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Eosinophilic esophagitis: What can we learn from Crohn's disease?

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Abstract

Eosinophilic esophagitis (EoE) is an emerging esophageal inflammatory disorder affecting children and young adults. As a relatively new disease, EoE is still burdened by frequent diagnostic and therapeutic pitfalls in clinical practice. This manuscript posits a number of similarities with Crohn's disease, which may help optimize EoE patient management. Commonalities include epidemiologic trends (Westernized diseases, rising incidence, early-life risk factors), diagnostic considerations (symptoms are poor predictors of disease activity, difficulties in disease activity assessment) and therapeutic issues (similar natural history and therapeutic goals, induction and maintenance phases, combination of drug and endoscopic treatment, potential drug interchangeability, long-term unsolved issues). Physicians devoted to EoE should learn from the extraordinary achievements fulfilled in Crohn's disease: increased disease awareness, multidisciplinary specialized clinics, structured childhood and transition programs, and an ongoing roadmap for personalized treatments, including genetic susceptibility, risk factors for progression, genotype-phenotype correlation, drug monitoring and microbial data.

Keywords

Eosinophilic esophagitis, Crohn's disease, inflammatory bowel disease

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Introduction

Eosinophilic esophagitis (EoE) is a chronic, immune/antigen-mediated esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil (eos)-predominant inflammation.[1] In the early 1990s, two groups of investigators independently reported a series of young adult patients, mostly male, with dysphagia, typical endoscopic findings and marked esophageal eosinophilia, in the absence of clinical evidence of gastro-esophageal reflux disease (GERD).[2,3] Nevertheless, the disorder was largely neglected during the 1990s and early years of the 21st century, mostly because previous studies from the 1970s and 1980s equated the presence of esophageal eosinophils (eos) and GERD.[4] A prime example is a series of 19 patients with dysphagia/food impaction, ringed narrowed esophagus and dense eosinophilia requiring esophageal dilation, reported as GERD patients in 2001.[5] Like in GERD, the most common esophageal disease, many pediatric and adult EoE patients are still treated in clinical practice for four to eight weeks, followed by repeat courses of on-demand treatment intended to control symptoms. Only since 2007 has EoE been recognized as a distinct new condition with the publication of updated guidelines for diagnosis and management.[6–8] Mounting knowledge over the past decade has contributed to situating EoE as a distinct chronic and progressive inflammatory condition affecting pediatric and young adult patients, with familial aggregation.[9,10] Symptom pattern usually consists of intermittent flare-ups, with symptoms of esophageal dysfunction and acute

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episodes of food impaction, followed by remission periods.[8] Symptom severity and dietary restriction negatively affect the quality of life of patients, especially children and young adults.[11,12] Furthermore, untreated inflammation usually leads to long-term fibrostenotic complications, like narrow-caliber esophagus and esophageal strictures.[13,14] Disease management is increasingly complex, with different therapeutic assets such as proton pump inhibitor (PPI) therapy, swallowed topical steroids, dietary therapy, endoscopic dilation and even biologic agents.[15]

This manuscript aims to discuss a relevant number of potential similarities between EoE and Crohn's disease (CD), particularly emphasizing epidemiologic trends, symptom pattern, impaired quality of life, natural history, disease activity assessment and therapeutic approach.

Differences between EoE and CD

From an etiologic and pathophysiologic standpoint, EoE and CD clearly are different diseases. EoE is an antigen-mediated allergic disease, thought to be predominantly but not exclusively triggered by food antigens.[6–8] Elimination diets (mainly involving cow's milk, wheat and eggs) are effective in achieving clinical and histological remission in a relevant proportion of patients.[16] In genetically predisposed individuals, environmental antigens stimulate an anomalous Th2 inflammatory response, which promotes trafficking of eos limited to the esophageal mucosa. Activated eos secrete proinflammatory and profibrotic mediators, cause local tissue damage, and recruit additional inflammatory cells (mast cells and fibroblasts), perpetuating the inflammatory response and resulting in esophageal remodeling.[17] In contrast, the ultimate etiology of CD remains unknown. One possibility is that environmental factors in genetically predisposed individuals trigger a Th1/Th17 inflammatory response resulting in a disturbed innate and adaptive immune response toward a diminished diversity of commensal microbiota.[18] An interesting hypothesis in CD is that food-triggered changes of the intestinal microbiome might cause a proinflammatory state preceding the development of inflammatory bowel disease (IBD). Indeed, an intact intestinal epithelial barrier ensuring a normal bacterial clearance of the intestinal surface is crucial to guarantee intestinal homeostasis. Exclusive enteral nutrition is an extensively studied, well-established, and valid approach to the remission of pediatric CD.[19] Interestingly, a fermentable carbohydrate restriction, namely the low fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAP) diet, has been shown lately to be effective in controlling functional gastrointestinal symptoms, but not the underlying inflammation, in patients with IBD.[20,21]

Needless to say, functional status in EoE patients is much better than that for patients with CD, in which anemia, malnutrition, infections, surgical procedures and drug toxicity might be common. EoE and CD are also different in terms of extension through the gastrointestinal tract, gender predominance, extraintestinal manifestations, noninvasive monitoring, therapy principles, and long-term complications. The main differences between EoE and CD are exhibited in Table 1. A recent population-based study has suggested an increased risk of multiple autoimmune diseases in EoE patients, including CD and ulcerative colitis,[22] but these findings should be further replicated.

Potential commonalities between EoE and CD

The main similarities shared by both disorders are sketched in Table 2.

Genetic predisposition and risk of inheritance

A genetic predisposition to EoE and CD is supported by evidence of familial clustering and twin studies. Regarding EoE, family history has been reported in 2%–7% of patients[9,10] and susceptibility has been associated with genetic variants at 5q22 (*TSLP*) and 2p23 (*CAPN14*).[17] Likewise, first-degree relatives of patients with CD have a greater increased risk of developing either CD and ulcerative colitis. Genetic studies have identified so far 163 susceptibility loci for IBD, mostly shared between CD and ulcerative colitis.[23]

Epidemiologic trends

The first case series of EoE as a distinct new condition were published in 1993 and 1994.[2,3] Since then, EoE has rapidly become a common global disease with a steadily rising incidence in multiple, mostly industrialized, locations. A first systematic review with meta-analysis exhibited a current pooled EoE incidence rate of 7.2/100,000 people/year and prevalence rate of 26.3 cases/100,000 people both in children and adults.[24] However, this could be an underestimate. In Switzerland (Canton of Vaud), the prevalence rate in 2013 was 24.1/100,000 people,[25] but the annual EoE incidence was 10.6 times higher in the period from 2010 to 2013 when compared to that in the period from 1993 to 2009. Recent adult data in Spain (Castilla La Mancha) have shown prevalence rates of 44.6 cases/100,000 people.[26] Finally, prevalence rates in the United States have been reported to be 56.7 cases/100,000 people, peaking in men 35–39 years old with a rate of 114.6/100,000 people.[27]

Table 1. Main differences between eosinophilic esophagitis and Crohn's disease.

First description as a distinct entity	1993	1932
Etiology	Antigen-induced (mainly food)	Uncertain
Pathophysiology	Anomalous Th2 response	Anomalous Th1/Th17 response
Extension	Limited to the esophagus	Entire GI tract
Functional status	Better (usually without anemia, malnutrition, systemic manifestations, infectious complication, surgeries, or drug toxicity)	Worse (anemia, malnutrition, systemic manifestations, infectious complication, surgical procedures, and drug toxicity may be common)
Gender	Male predominance (2–4:1)	Slight female predominance
Noninvasive markers of activity	None yet	Imaging studies/stool markers
Extraintestinal manifestations	To be defined	Mainly musculoskeletal and dermatologic, less common hepatobiliary, ocular, renal and pulmonary.
Therapy principles	Locally acting anti-inflammatory drugs Esophageal dilation for fibrostenotic findings	Systemically active immunomodulatory drugs (± combination with topical therapies) Surgery in case of complications
Efficacy of dietary therapy	Empiric elimination diet (mainly involving milk, wheat and eggs) can lead to disease remission	Exclusive enteral nutrition can lead to disease remission in pediatric patients A low FODMAP diet may improve functional gastrointestinal symptoms
Long-term clinical complications	Esophageal strictures As of yet no increased risk for esophageal cancer demonstrated	Intestinal strictures and fistulizing disease Increased risk for colorectal cancer and small bowel cancer
Long-term drug-related complications	Unknown yet for PPI and topical steroids	Increased risk for lymphoproliferative disorders with thiopurines Increased melanoma and other skin cancer risk for patients under TNF-antagonists Increased risk for infectious diseases Side effects of systemic steroids

GI: gastrointestinal; FODMAP: fermentable oligosaccharides, disaccharides, monosaccharides and polyols; PPI: proton pump inhibitors; TNF: tumor necrosis factor.

Overall, incidence rates for EoE are coming steadily closer to that recently reported for CD in North America,[28] Europe,[29] Spain[30] and Switzerland[31] (incidence rates 9–20 cases per 100,000 people/year). Since CD was first described in 1932,[32] prevalence rates (100–320 cases per 100,000 people) still remain higher compared to those in EoE.[30,31] These epidemiological data are summarized in Table 3.

Large numbers of EoE cases have been reported in North America, Western and Eastern Europe, and Australia. Fewer cases have been reported in South America, Asia and the Middle East; cases from Northern Africa have recently been reported,[33] and, as of yet, none in Sub-Saharan Africa or India.[34] In contrast, CD has been reported worldwide, but the incidence and prevalence appear to be lower in Asia and the Middle East.[28] Collectively, we do believe that epidemiological figures of EoE will soon catch up with CD. EoE is becoming a global disease affecting children and young adults who will suffer this chronic condition for several decades, without reported complications or mortality. Hence, similar and even higher prevalence rates to that of CD are likely expected for EoE in the next 10–20 years if current epidemiologic trends persist.

Environmental risk factors

It is intriguing to speculate about why the incidence of EoE and, to a lesser extent CD, is increasing so rapidly in Western countries, although these types of changes usually indicate an environmental rather than a genetic cause. The hygiene hypothesis has been largely suggested as a potential cause of rising allergic and autoimmune disorders in industrialized countries.[35] Improved domestic hygiene and sanitation and smaller families with less-crowded living conditions might

Table 2. Potential similarities between eosinophilic esophagitis and Crohn's disease.

Genetic basis and inheritance risk	Susceptibility loci identified Family history
Environmental risk factors	Lack or non-exclusive use of breastfeeding Early exposure to repeat antibiotic therapy Westernized diet
Epidemiology	Rising incidence, more common in Western/Northern countries Affects predominantly pediatric and young adults
Natural history	Chronic disease, typically with intermittent relapsing symptoms Progression from inflammation to fibrostenotic remodeling
Quality of life	Impaired with symptom severity and dietary restrictions Improved with therapeutic interventions
Depth of inflammation	Transmural
Phenotypes	Inflammatory/fibrostenotic
Disease activity assessment	Clinical manifestations poorly predict biological activity
Diagnosis	Symptoms, endoscopic findings and histology
Therapeutic management	Induction and maintenance of remission
Therapeutic goals	Clinic, endoscopic and histologic remission (deep remission), but still lacking validated definitions in both entities. Resolution of fibrostenotic features
Therapeutic modalities	Medical/dietary therapy plus endoscopic dilation if required
Therapeutic agents targeting selective interleukins in the inflammatory cascade	Modest results, lack of response in all patients.
Unsolved issues	Predictors of treatment response Predictors of disease progression Monotherapy vs. combination therapy Do all patients need maintenance treatment? Maintenance therapy discontinuation: who and when?
Challenges perceived by patients and their relatives	Lack of disease awareness Lack of childhood and transition experts Lack of specialized multidisciplinary units Limited access to quality endoscopy Personalized treatments

Table 3. Incidence and prevalence rates of Crohn's disease and eosinophilic esophagitis (EoE) in North America and Europe, including Switzerland and Spain.

	Incidence		Prevalence	
	Crohn's disease	**EoE**	**Crohn's disease**	**EoE**
North America[27,28]	Up to 20/100,000 year	Up to 11/100,000 year	200/100,000	56.7/100,000
Europe[29]	14/100,000 year	–	322/100,000	–
Castilla La Mancha, Spain[26,30]	8.9/100,000 year	6.37/100,000 year	137/100,000	44.6/100,000
Canton of Vaud, Switzerland[25,31]	Not determined	6.3/100,000 year	100.7/100,000	24.1/100,000

account for a lower exposure to infectious agents important for the development of immunoregulatory mechanisms. In this regard, an inverse association between *H. pylori* infection and EoE has been suggested.[36] Interestingly, several early-life exposures that could theoretically affect the early-life microbiome have been associated both with EoE and CD. Lack or non-exclusive breastfeeding[10,37–39] and early antibiotic exposure[40,41] have been consistently associated with both diseases. As for EoE, cesarean delivery has also

been identified as an early-life risk factor.[40] Therefore, markers of early altered esophageal/intestinal microbiome may modulate the risk of EoE and CD later in life. It is important to note that these interesting findings have not been replicated in some studies.[41,42] All of these concepts have paved the way for the development of fecal microbiota transplantation as an effective therapy for a subset of patients with CD.[43] Several differences in the composition of the esophageal microbiome have been demonstrated in EoE as compared to healthy controls, and its pathogenic role is currently being evaluated.[44]

This incidence rise of both diseases in Western countries has been steadily followed in developing countries paralleling the increase of Westernized diets, characterized by high protein and fat as well as excessive sugar intake, with fewer vegetables and less fiber. The consumption of caloric sweeteners in beverages, intake of fast food (pizza, hamburgers, snacks, beverages) and wheat-containing foods (pasta, bread, cakes) has increased enormously over the past two decades and continues to grow, since away-from-home-foods and snacks account for almost 50% of daily consumed food and energy.[45] Noteworthy, this concept linking Western lifestyle and CD led to the application of the low FODMAP diet to CD.[45] A recent meta-analysis has shown that high dietary intakes of polyunsaturated/omega-6 fatty acids and meat were associated with an increased risk of CD, whereas high fiber and fruit intakes were associated with decreased CD risk.[46] Exclusive enteral nutrition and a low FODMAP diet have recently been shown to be effective dietary interventions for CD.[19–21] Since oligosaccharides contained in fruits, cereals and vegetables exert a prebiotic effect on the gastrointestinal microbiota, it seems conceivable that the effects of microbiota and diet are directly interrelated in CD.[47,48] As for EoE, it remains unknown what has actually changed in cow's milk, wheat and eggs, which have been staple foods in Western countries for millennia. Changes in food sources, addition of antibiotics/fertilizers, genetic modifications to plant and animal foodstuffs, drastic accelerated processing of food supplies and plastic or synthetic food packaging have all been proposed as potential causes.[34]

Disease activity assessment

By definition, EoE is a clinicopathological disease. Both clinical and pathologic information should be taken into consideration and neither of these parameters should be interpreted in isolation.[1] The development and validation of a symptom assessment instrument for pediatric and adult EoE patients is a challenge for a number of reasons. Children may not be able to fully describe their symptoms and toddlers and small children do not suffer from dysphagia and food impaction, which nearly universally appears in adolescents and adults. Furthermore, dysphagia may depend not only on the existence of esophageal caliber abnormalities or active mucosal inflammation, but also on the consistency of the ingested food and behavioral adaptations, such as food avoidance, food modification, or an altered eating pace. In spite of these considerations, most physicians still feel symptoms are strong predictors of disease activity.[49] In 2014, an international group of experts developed and validated the EoE activity index (EEsAI), a patient-reported outcome (PRO) instrument to be used in adult patients that quantifies not only the difficulties foreseen by patients in eating eight different food consistencies, but also dietary or behavioral modifications for the same food consistencies.[50] Two years later, this instrument was evaluated in a multicenter multinational cohort of 269 adult EoE patients and compared to endoscopic and histologic assessment.[51] Esophageal symptoms alone showed a quite modest predictive capacity for estimating the presence of either histological or endoscopic remission in adult patients with EoE. Therefore, clinicians should not make assumptions about the biological activity of EoE based exclusively on symptoms, and endoscopy and biopsy for diagnosis and monitoring of the disease continue to be necessary.[52] Regarding CD, commonly used activity scores are the Crohn's Disease Activity Index (CDAI) and the Harvey-Bradshaw Index. The CDAI was developed in the 1970s to assess the degree of illness in individuals with CD and has since been used widely in clinical trials of the condition. The Harvey-Bradshaw Index is a simplification of the CDAI, designed to make data collection and computation easier.[53] Both have been extensively criticized for heavy weighting on subjective clinical symptoms, besides not being specific to discriminate reliably functional symptoms related to specific irritable bowel syndrome, which may be common in patients with CD in remission.[54] Conversely, it was recently shown that half of the patients under azathioprine and/or infliximab in clinical remission, according to CDAI score, had endoscopic and/or C-reactive protein evidence of residual active CD.[55] The authors concluded that clinical symptoms scored by CDAI are not a reliable measure of the underlying biological activity of CD. As such, additional modalities such as biomarkers, endoscopy, or imaging should be implemented to understand the full image of biological disease activity at baseline and during follow-up.[56,57]

Quality of life

IBD is a chronic debilitating illness with a significant impact on the health status of children and young

adults. Intestinal and extra-intestinal disease activity, surgical interventions, drug-induced side effects and related psychosocial factors all adversely affect several patient outcomes including quality of life, psychological functioning and treatment adherence.[58] Patients also show diminished ability to undertake household and social activities; furthermore, recent studies suggest that 9% to 19% of patients with CD suffer from short-term absences from work and 19% to 22% are on long-term disability.[59] Enormous efforts have been made over the past decade to overcome the most common challenges perceived by patients and their relatives: lack of awareness of the disease, lack of multidisciplinary and specialized clinics, lack of experts on childhood-onset IBD and transition from pediatric to adult care, difficulties in bathroom access, limited access to skilled psychologists, dietitians and IBD experts, as well as open discussions of personalized treatments.[60,61]

As for EoE, evolving evidence has lately highlighted that symptom severity, biological disease activity and dietary therapy negatively influence patient quality of life, which is improved during the course of evaluation and treatment.[11,12,62] Therefore, reducing symptoms, esophageal inflammation, optimizing dietary restrictions, and close monitoring of patients might be key for improvement of quality of life.

Natural history

EoE and CD both are chronic and progressive diseases, and in some patients persistent transmural inflammation with subsequent tissue remodeling results in fibrostenotic stricturing. In EoE, untreated symptoms and inflammation can remain over years because of diagnostic delay,[63] and there is a high likelihood of recurrence after discontinuing any modality of treatment.[1] Two recent studies nicely showed that the prevalence of esophageal strictures correlates with the duration of untreated disease.[13,14] Furthermore, subepithelial fibrous remodeling significantly increases with age.[64] As for CD, approximately 80% of patients have small bowel involvement (30% distal ileitis, 50% ileocolitis), 20% have disease limited to the colon and 5% predominant involvement of the upper gastrointestinal tract. The typical course in patients with CD involving the small and/or large intestine is one of intermittent exacerbation of symptoms followed by periods of remission. Almost 20% of patients progress to a more aggressive phenotype at 90 days of diagnosis and 50% will eventually develop a stricturing or fistulizing complication 20 years after initial diagnosis, especially when ileal and perianal disease were present at the time of diagnosis.[18] More specifically, strictures may occur in one of three patients within 10 years of diagnosis.[65]

Therapeutic endpoints

The ideal treatment endpoints both for EoE and CD would be complete resolution of symptoms, endoscopic findings, and histologic inflammation in order to prevent remodeling and related complications.[18,66,67] Lately, mucosal healing (endoscopic remission) and deep remission (clinical, biologic, endoscopic and histologic remission) have been associated with improved outcomes in CD, and consequently, are currently recommended as therapeutic targets.[68] The lack of validated definitions, however, for symptom, endoscopic and histologic remission both in EoE and CD constitutes a major challenge. A panel of experts recently defined clinical remission in CD as resolution of abdominal pain and diarrhea/altered bowel habit, whereas endoscopic remission was defined as resolution of ulceration at ileocolonoscopy or finding of inflammation on cross-sectional imaging.[69] No consensus is available on histologic remission yet.[70] Regarding EoE, the precise clinical (resolution of dysphagia?, what score to use?, what about other symptoms?) and histologic (no eosinophilic inflammation?, < 5 eos/high-power field (HPF)?, < 15 eos/HPF?) targets for EoE should also be a matter of debate.

Therapeutic management

The choice of therapy both for EoE and CD will vary depending on the anatomic location of disease (only for CD), the severity of the disease, phenotype, comorbidities, individual characteristics of the drug and patient, local expertise, costs and the ultimate goal of therapy (i.e. induction or maintenance of remission).[18,66,67] Both diseases have an induction phase, in which the condition is brought under control, and a maintenance phase, in which the main goals are preventing flares by keeping patients in remission, thereby restoring their quality of life. The therapeutic armamentarium for both diseases includes dietary, pharmacologic and endoscopic interventions. Drugs and dietary changes target the inflammation associated with the disease pathogenesis, whereas endoscopic dilation treats fibrous remodeling and complications, but has no effect on underlying inflammation.[66,67]

A further frustrating commonality between EoE and CD is the lack of response in all patients when attempting to target specific interleukins (IL) within the inflammatory cascade with biologic therapies. Despite potentially sound theoretical mechanisms of action and initially promising data, many biologic drugs targeting ILs have failed both in EoE (IL-5, IL-13)[15] and CD (IL-10).[71] Possibly, the lack of a final common inflammatory pathway likely inhibits yielding complete response. Both conditions encompass a heterogeneous

group of patients with variable disease courses. A roadmap for personalized disease treatment, based on genetic susceptibility, genotype-phenotype concordance, biomarkers, drug monitoring and microbial data, is currently under development for CD,[72,73] and so should be in the foreseeable future for EoE.

Induction therapy. This treatment phase aims to achieve symptoms and endoscopic remission (CD) and symptom and histologic remission (EoE). In the majority of EoE patients, a PPI should still be considered first, with dietary therapy or swallowed topical corticosteroids used if there is no PPI response.[66,67] Patients with severe fibrostenotic EoE or malnutrition at onset might be better treated with potent anti-inflammatory drugs (i.e. swallowed topical corticosteroids).[1,66,67] A follow-up endoscopy after an initial six- to eight-week course of therapy should be carried out to document histologic response.[66] Regarding CD, a fast-acting short-term agent (i.e. steroids or anti-tumor necrosis factor (TNF)) is used to achieve rapid symptom relief.[18] Monitoring of treatment efficacy is usually assessed by means of changes in symptom scores, non-invasive biomarkers (serum reactive C protein and fecal calprotectin), endoscopy and imaging techniques (e.g. magnetic resonance enterography).[57,74,75]

Maintenance therapy. The choice of a long-term intervention for maintenance therapy should aim to balance efficacy with side effects and complications within a given individual. For instance, dietary therapy in EoE may not be a good choice in patients with a pre-existing restrictive diet because of multiple food allergies or with predictable poor compliance, but it can be evaluated in patients unwilling to take long-term medications. Likewise, methotrexate in CD might be a poor choice for a patient of childbearing age or with pre-existing liver disease, but can be an excellent option for a patient with CD and arthropathy.

Maintenance therapy in EoE must be considered for all patients, but particularly in those with severe dysphagia or food impaction, high-grade esophageal stricture, and rapid symptomatic/histologic relapse following initial therapy.[1,66,67] However, there is controversy about whether treatments should be continued indefinitely, particularly in light of the potential side effects and limited long-term data. In contrast to CD, a trend toward tapering maintenance doses for PPI and topical steroids is evident in EoE.[76,77] Whether drug doses for EoE may be used like in CD, not changing what works for a patient from induction to maintenance, should be clarified. It also remains unclear when long-term endoscopic monitoring of disease activity should be performed (every year, three or five years), whether combination therapy may potentially and synergistically enhance an anti-inflammatory response,[78] or if sustained histologic remission may alter the natural history of the disease. Like in CD, switching drug classes or from medications to diet might also be feasible, as lately shown by two series of patients with esophageal symptoms and eosinophilia that responded not only to PPI therapy, but also to diet/topical steroid therapy, and vice versa.[79,80]

Maintenance therapy and its unsolved issues in EoE have correlates in CD. Medical therapies are intended to modify the underlying disease process, in the hope of achieving biologic remission and preventing harmful complications. Mainly since 2013,[81] endoscopic mucosal healing has been incorporated as a primary or secondary long-term endpoint in therapeutic algorithms. A recent meta-analysis has shown that mucosal healing predicts long-term clinical remission and fewer hospitalizations and surgeries.[82] On the other hand, superiority of combination therapies with thiopurines and TNF blockers for improved symptom control and mucosal healing should be balanced with the increased risk of infectious and malignant complications. A recent systematic review showed that more than 50% of patients with IBD who discontinued an immunomodulator after combination therapy had a disease relapse.[83] Therefore, accurate identification of subgroups of patients who are good candidates for discontinuation of treatment is required. Switching drug classes or agents is common in CD for a number of reasons like primary non-response, loss of response, insufficient efficacy (i.e. absence of mucosal healing), and intolerance or unacceptable side effects.[18] The optimal duration of maintenance therapy is unclear yet, and studies are needed to identify subgroups of patients in whom treatment can be discontinued.

Treatment of stricturing disease. Endoscopic dilation can offer symptomatic response in case of stricturing EoE and CD. However, repeated dilations are often needed, and long-term outcomes of endoscopic balloon dilation remain to be investigated.[84,85] Topical steroids and dietary therapy in EoE have shown their ability to reverse subepithelial fibrosis.[64,86,87] Whether medical/dietary therapy can be effective coadjuvant treatments for dilation or after dilation in EoE is yet to be determined. Likewise, the role of medical therapy in stricturing CD is controversial. Differentiating inflammatory from fibrotic strictures remains challenging. Medical therapy with biologics may play a role in CD stricture with an inflammatory component and/or concurrent inflammation adjacent to the stricture area. Although biological therapy may reduce the risk for the formation of strictures from mucosal inflammation, rapid mucosal healing from potent biological agents may predispose patients to the development of new strictures or

worsening of existing strictures.[85] Additionally, there is no clear evidence about the efficacy of postdilation medical therapy to prevent recurrence of strictures.[85]

Conclusions and research agenda

Through a relevant number of comparisons between EoE and CD, this review paper underscores salient features, and unmet diagnostic and therapeutic needs, that may be common for both disorders. Like in CD, the upcoming research agenda for EoE should be oriented to fill diagnostic gaps, mainly measuring disease activity and deep remission, and pursue personalized treatments reversing the progressive natural history of the disease, by means of increasing our knowledge of risk factors for progression, adequate identification of phenotypes, genotype-phenotype concordance, drug doses and monitoring, and esophageal microbiome data. All these data will allow us to better predict outcomes for individual patients and to precisely tailor therapy.

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