Novel corticosteroid formulations in the treatment of eosinophilic esophagitis: what is the evidence?

S. Walgraeve[1], T. Vanuytsel[2]

(1) Faculty of Medicine, KU Leuven, Leuven, Belgium; (2) Department of Gastroenterology and Hepatology, University Hospitals Leuven, Leuven, Belgium.

Abstract

Background and study aims: **Eosinophilic esophagitis (EoE) is a food allergen-induced disease of the esophagus. Chronic, eosinophil-predominant inflammation eventually leads to fibrosis, esophageal dysfunction and severe morbidity. Swallowed topical corticosteroids (STCs) are a mainstay of anti-inflammatory therapy in the treatment of active EoE. Data on the efficacy of novel corticosteroid formulations, developed specifically for esophageal delivery, have recently become available.**

Methods: **A comprehensive review was performed aiming to summarize evidence on the role of STCs in the treatment of EoE. Two biomedical bibliographic databases (PubMED, EMBASE) were searched for articles providing original information on the efficacy and safety of STCs in adult EoE patients.**

Results: **Budesonide orodispersible tablet (BOT) and budesonide oral suspension (BOS) both surpassed placebo formulations regarding the efficacy of inducing and maintaining histologic, symptomatic and endoscopic remission. Overall, BOT displayed the highest grade of efficacy with clinico-histologic remission rates up to 75% after 1 year. Fluticasone propionate (APT-1011) achieved and maintained histologic and endoscopic responses in the majority of patients, whereas only a positive trend was demonstrated for symptomatic improvement. Mometasone and ciclesonide were studied in a limited number of smaller-scale trials and placebo-controlled data are required to substantiate the promising findings. All STCs displayed a similar side effects profile and were generally considered safe and well-tolerated.**

Conclusions: **Current evidence supports long-term treatment with novel corticosteroid formulations, challenging the established treatment paradigm of EoE. BOT appears to be the most effective steroid therapy, although head-to-head comparative trials between STCs are needed.** (Acta gastroenterol. belg., **2023,** 86, **437-448**).

Keywords: eosinophilic esophagitis, dysphagia, pharmacologic treatment, topical corticosteroids, fluticasone, budesonide.

Introduction

Eosinophilic esophagitis (EoE) is a chronic, food allergen-induced disease of the esophagus (1). An eosinophil-predominant infiltration causes chronic inflammation and fibrosis, eventually leading to esophageal dysfunction and severe morbidity (2). It is a relatively new disease that has only recently entered the gastroenterological diagnostic landscape (3). Clinically, EoE is defined by symptoms of esophageal dysfunction, such as dysphagia and chest pain, histologically by ≥15 eosinophils per high power field (eos/hpf) or ≥60 eos/mm^2. Common endoscopic findings are edema, rings, exudates, furrows and strictures (4,5). When first described in the 1990s by Straumann and Attwood, it was thought to be a rare clinicopathological phenomenon (6,7). In contrast, EoE is now recognized as a leading cause of chronic esophagitis, esophageal dysphagia and food bolus impactions (8,9). The estimated global prevalence in adults is around 42.2/100.000 inhabitants and the incidence has been increasing substantially over past decades. An improved disease recognition only partially explains this epidemiological escalation (9,10).

The pathophysiology of EoE is incompletely understood (Figure 1). A consensus exists that genetic, antigenic, environmental and intrinsic immune system-related factors interact in a complex, multifactorial fashion (11). Therefore, EoE is strongly related to other allergic diseases such as asthma and atopic dermatitis, which co-exist in 50-80% of patients with EoE (12-14). In contrast to these IgE-mediated allergic conditions however, recent evidence suggests that EoE is more likely related to immunoglobulin G4 (IgG4) (15-17). A T-helper 2 (Th2) cell-associated inflammatory response lies at the root of these molecular pathways, usually provoked by exposure to food allergens, which triggers the release of epithelial cytokines such as thymic stromal lymphopoietin (TSLP) (18,19). Subsequently several other chemokines and cytokines are released in abundance, of which interleukine 4 (IL-4), IL-13 and IL-5 are of pivotal importance. These activate the STAT6 pathway and prompt the secretion of a large set of proteins, with two major consequences (11). First, VCAM-1, ICAM-1 and eotaxin-3 contribute to the homing and survival of eosinophils in the esophageal epithelium (20,21). Second, IL-13 and transforming growth factor β (TGF-β) induce tissue remodeling through the secretion of calpain 14 (CAPN14) and inhibition of filaggrin, desmoglein-1 (DSG-1) and claudin-7 (22-24). This inflammatory reaction results in collagen deposition, smooth muscle hyperplasia and a disrupted epithelial barrier (25).

Multiple reasons exist to treat active EoE. First, EoE knows a chronic and progressive evolution when left untreated (4). Second, histologic and symptomatic relapse is common and occurs on average within 3 months after cessation of a successful treatment (26). Third, incomplete control of eosinophilic inflammation leads to fibrostenotic

Correspondence to: Tim Vanuytsel, MD PhD., Dienst Maag-Darm-Leverziekten, UZ Leuven, Herestraat 49, 3000 Leuven..
Email: tim.vanuytsel@uzleuven.be

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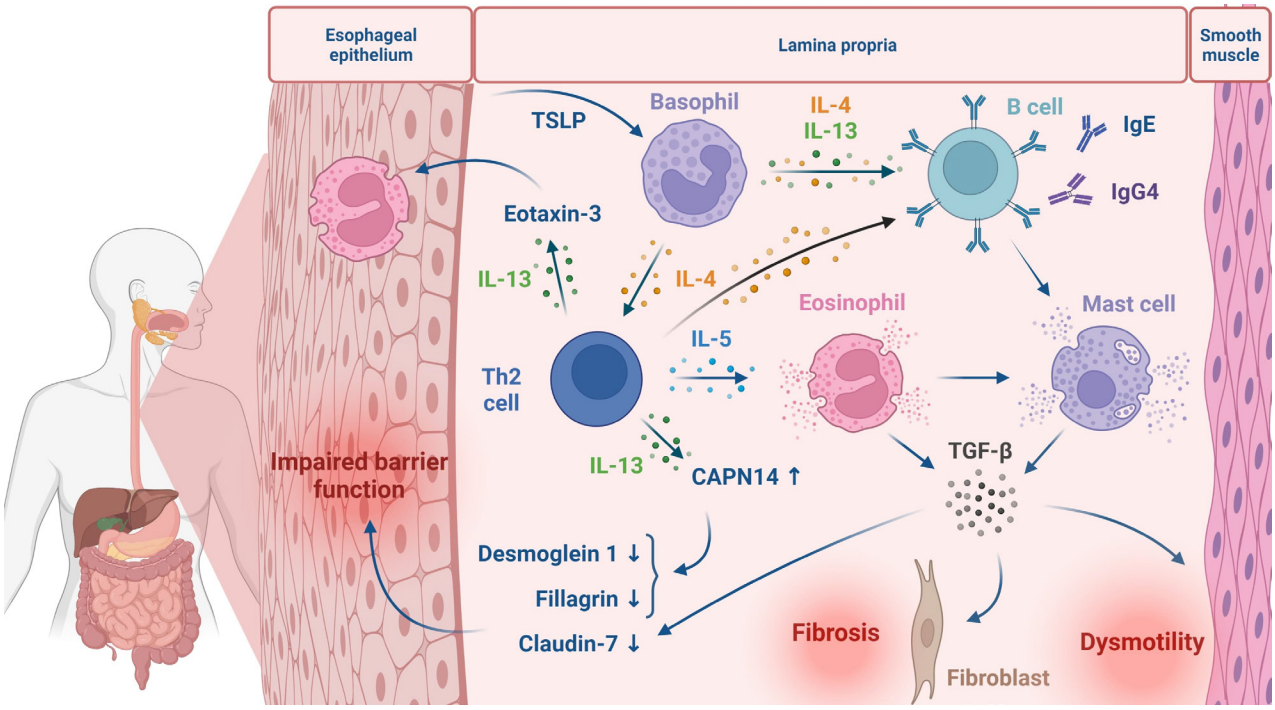

Figure 1. — Pathophysiology of eosinophilic esophagitis (EoE). Food allergens trigger a type 2 inflammatory cascade in which IL-4, IL-13 and IL-5 are secreted. IL-4 induces the transformation of naïve Th cells into Th2 cells and activates B cells to produce IgE and IgG4. IL-13 induces eotaxin-3 secretion, a cytokine homing eosino-phils to the esophageal epithelium, and regulates CAPN14 expression. An increase of CAPN14 is related to downregulation of desmoglein-1 and fillagrin, leading to dysfunction of the epithelial barrier. IL-5 is essential in the priming, expansion and survival of eosinophils. TGF-β, produced by eosinophils and mast cells, is a pivotal cytokine in the formation of cellular junctions and tissue remodeling. Impaired barrier function, fibrosis and dysmotility of the esophagus are the result of this inflammatory reaction. CAPN14, calpain 14; IgE, immunoglobulin E; IgG4, immunoglobulin G4; IL, interleukin; TGF-β, transforming growth factor β; Th, T helper cell; TSLP, thymic stromal lymphopoietin. Created with BioRender.com.

remodeling with stricture formation and functional damage (27,28). Patients with a fibrostenotic phenotype have a higher risk of experiencing food impactions and an increased need for endoscopic esophageal dilation (29,30). Fourth, symptoms of esophageal dysfunction have an important negative impact on the quality of life (QoL) due to associated emotional anxiety and hindrance of social activities (31-34).

Therapeutic strategies in EoE revolve around three D's: diet, drugs and dilation. Options for dietary modification include elemental formula diets, elimination diets guided by food allergy testing and empiric food-elimination diets (FEDs). Due to impracticality or inconsistency of elemental diets and testing-directed diets respectively, only FEDs are routinely used in clinical practice (35). Empiric FEDs exclude the most frequent allergen-inducing food items: cow's milk, wheat, eggs, soy, peanuts/tree nuts and fish. These are all eliminated in six food-elimination diets (6-FED), whereas less restrictive 4-FEDs and 2-FEDs will only eliminate the first four and two food items listed (36). Pharmacologic therapies used consist of proton-pump inhibitors (PPIs), swallowed topical corticosteroids (STCs) and biologics. The prevailing first-line treatment consists of either an empiric FED or pharmacologic therapy with PPIs or STCs (1).

In spite of the increasing incidence and our advancing knowledge of EoE, only one corticosteroid formulation, namely budesonide orodispersible tablet (BOT), is currently approved by the European Medicines Agency (EMA) for on-label use in EoE (37). Moreover, due to the absence of reimbursements, off-label treatment with budesonide suspensions or swallowed powder from inhalers used in asthma is still the mainstay of therapy in several areas, including Belgium. This comprehensive review aims to provide evidence on the strengths and limitations of novel corticosteroid formulations in EoE, recommendations on their use in the management of EoE and a future research agenda.

Materials and methods

One researcher (SW) performed a literature search in two biomedical bibliographic databases (PubMED, EMBASE). A registry of clinical trials (ClinicalTrials.gov) and a clinical resource tool (UpToDate) were also consulted. The search took place from March 2022 up until December 2022, using a combination of free text and Mesh Terms. The following search strategy was used to explore the MeSH and Emtree thesaurus: ("eosinophilic esophagitis" OR "EoE") AND ("Glucocorticoids" OR "Budesonide" OR "Fluticasone" OR "Mometasone

Table 1. — **Summary of swallowed topical corticosteroid formulations tested in eosinophilic esophagitis for induction treatment**

Medication	Formulation	First author, date and title	Study status, population size and follow up	Dosing	Primary outcome	Key secondary outcome	Conclusion
Budesonide	Orodispersible tablet (BOT)	Lucendo, et al. (2019) (38).	Phase 3 n = 88 6 weeks	1 mg twice daily	58% clinico-histologic remission rates in the BOT group vs. 0% in the placebo-treated patients *(p<0.0001)*.		BOT treatment was superior to placebo regarding clinical and histologic outcomes.
	Oral suspension (TAK-721)	Dellon, et al. (2017) (39).	Phase 2 n = 93 12 weeks	2 mg twice daily	Following treatment with BOS, the decrease in DSQ score *(p=0.0096)* and in histologic response (≤6 eos/hpf, *p<0.0001*) was significantly larger compared to treatment with placebo.	The EREFS score decreased on average 3.8 points more after BOS treatment than after placebo treatment *(p<0.0001)*.	Histologic, symptomatic and endoscopic endpoints improved significantly more following BOS treatment compared to placebo, whilst being well tolerated.
		Hirano, et al. (2021) (40).	Phase 3 n = 318 12 weeks	2 mg twice daily	53% histologic response *(p<0.001)* and 53% dysphagia symptom response *(p=0.024)* in BOS-treated patients vs. 1% and 39% respectively with placebo.	30% of BOS-treated patients achieved full clinico-histologic response compared to 0% with placebo *p<0.001)*.	BOS achieved significantly higher histologic, symptomatic and endoscopic response rates compared to placebo.
Fluticasone	Orodispersible tablet (APT-1011)	Hirano, et al. (2020) (41).	Phase 1/2a n = 24 8 weeks	1.5-3.0 mg once or twice daily	12 patients receiving APT-1011 experienced 26 adverse events related to the treatment, of which none were severe, harmful or led to cessation of treatment.		APT-1011 was deemed safe and well-tolerated in the majority of patients.
		Dellon, et al. (2022) (42).	Phase 2b n = 106 52 weeks	1.5-3.0 mg once or twice daily	86% vs. 0% histologic response at week 12 in patients treated with APT-1011 and placebo respectively *(p<0.001)*.	At week 12, all APT-1011 dosing groups were superior over placebo regarding improvement in EREFS score and all symptom metrics scores used.	After 12 weeks, all dosages of APT-1011 achieved higher histologic, endoscopic and symptomatic response rates compared to placebo.
Mometasone	Viscous suspension	Syverson, et al. (2019) (43).	Retrospective cohort study n = 34	750-1500 µg once daily	68% histologic remission rates (≤5 eos/hpf, *p<0.001*) following treatment with viscous mometasone.		Treatment with swallowed viscous mometasone achieved high rates of histologic remission, including in previously steroid-resistant patients.
	Swallowed spray	Tytor, et al. (2021) (44).	Phase 2 n = 36 8 weeks	200 µg 4 times daily	Average WDS score decreased by 6.5 after mometasone treatment *(p<0.01)*.	In the mometasone group, the average EORTC QLQ-OES18 and SF-36 questionnaire score did not significantly decrease.	Improvement of dysphagia was achieved with topical mometasone treatment, yet a significant effect on the quality of life could not be demonstrated.
Ciclesonide	Swallowed aerosolization	Nistel, et al. (2021) (45).	Retrospective cohort study n = 81	160-1280 µg once daily	53% histologic response rate (<15 eos/hpf, *p<0.001*) and 68% symptomatic improvement rate *(p<0.001)*.		Histologic inflammation and symptoms improved in the majority of patients treated with ciclesonide swallowed aerosolization.

BOS, budesonide oral suspension; BOT, budesonide orodispersible tablet; DSQ, Dysphagia Symptom Questionnaire; EORTC QLQ-OES18, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Oesophageal Module 18; eos/hpf, eosinophils per high power field; EREFS, endoscopic reference score; n, amount of patients included; SF-36, Short Form-36 Quality of Life Questionnaire; WDS, Watson Dysphagia Scale.

Furoate" OR "Ciclesonide" OR "Glucocorticoids/adverse effects"). Our comprehensive review included studies published in English with an adult patient population, regardless of study design, ethnic group or gender. Narrative reviews and studies carried out in animals and pediatric patients were excluded. Titles and abstracts were screened and if concordant with our inclusion and exclusion criteria, the full-text articles were analyzed. One senior researcher (TV) supervised and edited the literature review.

BOS, budesonide oral suspension; BOT, budesonide orodispersible tablet; DSQ, Dysphagia Symptom Questionnaire; EORTC QLQ-OES18, European Organization for Research and Treatment of Cancer Quality of

Table 2. — **Summary of swallowed topical corticosteroid formulations tested in eosinophilic esophagitis for maintenance treatment**

Medication	Formulation	First author, date and title	Study status, population size and follow up	Dosing	Primary outcome	Key secondary outcome	Conclusion
Budesonide	Orodispersible tablet (BOT)	Straumann, et al. (2020) (46).	Phase 3 n = 204 48 weeks	0.5-1 mg twice daily	Clinico-histologic remission after 48 weeks was maintained in up to 75% of patients in the BOT group compared to 4% in the placebo group *(p<0.001)*.		Prolonged therapy with BOT was superior to placebo in maintaining clinico-histologic remission, with limited adverse events.
	Oral suspension (TAK-721)	Dellon, et al. (2022) (47).	Phase 3 n = 219 52 weeks	2 mg twice daily	64% of BOS-treated patients maintained clinico-histologic response at week 52 vs. 0% with placebo *(p<0.001)*.	At week 52, 19% of initial partial and non-responders achieved clinico-histologic response.	Continuation of BOS improved maintenance of efficacy compared to withdrawal from treatment, whilst assuring safety.
Fluticasone	Orodispersible tablet (APT-1011)	Dellon, et al. (2022) (42).	Phase 2b n = 106 52 weeks	1.5-3.0 mg once or twice daily	After 52 weeks of APT-1011 treatment, histologic response (≤6 eos/hpf) in initial responders was maintained in up to 84% of patients.	At week 52, mean EREFS scores were maintained below 2.0 in initial responders.	Histologic, endoscopic and symptomatic responses remained superior in the APT-1011 treated group and were maintained after 52 weeks of treatment.

BOS, budesonide oral suspension; BOT, budesonide orodispersible tablet; eos/hpf, eosinophils per high power field; EREFS, endoscopic reference score; n, amount of patients included.

Life Questionnaire Oesophageal Module 18; eos/hpf, eosinophils per high power field; EREFS, endoscopic reference score; n, amount of patients included; SF-36, Short Form-36 Quality of Life Questionnaire; WDS, Watson Dysphagia Scale.

BOS, budesonide oral suspension; BOT, budesonide orodispersible tablet; eos/hpf, eosinophils per high power field; EREFS, endoscopic reference score; n, amount of patients included.

Results

General

STCs are a mainstay of pharmacologic therapy in the treatment of active EoE. Especially budesonide and fluticasone propionate are used in this setting, although recent evidence suggests that ciclesonide and mometasone might serve as comparable options (48). The premise of the efficacy of corticosteroids in treating EoE is derived from its use in other allergic diseases with a similar pathophysiology, such as asthma, atopic dermatitis and rhinosinusitis (49). This hypothesis was first confirmed for fluticasone in 2006 when Konikoff et al. demonstrated that after 3 months of treatment, histologic remission (peak eosinophil count ≤1 eosinophil per high power field (eos/hpf)) was achieved significantly more in fluticasone-treated patients (50%) compared to patients receiving placebo (9%, p = 0.047) (50). The potency of topical corticosteroids to induce histologic remission was thereafter confirmed in several randomized clinical trials (RCTs) (26,51-54). A limiting factor in the comparison of these studies is the lack of uniformity in study design, patient population, the dosages and types of corticosteroids tested and the definitions used for histological, clinical and endoscopic endpoints (55). In addition to histologic remission, recent phase 2 and 3 trials demonstrated the superiority of STCs over placebo in achieving symptomatic improvement (38-40,42,56). Table 1 and table 2 offer an overview of these trials in respectively inducing and maintaining therapeutic response in EoE. Intriguingly, it is not the type of corticosteroid, but the formulation used to administer the compound to the esophageal surface that seems crucial in determining the pharmacological potency (51,57). The corticosteroid formulations used in EoE were originally designed for airway administration in asthma therapy. These formulations are not optimized nor effective for esophageal delivery and result in insufficient control of inflammation (58). Several alternative preparations, such as oral suspensions and orodispersible tablets, have been developed and evaluated for improved drug delivery in EoE.

Induction treatment

Budesonide orodispersible tablet (BOT)

Budesonide orodispersible tablet (BOT) is an effervescent corticosteroid formulation which stimulates the production of saliva, after which budesonide-infused saliva is swallowed in small volumes (38). BOT (Jorveza®, Dr. Falk Pharma) is currently the only steroid formulation approved by the EMA for use in adults with active EoE (37). The effects were studied in a phase 3, multicenter study by Lucendo et al., reporting on the highly effective nature of BOT in the treatment of EoE (38). Clinico-histologic remission, defined as remission on both clinical and histologic rating scales, was achieved in 57.6% of patients treated with BOT 1 mg twice daily

vs. 0% of placebo-treated patients after 6 weeks ($p < 0.0001$). This combined primary endpoint is authentic to clinical practice, as both symptoms of esophageal dysfunction and eosinophilic infiltration of the esophagus are required to diagnose EoE (1). All additional major endpoints (isolated histologic or clinical remission, weekly Eosinophilic Esophagitis Activity Index (EEsAI-PRO) score ≤ 20, change in total modified Endoscopic Reference Score (EREFS)) further proved superiority of BOT over placebo. A relevant and significant decrease in the endoscopic fibrotic subscore was noted, suggesting that a long-term treatment with BOT might also reverse esophageal remodeling. This hypothesis is substantiated by a subset analysis that demonstrated markedly improved esophageal distensibility in these patients (59). Analogous to preceding RCTs, histologic remission rates (93.2%) exceeded clinical remission rates (59.3%) in the phase 3 trial. A phase 2 study consisting of the same type of patients reported similar data, with up to 100% histologic remission, equally in all esophageal segments (56). As the duration of mucosal contact time is directly correlated with the resolution of histologic features, this finding likely illustrates the potent nature of BOT in attenuating EoE (51). In this patient population, BOT also appeared to be the budesonide formulation of choice, with patient preference rates of 80% for BOT vs. 17% for budesonide oral suspension (BOS).

Budesonide oral suspension (BOS)

BOS is a viscous, mucoadhesive corticosteroid preparation designed to lengthen the esophageal contact time (39,40,60). In a multicenter phase 3 trial, 2 mg BOS administered twice daily was superior compared to placebo regarding all predefined endpoints (40). Rates of isolated clinical response (≥30% reduction in Dysphagia Symptom Questionnaire (DSQ) score), isolated histologic response (≤6 eos/hpf) and combined clinico-histologic response were 52.6%, 53.1% and 30.0% respectively following 12 weeks of BOS, vs. 1.0% ($p < 0.001$), 39.1% ($p = 0.025$) and 0.0% ($p < 0.001$) with placebo. Amongst all BOS histologic responders, 62.0% achieved any histologic response (<15 eos/hpf) and 32.4% achieved a strict histologic response (≤1 eos/hpf). Furthermore, patients treated with BOS experienced significantly greater reductions in mean total EREFS score, peak eosinophil count and mean EoE Histology Scoring System (EoEHSS). Noteworthy is the response distribution per esophageal region: especially the proximal and distal esophageal segments of placebo-treated patients lacked endoscopic and histologic response, whereas the BOS group achieved a more evenly distributed response amongst all segments. Nevertheless, a full clinico-histologic response achieved in only 30% of patients emphasizes the difficulty of achieving a combined histologic and symptomatic response, even in a clinical trial setting. These data build on previous phase 2 trials, which reported similar results about the safety and potency of BOS with regards to the histologic, symptomatic and endoscopic outcomes (39,56). A secondary analysis of the former trial showed a clear correlation between symptomatic improvement in dysphagia and pain with swallowing, and a simultaneous histologic or endoscopic response (60).

Fluticasone propionate

APT-1011 is a fluticasone propionate tablet developed specifically for treatment of EoE. Like BOT, it dissolves on the tongue and coats the esophagus when swallowed (61). The initial proof of concept was established in a phase 1/2a study, demonstrating APT-1011's superiority over placebo in histologic, endoscopic and symptomatic outcomes (41). This formulation was most recently tested in a phase 2b, dose-ranging trial by Dellon et al. (42). Here, they evaluated 3 total daily doses (1.5 mg, 3 mg and 6 mg) in 2 different dosage schedules (once daily or twice daily). Histologic response (≤6 eos/hpf) was achieved in 48%-86% of patients ($p < 0.001$) treated with APT-1011, with the highest response rates seen in patients receiving at least 3 mg daily. Generally speaking APT-1011 surpassed placebo in terms of endoscopic and symptomatic response, although the beneficial effect on symptoms was not significantly superior in all dosing groups. This finding was unlike previously conducted, smaller-scale trials with swallowed fluticasone which failed to demonstrate a significant symptomatic response altogether (53,54).

Mometasone and ciclesonide

A limited number of studies have been published on mometasone and ciclesonide, corticosteroid formulations with a high local effect and a theoretically lower systemic bioavailability compared to fluticasone or budesonide (62,63). A recent RCT from Sweden demonstrated that topical mometasone furoate improved dysphagia compared to placebo ($p < 0.05$), although a parallel benefit for the QoL could not be confirmed (44). These results complement a prior retrospective cohort study with a histologic response (<6 eos/hpf) in 68% of patients ($p < 0.001$), of which 72% was previously steroid nonresponsive (43). The potency and tolerability of mometasone is currently being investigated in an ongoing phase 2 trial (64). A retrospective cohort study consisting of 81 patients assessed the viability of ciclesonide in EoE, with favorable results (45). 75% of the ciclesonide-treated patients experienced a significant improvement in predominant EoE-related symptoms ($p < 0.001$ for dysphagia and abdominal pain, $p < 0.05$ for vomiting, chest pain and behavior changes). Histologic remission rates were 53%, with 29% of patients experiencing prior steroid resistance. Placebo-controlled data are required to further substantiate these findings.

Maintenance therapy

Budesonide orodispersible tablet (BOT)

Only recently data on the long-term efficacy of treatment with STCs in EoE have been published, addressing a crucial, previously unmet medical need (48,55). Maintenance therapy with BOT was reviewed in an extensive phase 3, multi-center European trial (46). Treatment with 0.5 mg and 1 mg BOT twice daily during 48 weeks was, similar to induction therapy, highly effective in maintaining complete clinico-histologic remission (≤15 eos/hpf and symptom resolution) in more than 70% of patients ($p < 0.001$). With the exception of histologic remission rates in patients with extensive pan-esophagitis, which were higher in the group receiving 1 mg twice daily (80% vs. 68% with 0.5 mg), the therapeutic efficacy was not influenced by dosage. These findings illustrate again the efficacy of the BOT formulation for esophageal delivery and the need for sustained anti-inflammatory therapy. First, relapse occurs in most patients within the first 100 days of treatment withdrawal and second, unlike previous assumptions, the effectiveness of BOT appears to diminish only slightly over time (65,66).

Budesonide oral suspension (BOS)

BOS' long-term potency, safety and relapse rate upon randomized withdrawal was evaluated in a phase 3, 36-week extension study (47). Patients with a complete clinico-histologic response after 12 weeks of BOS 2 mg twice daily were randomized to continuation with BOS (BOS-BOS) or discontinuation to placebo (BOS-PBO); incomplete and non-responders exclusively received BOS. At week 36 of treatment, the BOS-BOS group experienced higher rates of histologic response (≤6 eos/hpf; 76.0%), dysphagia symptom response (44.0%) and less frequent relapse (50.0%), compared to 4.5% ($p < 0.001$), 9.1% ($p = 0.008$) and 16.7% ($p = 0.038$) respectively in the BOS-PBO group. In contrast to the treatment results with BOT, histologic and endoscopic response did decrease over time with BOS (46). However, 13.2% of incomplete and non-responders did respond after 52 weeks, indicating that long-term continuation of BOS slightly improves the probability of patients eventually acquiring a response. Similar to BOT, prolonged BOS treatment also appears to alter esophageal remodeling. A previous RCT including 28 patients demonstrated an analogous trend, with reversal of esophageal fibrosis after 50 weeks of treatment with a budesonide suspension (26).

Fluticasone propionate

Maintenance treatment with APT-1011 was also analyzed in the aforementioned phase 2b trial (42). At week 52, 30%-69% of patients maintained histologic response (≤6 eos/hpf). The highest rates were seen in patients receiving at least 3 mg daily. A lower mean EREFS score and mean dysphagia frequency was similarly maintained during the 52 week extension phase. Symptomatic improvement however, rated by the Global EoE Symptom Score and EEsAI total score, was only significant in the higher dosage groups. The optimal balance between safety and efficacy was achieved in the group receiving 3 mg once daily before bedtime: endpoints were met at higher rates whilst limiting the incidence of esophageal candidiasis. Moreover in this group, pre-existing fibrostenotic strictures improved or resolved in most patients and once-daily dosing is potentially beneficial for treatment compliance. FLUTE-2, a phase 3 trial with APT-1011 treatment in adults, is currently underway (67).

Safety and side effects

Budesonide and fluticasone formulations displayed a similar side effects profile across most phase 2 and 3 trials. Generally, both were safe, well-tolerated and most treatment-related side effects were mild or moderate in severity. Patients seldom reported serious side effects and when present, they were deemed unrelated to the study treatment (39,46,47,53,56). The most frequently reported side effects included upper airway symptoms, such as nasopharyngitis and sinusitis, and local fungal infections, such as oral and esophageal candidiasis (40,42). Local candidiasis occurred in up to 16.2% of patients, although it usually had no impact on daily life activities, did not lead to discontinuation of treatment and was easily treated with antimycotics (38,41,46,47). For APT-1011, local candidiasis was especially prevalent in the doses administered twice daily (42). Signs of adrenal dysfunction, such as adrenal suppression, insufficiency or reduction in peak ACTH-stimulated cortisol, were reported in a limited number of cases and were usually asymptomatic (40-42). Noteworthy, there appears to be no association between the duration of treatment and the type or severity of side effects experienced (42,46,47).

Discussion

Swallowed topical corticosteroids are recommended as a first-line therapy in EoE (68). Trials evaluating the long-term maintenance of disease remission with STCs have only recently been published. Whereas suspensions or asthma inhalers were formerly used off-label to administer these steroids in EoE, several novel corticosteroid formulations have now become available, designed specifically for esophageal delivery.

For budesonide, two formulations have been developed: budesonide orodispersible tablet (BOT) and budesonide oral suspension (BOS). Overall, BOT displayed the highest grade of efficacy with clinico-histologic remission rates up to 75% after 1 year (46). Treatment with BOS seems to result in lower remission rates, both in terms of timing (induction and

maintenance) and the type of remission (histologic, symptomatic or endoscopic) (40,47). There are several potential explanations for this disparity. Specifically when comparing phase 3 trials, the BOS trial consisted of a patient population with a higher baseline disease severity and included patients simultaneously receiving topical steroids for other conditions (40). Nonetheless, efficacy rates of BOT and BOS surpass those of placebo and budesonide formulations previously used, with which persisting eosinophilia and symptom relapse was more common (26). This finding likely reflects the enhanced mucosal contact time achieved by these specialized formulations. At this time, especially BOT appears to be tailor-made for the purpose of treating EoE. Remission under BOT is achieved regardless of the baseline esophageal inflammation and equally in all segments of the esophagus (38,46). Moreover, BOT proves durable in the long-term and appears to be favored over BOS by patients (56).

For fluticasone, slightly different conclusions are drawn. In the phase 3 trial with APT-1011, especially histologic and endoscopic response was achieved and maintained in a sizable amount of patients (42). Symptomatic improvement showed positive trends but was less convincing, even more so in the smaller-scale trials (41,53,54). Worth noting is that the induction and maintenance of remission was highly dependent on the dosage and the administration schedule. The ideal equilibrium of long-term pharmacological efficacy and clinical safety seemed to exist in the patients receiving 3 mg APT-1011 once daily before bedtime (42). Interestingly, once-daily dosing is probably also beneficial regarding treatment compliance.

Mometasone and ciclesonide are potentially suitable alternatives for the treatment of EoE and a few small-scale trials report promising results (43-45). Larger-scale, prospective trials, such as the phase 2 mometasone trial which is currently underway, are mandatory to allow comparison with more established treatments (64).

A phenomenon that surfaces in nearly all STCs trials is the discrepant relationship between the biological activity of EoE and the resulting esophageal symptoms (69). There are likely several explanations to this anomaly. Patient-reported symptoms might be caused by other comorbidities or endoscopic features which are easily underestimated with endoscopy, such as mild esophageal strictures, a narrowed esophageal caliber or a decreased esophageal distensibility (70,71). In addition, the predominant symptom of solid food dysphagia is not only influenced by biological activity, but also the patient's compensatory eating habits (72). Therefore the diagnosis of EoE should be based on both histologic and symptomatic findings. Some trials strive to incorporate this characteristic in their study design through the use of a composite clinico-histological endpoint, which is now requested by the EMA and Food and Drug Administration (FDA) (38,46,73). Interestingly, recent data even demonstrate that symptom severity in EoE is correlated more significantly with symptom-specific anxiety and esophageal hypervigilance than with histologic or endoscopic rating scales (74). This finding implicates that EoE is no exception to brain-gut interactions and that signs of anxiety should be addressed accordingly by the treating clinician (75).

Current evidence supports long-term therapy with STCs. First, STCs effectively maintain remission in a subgroup of steroid responsive patients (42,46). Second, therapy discontinuation at any point of treatment often results in relapse and the risk of developing fibrostenotic disease in an environment with unbridled inflammation (26-28,47). This evolution is highly undesirable because it is linked to a higher risk of food impaction, subsequent need for endoscopic dilation and a lower treatment response (29,30,76). STCs appear to be able to reverse fibrostenotic features, even after only 6 weeks of treatment (38,59). Third, loss of treatment response over time is likely less important than initially thought. For BOT there was no increase in relapse rate over the duration of 1 year (46). For BOS and APT-1011 there was more fluctuation and loss of efficacy, yet response always remained superior to baseline levels (42,47,77). These findings oppose previous trials describing a substantial loss of STCs response over time, particularly in patients with dose reductions (78,79). Fourth, the likelihood of therapeutic response to STCs in steroid non-responders can be slightly improved by continuing therapy (47). The window of opportunity for treatment response with BOS approximates 12 weeks. Hereafter, a full theoretical treatment effect is achieved and further improvement of response is unlikely. Whether this is also the case for other steroid formulations remains unclear. Fifth, there appears to be no association between the duration of treatment and the type or severity of side effects experienced (42,46,47). During the long-term maintenance phase, similarly to the induction phase, STCs remain safe, well-tolerated and confined in treatment side effects.

It has been widely established that EoE poses a considerable burden on the quality of life (QoL) of patients. Unfortunately, QoL is seldom included as a prominent study endpoint in therapeutic trials. Aspects negatively impacting the QoL of patients with EoE are symptom severity, especially food impaction, and the disease duration (74). Severity of endoscopic features and female sex also appear to play a role (32,33). This can result in disease anxiety, absence from school or work and a higher need for medication (34). These findings further emphasize the importance of acknowledging both the biologic and symptomatic components in EoE: to make a diagnosis, to assess treatment response and to evaluate the potential impact on patients' QoL. Evidence on the effect of treatment modalities on QoL is still scarce and debated. Recent data suggest a significant improvement of health-related quality of life (HRQoL) after BOT treatment compared to a worsening in placebo-treated patients (46). Future research is necessary to assess the effect of other therapies.

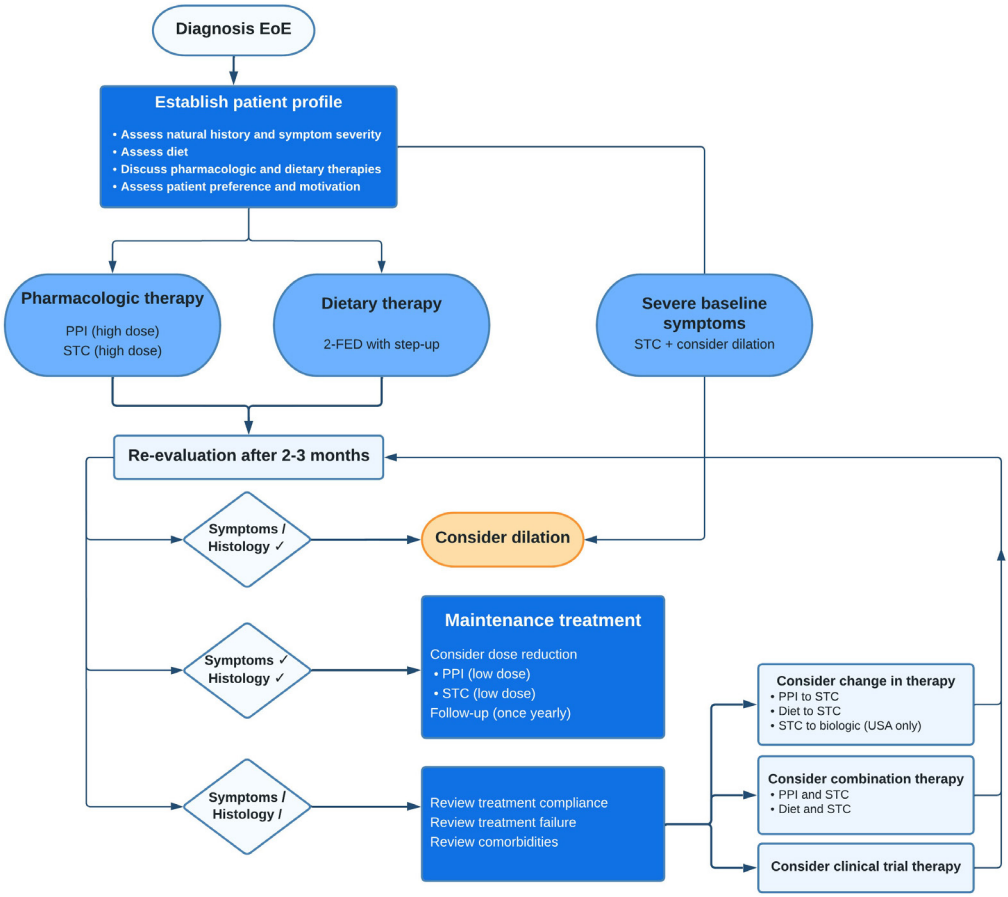

Figure 2. — Proposed management algorithm in EoE. Duration and severity of symptoms and patient preference are major determinants of the therapeutic approach. Re-evaluation with repeat endoscopy and biopsies should be performed after 2-3 months following treatment initiation or after each therapeutic change. Endoscopic dilation should be considered in patients with severe baseline symptoms or persistence of symptoms despite histologic response. Major symptoms at presentation, such as multiple food impactions, are likely to be caused by a esophageal stricture. Dilation may be performed in these patients prior to an obligatory induction therapy with STCs, as PPIs or dietary therapy are less likely to achieve sufficient response in this population. EoE, eosinophilic esophagitis; high dose PPI, e.g. omeprazole 20 mg twice daily; high dose STC, eg. budesonide 1 mg twice daily; low dose PPI, e.g. omeprazole 20 mg once daily; low dose STC, eg. budesonide 1 mg once daily, PPI, proton pump inhibitor; STC, swallowed topical corticosteroid; successful histologic response, <15 eosinophils/high power field; unsuccessful histologic response, ≥15 eosinophils/high power field; 2-FED, two-food elimination diet; ✓, successful response; /, unsuccessful response.

Noteworthy is the off-label use of steroid inhalers and nebulizers for EoE. As reimbursement for BOT (Jorveza) is still lacking in several areas, including Belgium, swallowed inhalation corticosteroids are still widely used in present gastroenterological practice. Both fluticasone in a metered-dose inhaler (MDI) or budesonide, administered with a nebulizer or mixed with a viscous solvent such as sucralose or xanthane gum (oral viscous budesonide, OVB), are used in this context. Literature on the efficacy of swallowed inhalation corticosteroids for EoE varies considerably. Histologic response rates fluctuate between 16-65% for MDI and 35-72% for OVB (26,52,53,80). Comparative trials between MDI and OVB showed that both formulations improve histologic, clinical and endoscopic findings, with no significant difference between both medications (81,82). Symptomatic improvements for either formulation were seldom superior when compared to placebo however. The variation in response is partially explained by the substantial heterogeneity in the dosage and duration of therapy and definition of response, although suboptimal drug delivery likely outweighs the former in significance (80). An inventive open-label study by Delon et al. highlighted the flaws of utilizing asthma preparations for esophageal administration of corticosteroids (51). Nuclear scintigraphy scans demonstrated the favorable deposition of OVB in the esophagus and stomach, with no deposition in the lungs compared to nebulized budesonide. This superior mechanism of drug delivery, reflected by a greater mucosal contact time and histologic response rates, is a highly relevant pharmacologic quality of swallowed topical corticosteroids such as BOT or BOS. Theoretically, this finding asserts the claim against use of swallowed inhalation corticosteroids in EoE. In practice however, lacking reimbursement forces gastroenterologists to resort to suboptimal therapeutic strategies.

Nearly 3 decades after EoE was first described as a distinct disease entity, prospective double-blind RCTs comparing the efficacy of PPIs, STCs and diets remain lacking. Therefore many areas of ambiguity and controversy still exist in the management of EoE. Multiple guidelines are available to offer exhaustive and evidence-based treatment recommendations. We propose a treatment algorithm based on these guidelines, systematic reviews and expert consensus (figure 2) (1,4,36,68,83-88).

In patients who acquire complete clinico-histologic remission following induction therapy, treatment should be continued with a lower maintenance-dose of PPIs or STCs (e.g. budesonide 1 mg once daily) and the patient should be followed-up approximately once every year. The optimal maintenance dose for PPIs remains undetermined (89). Depending on the patient's preference and motivation, an empiric 2-FED is an alternative initial treatment. When symptoms remain present despite histologic remission, the patient should be evaluated for fibrostenotic disease and/or symptom-specific anxiety. For fibrostenotic disease, esophageal dilation should be considered in addition to an anti-inflammatory treatment. Patients with symptom-specific anxiety and esophageal hypervigilance are ideally referred for cognitive behavioral therapy, preferably carried out by a psychogastroenterology practitioner (74). When both symptoms and histologic activity persist, refractory EoE should be considered in that patient. However, a change in therapy is due only when inadequate compliance and alternative diagnoses have been excluded. We can switch therapies, either from PPIs or diets to STCs or from STCs to biologics, resort to combined therapies or include the patient in a clinical trial with an experimental treatment. Switching to biologics outside of a trial setting is currently only possible in the United States as dupilumab is exclusively FDA-approved (90).

Patients with EoE should regularly receive a clinical follow-up to assess symptoms and possible treatment side effects. We suggest a check-up frequency of approximately once every 2-3 months in patients with insufficient disease control and once every 12-18 months when disease remission is achieved. Only 50% of patients in remission receive regular follow-up visits, yet these visits appear pivotal in the early detection of histologic relapse and stricture formation (88). More frequent endoscopic examinations are not recommended, unless after changes in treatment strategy or when disease recurrence is suspected. Monitoring of adrenal function should not systematically be performed unless in pediatric and adolescent patients who are treated with high doses of STCs for longer periods of time.

Research agenda

Even though our understanding of EoE has made great strides, many challenges still have to be tackled by future research. The recently published phase 3 trials discussing topical corticosteroids offer important insight into the durability and safety of these products. Several pertinent questions remain however. For all STCs, the lowest effective medication dosages are undetermined and alternative administration regimens such as periodic or on-demand schemes should be reviewed. Dosage-finding studies are especially lacking for budesonide formulations as these trials have, in comparison to fluticasone, currently only focused on twice-daily dosage schemes. Additionally, novel and preferably non-invasive biomarkers should be developed to assess disease severity and determine which patients might benefit from higher and prolonged maintenance dosages. Current evidence suggests that BOT is likely the most effective corticosteroid at inducing and maintaining treatment response in EoE. However, only head-to-head comparative trials between STCs mutually will allow us to truthfully confirm this presumption.

Even more fundamental: no prospective, randomized clinical trials comparing the efficacy or cost-effectiveness of STCs, PPIs, diets and biologics have been published to date. Such comparative research is crucial to substantiate the evidence-based foundations of our treatment algorithms and stimulate EMA and FDA approval of treatments besides BOT and dupilumab. Options for combining existing treatment modalities should be further looked into, especially for patients with insufficient response to initial therapies.

For most treatments, outcomes beyond a 1 year timeframe still have to be addressed. Despite our growing understanding of the long-term evolution of EoE, both in the presence and absence of adequate therapy, we should continue to follow groups of patients. Epidemiologically speaking, EoE is a new kid on the block and as many patients are diagnosed during young adulthood, our therapeutic approach beyond 10-20 years remains undetermined.

Conclusion

EoE has manifested itself as a dominant and growing cause of esophageal dysfunction since first being described in gastroenterological literature. In comparison to our expanding knowledge, standardized, effective and patient-friendly therapies have lagged behind for many years. The first-line treatment, conventionally consisting of dietary restriction, PPI therapy and topical corticosteroids, is now being challenged by emerging products. Novel corticosteroid formulations and biologic therapies show great promise but future studies still have to clarify their exact role in the treatment paradigm. Cost-effectiveness, patient selection and duration of treatment are decisive factors to take into account, especially in times of skyrocketing healthcare costs. Despite these considerations that remain only partially clarified, EoE awaits a more bright and promising future.

Conflict of interest

TV has received consultancy and lecture fees from Dr Falk Pharma. SW has no conflict of interest.

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