nonstandardized tools, such as VAS, is discouraged. Although there are no clear definitions of disease severity based on the EREFS, a score of 0 or 1 is usually considered as endoscopic remission. This is based on the threshold of 2 that has a positive predictive value for the diagnosis of EoE of 84% and a negative predictive value of 94%, with an accuracy of 91%.[38] In fact, an EREFS of 0 or 1 has been associated with an almost 100% response to topical corticosteroids. However, secondary analyses of a randomized controlled budesonide trial identified an EREFS of less than or equal to 2 as the best clinical threshold for endoscopic response to corticosteroid treatment, and this EREFS was consistent with clinical and histologic response (defined by a peak eosinophil count of <15 eosinophils/high-power field [hpf]).[39] The phase 3 trials for topical budesonide (budesonide orodispersible tablet, budesonide oral suspension) and dupilumab (Dupixent, Sanofi and Regeneron) all showed endoscopic response within 6 to 24 weeks.[27,28,40] Thus, although shorter follow-up endoscopic data are missing, it can be assumed that endoscopic response/remission is a short-term or intermediate-term therapeutic target that should be achieved within 6 to 24 weeks. Because endoscopic activity correlates with histologic activity, nonachievement of endoscopic remission should be considered a treatment failure triggering changes to the current therapeutic strategy (treatment intensification or switch to another agent).

Histologic Remission

An eosinophilic infiltration of esophageal tissue is the hallmark of EoE and is therefore included in the disease definition.[1,4] Despite several technical limitations—for instance, lack of subepithelial tissue in most biopsies, microscope-dependent size of a hpf, spotty nature of the inflammation—a threshold of at least 15 eosinophils/hpf (magnification ×400) was arbitrarily fixed for establishing a firm diagnosis of EoE.[1] Of note, the same value of 15 eosinophils/hpf is accepted as a criterion in order to differentiate between active and inactive EoE in patients once the diagnosis has been established.[41] Furthermore,

from the early beginning of research, inflammatory activity of EoE has been linked to the intensity of this eosinophilic tissue infiltration.[42] The histologic cutoff of 15 eosinophils/hpf is therefore almost always used as an inclusion criterion and as the (main) outcome measure in clinical trials. A decrease to less than 5 eosinophils/hpf is in general regarded as histologic remission and values between 5 and 15 as histologic response, although more recently histologic remission has been defined by a peak eosinophil count of 6 or less. In analogy to the endoscopic outcome, all current phase 3 trials for topical budesonide (budesonide orodispersible tablet, budesonide oral suspension) and dupilumab showed histologic response within 6 to 24 weeks (depending on when the first follow-up endoscopy was scheduled).[27,28,40] The threshold of 15 eosinophils/hpf is arbitrary, although emerging data suggest that 15 eosinophils is an adequate cutoff to predict symptom, endoscopic, and combined responses.[43] A lower threshold (<5 eosinophils/hpf) has been shown to identify most patients with a combination of symptom and endoscopic responses.[43] There is still no study evaluating the long-term consequences of different threshold levels. Thus, it is not known whether patients with a peak eosinophil count of 14 eosinophils/hpf have a better outcome than those with a peak eosinophil count of 18 eosinophils/hpf. In Swiss EoE clinics, we mainly advocate for the control of histologic activity to a level of less than 15 eosinophils/hpf, or ideally to 5 or less, based on natural history data that linked ongoing inflammation to the development of esophageal strictures.[44]

The role of eosinophils in the pathogenesis of EoE has been questioned lately and various histologic changes beyond pure eosinophil infiltration have been described. Recently, a novel histologic score, the so-called EoE Histologic Scoring System (EoE-HSS), has been developed. This score assesses the following histologic changes: number of eosinophils, basal zone hyperplasia, eosinophil abscesses, eosinophil surface layering, dilated intercellular spaces (spongiosis), surface epithelial alteration, dyskeratotic epithelial cells, and lamina propria fibrosis.[45] In fact, by including all these aspects, the EoE-HSS appears to outperform peak eosinophil counts for disease diagnosis and monitoring.[45,46] Thus, current phase 2 trials have included the EoE-HSS as one of their secondary outcomes. Still, it remains a challenge how to define histologic remission when using the EoE-HSS.

Other Outcome Measures

One established technology is the endoluminal functional lumen imaging probe (EndoFLIP, Medtronic) that evaluates hollow organ distention by using high-resolution impedance planimetry through an orally passed catheter with an inflatable balloon.[47] In the esophagus, pressure volume characteristics are determined from stepwise inflations of the balloon and converted into a 3-dimensional color plot reflecting the degree of esophageal distensibility (and fibrosis). This technique not only represents an accurate and simple assessment of esophageal distensibility but is at the edge of becoming the key tool to monitor disease progression in EoE.[47] In fact, EndoFLIP has been increasingly used to assess esophageal distensibility in EoE.[48,49] Decreased distensibility measured by EndoFLIP is a surrogate marker for tissue remodeling as it is associated with an increased risk for food-bolus impaction.[50,51] Moreover, it is well known that patients with EoE have a lower distensibility than control patients without EoE.[47] Endoscopic biopsies may not adequately reflect esophageal fibrosis owing to the patchy distribution of the disease and the lack of lamina propria in most tissue samples. Given this unknown utility of histologic assessment of fibrosis and the fact that fibrosis can be easily missed by endoscopic assessment,[32] EndoFLIP might be the best outcome measure to assess tissue remodeling. Therefore, recently planned and launched studies have included EndoFLIP as one of the main outcomes. Objective measurement of physiomechanical function in EoE is key for a standardized assessment of esophageal distensibility and motility but is currently not performed. The recently proposed composite score of FLIP panometry, which includes metrics of the esophageal body compliance, contractile response, distensibility plateau, and maximum esophagogastric junction diameter (C2D2), could close this important gap.[52] The C2D2 is scored as 0 for normal vs 1 or 2 for increasing degree of abnormality.

Quality of life is known to be considerably affected in EoE patients. It is usually assessed by using either a general health-related quality-of-life survey, such as the 36-item Short-Form health survey or the disease-specific Adult EoE Quality of Life questionnaire.[53] Quality of life strongly correlates with symptom severity but also with endoscopic and histologic disease activity.[54] Thus, reduction of symptoms and improvement of biologic disease activity result in an increase of quality of life. Recent phase 3 trials included quality-of-life measures as secondary outcomes. Already within the induction phase after 6 to 24 weeks, quality of life has been significantly improved with treatment compared with placebo, which is maintained during the maintenance treatment phase.[27,28,40] Coping strategies are frequently seen with EoE patients, such as drinking water during a meal, and use of these strategies can interfere with severity of dysphagia symptoms. Therefore, patients are actively queried about coping strategies by using the validated symptom score EEsAI-PRO.[26]

This article discusses adult EoE only, but it needs to be mentioned that normal growth is one of the key outcomes

in pediatric EoE, both as a marker for disease control and as a marker for side effects of topical corticosteroids.

Outcome Measures on the Horizon

Currently, the assessment of biologic inflammatory activity in EoE still is exclusively based on the histologic examination of esophageal tissue. Tissue sampling requires upper endoscopy, an invasive and quite expensive procedure. Noninvasive and less expensive alternatives are being actively sought, ranging from blood tests to breath tests and semi-invasive swallowing tools. A simple blood test to monitor EoE activity would be highly desirable. Although serum eotaxin-3 is elevated in patients with EoE, it is not sufficiently accurate for clinical use.[55] Other elevated serum markers, including interleukin (IL)-4, IL-5, IL-6, IL-9, and IL-13; transforming growth factors alpha and beta; thymic stromal lymphopoietin; proteoglycan 2, pro eosinophil major basic protein; and ribonuclease A family member 2 (eosinophil-derived neurotoxin), were not able to differentiate patients with active from those with inactive EoE.[56] Measurement of fractional exhaled nitric oxide and of metabolites of Th2 inflammation with high-resolution mass spectrometry are both promising noninvasive attempts determining the inflammatory activity of EoE in the exhaled breath. Both methods are currently under investigation. Cytosponge (Medtronic) and the Esophageal String Test (EnteroTrack) are other minimally invasive methods compared with conventional endoscopy that have been quite successfully investigated but have not made it into routine clinical practice.[57,58] Cytosponge is a device that consists of an ingestible gelatin capsule containing a compressed sponge attached to a string. The capsule is swallowed and the gelatin dissolves in the stomach, resulting in the release of a spherical sponge. After being withdrawn through the mouth, a tissue specimen is collected from the sponge. In a pilot study, the sponge test accurately identified 83% of individuals with active EoE.[57] Eosinophils collected with the sponge correlated with peak eosinophil counts in the esophageal biopsies. The Esophageal String Test consists of a capsule that is filled with a string.[58] Upon swallowing, the capsule dissolves and after at least 1 hour, the string is withdrawn. Inflammatory mediators are absorbed by the string, which can then be stained for eosinophil-derived protein markers. The Esophageal String Test was able to distinguish active EoE from EoE in remission, gastroesophageal reflux disease, and normal esophagus. Levels of luminal eosinophil-derived proteins in string samples correlated with peak and mean eosinophil counts in esophageal biopsies.[58]

More recently, endoscopic measurement of esophageal impedance as a marker for ongoing inflammation has been introduced. Esophageal electrical impedance (EEI) measures the conduction of electricity, which is altered in the esophageal surface under inflammatory conditions, particularly from dilated epithelial intercellular spaces that increase paracellular fluid and electrolyte flow. As a result, measurement of mucosal impedance becomes a potential tool to measure histologic activity in EoE. Increased impedance correlates with biologic disease activity. In a trial of EoE using an endoscopic impedance probe, measurements demonstrated a 90% sensitivity and 91% specificity when compared with the degree of histologically assessed inflammatory disease activity.[59] In 2021, the MiVu Integrity Testing System (Diversatek Healthcare) received approval from the US Food and Drug Administration as a device to assess mucosal integrity. EEI has the potential not only to minimize the need for esophageal biopsies but also to endoscopically assess restoration of the esophageal epithelium and thereby revolutionize how to follow a treat-to-target concept in EoE.

A potential breakthrough has been reached by the recent development of the I-SEE, a novel clinical severity index for EoE. A multidisciplinary international consensus group developed this index that is based on the following disease aspects: (1) symptom severity, (2) disease complications, (3) endoscopic inflammatory changes, (4) peak eosinophil counts, (5) presence of fibrostenotic disease on endoscopy, and (6) histologic changes indicating fibrostenosis. Using a predefined point system, disease severity is graded into inactive (<1), mild (1-6), moderate (7-14), and severe (≥15).[60] The I-SEE has been recently shown to be associated with baseline clinical features and successful treatment response.[61] However, further data are needed before widespread use in clinical practice.

Treat-to-Target Algorithm

Historically, the only 2 targets having been considered in clinical routine were clinical and histologic response/remission. However, endoscopic assessment has considerably improved, EoE has been appreciated as a disease affecting more than just the esophageal epithelium, and novel tools have been introduced making it possible to assess functional changes of the esophagus (such as EndoFLIP). In addition, it has been increasingly recognized that—from a histologic perspective—EoE is more than just an eosinophil-predominant infiltration of the esophageal epithelium. In fact, the role of eosinophils as the diagnostic and pathophysiologic hallmark has been questioned lately. Therefore, complete restoration of the epithelium rather than reduction of eosinophils should probably be aimed for. Such restoration could potentially be measured by emerging tools, such as the MiVu system, keeping in mind that this is probably only a long-term treatment goal in a subgroup of patients. Given all these outcome measures, a stepwise treat-to-target approach

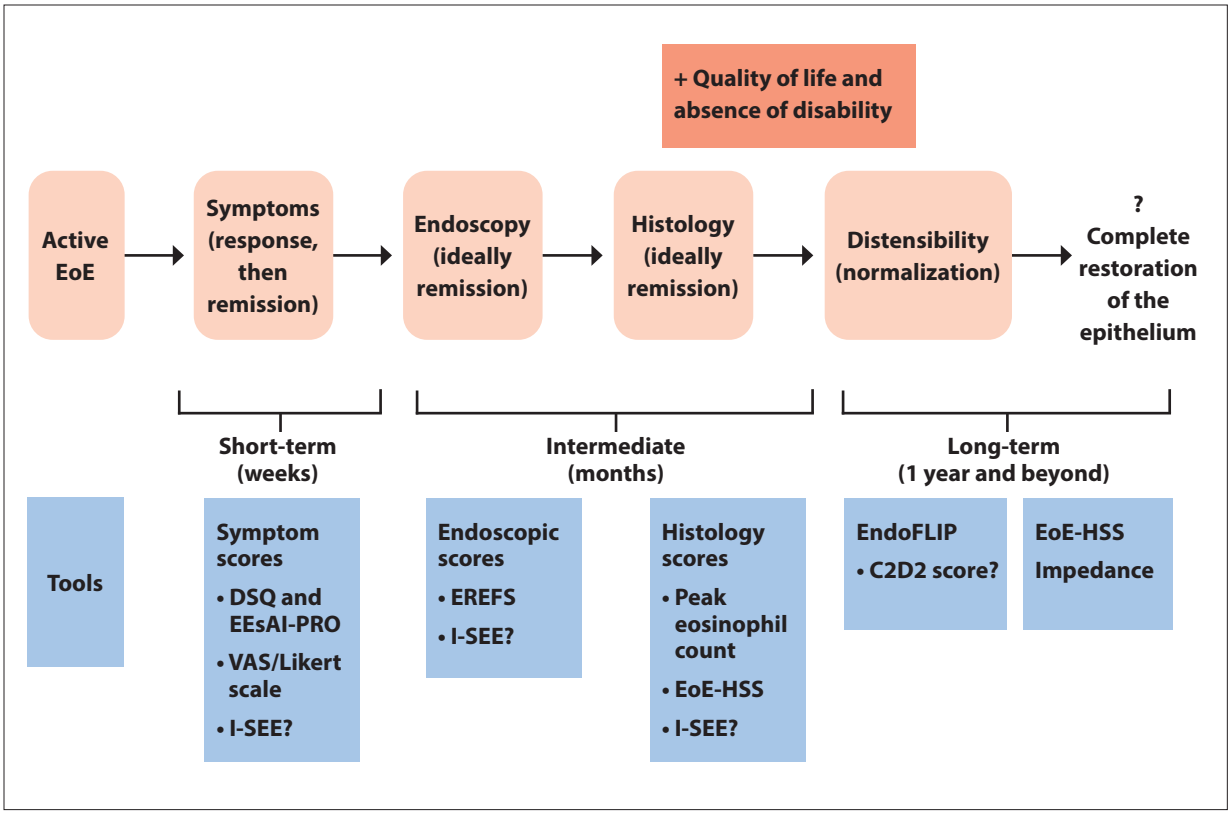

Figure. Treat-to-target algorithm for the management of adult patients with EoE.

C2D2, compliance, contractile response, distensibility plateau, and maximum esophagogastric junction diameter; DSQ, Dysphagia Symptom Questionnaire; EEsAI-PRO, Eosinophilic Esophagitis Activity Index patient-reported outcome; EndoFLIP, endoluminal functional lumen imaging probe; EoE, eosinophilic esophagitis; EoE-HSS, EoE Histologic Scoring System; EREFS, Eosinophilic Esophagitis Endoscopic Reference Score; I-SEE, Index of Severity for EoE; VAS, visual analogue scale.

consisting of the following can be recommended: (1) symptomatic response and remission; (2) endoscopic remission; (3) histologic remission, normalized quality of life, and absence of disability; and (4) normalization of esophageal distensibility (Figure). However, in contrast to IBD, such a treat-to-target concept is limited by the availability of efficacious drugs targeting these disease aspects. Although resolution of fibrosis and restoration of the epithelium are reasonable targets, no drug is available so far that efficaciously resolves fibrosis or completely restores the epithelium. Thus, the steps of the algorithm shown in the Figure should be considered as potential outcomes and not as targets that need to be reached in all cases.

In a similar approach, a core outcome set for therapeutic studies in EoE (COREOS) has been recently developed. Through a Delphi process, an international group of EoE experts identified the following 4 outcome domains: histopathology (peak eosinophil count and EoE-HSS), endoscopy (EREFS), patient-reported symptoms (PRO for dysphagia), and EoE-specific quality of life.[17,18] These core outcome measures are intended to be applied to future therapeutic studies and will facilitate meaningful treatment comparisons. They could also potentially be adopted for routine clinical care.[16]

Open Questions and Unmet Needs

A crucial open question is why a considerable discordance between symptoms and inflammation exists. Tissue eosinophilia is the diagnostic hallmark of EoE.[1] Traditionally, the inflammatory activity of EoE has therefore been characterized by the density of the eosinophilic infiltration. This biologic marker has gained a strong position as main readout in clinical trials. Several attempts have been made specifically targeting this late-inflammatory cell, mainly by using anti–IL-5 antibodies, such as mepolizumab,[22] reslizumab,[21] and benralizumab.[23] All of these anti–IL-5 antibodies resulted in an impressive reduction of tissue eosinophilia, but surprisingly symptoms and noneosinophil-related biomarkers persisted. In contrast, the anti–IL-4/IL-13 antibody dupilumab effectively treats EoE by both reducing esophageal eosinophilia and

targeting downstream Th2 mediators. Patients with EoE variants experience identical symptoms as patients with conventional EoE but have no, or almost no, eosinophils in their esophageal tissue.[62] Thus, the role of eosinophils in the pathogenesis of EoE and their contribution to symptom severity has been extensively questioned.[63] Without knowing the culprit cell or cellular steps, it will be difficult to target the right biologic process within a treat-to-target concept.

A practical unmet need is the identification of alternatives for serial upper endoscopies for EoE monitoring. Several less-invasive tools, such as transnasal endoscopies,[64] a sponge test,[57] and esophageal string test,[58] have therefore been evaluated in order to prevent endoscopies, but all have their limitations. Most importantly, these tools are diagnostic only, without the possibility of performing endoscopic dilation in the same session (when a stricture is detected). In addition, the sponge and esophageal string tests do not provide enough tissue for histologic assessment as done in esophageal biopsies from esophagogastroduodenoscopy.

Finally, and most interestingly, it is questioned whether or not a so-called disease clearance can be achieved in EoE management. Hitherto, data indicate that EoE cannot be healed as it is a chronic disease that quickly relapses upon cessation of treatment. In fact, even patients with long-lasting deep remission show a relapsing disease course once their treatment has been stopped.[65] However, novel drugs could potentially have disease-modifying effects, but the question remains at which point the disease could potentially be cleared. Mucosal impedance measurement together with histologic assessment of disease activity beyond simple esophageal eosinophilia has the potential to identify complete restoration of the esophageal mucosa.

Conclusion

The understanding of EoE has evolved from a purely clinicopathologic entity to a complex disease, where a plethora of aspects are considered, both at diagnosis and during follow-up. Currently, the aim is to control clinical, endoscopic, and histologic disease activity, but in the near future, gastroenterologists will probably treat to target, with disease clearance being the ultimate goal to achieve. To reach such a goal, however, efficacious disease-modifying drugs will be needed.

Disclosures

Professor Greuter has consulting contracts with Amgen, Eli Lilly, Pfizer, Sanofi-Regeneron, Janssen, Bristol Myers Squibb, Takeda, AbbVie, and Dr Falk Pharma GmbH; he has received travel grants from Dr Falk Pharma GmbH and Vifor, speakers fee from Norgine, and research grants from Novartis and Sanofi-Regeneron. Professor Straumann has consulting contracts with Actelion, Celgene-Receptos, Dr Falk Pharma GmbH, Roche-Genentech, GlaxoSmithKline, Novartis, Nutricia, and Sanofi-Regeneron.

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