Original Article

Disease Course of Eosinophilic Esophagitis Under Anti-inflammatory Treatment

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What is already known about this topic? Eosinophilic esophagitis (EoE)—if left untreated—progresses from an inflammatory phenotype toward a combined inflammatory-fibrotic phenotype over time. A long diagnostic delay, leading to ongoing disease activity due to the absence of treatment, is one of the best studied risk factors for such progression. It remains elusive if disease progression can also be observed in patients who are treated but show ongoing inflammation.

What does this article add to our knowledge? In an era of efficacious treatment options for EoE, complicated disease course still occurs relatively frequently. Bolus impactions necessitating endoscopic removal are rare when patients receive EoE treatment. Patients with controlled disease activity show a significantly better outcome than patients with ongoing disease activity.

How does this study impact current management guidelines? Our study highlights that current treatment strategies should aim to control both clinical and histological disease activity to prevent disease complications.

VISUAL SUMMARY

Disease course of eosinophilic esophagitis under anti-inflammatory treatment

Hypothesis

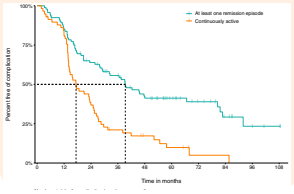
Long-term control of histological disease activity is associated with a favorable outcome with regards to disease complications

Experimental Models/ Study Design

Analysis of prospectively collected data within the Swiss EoE cohort study

Key findings

- 151 patients with a follow-up of 56.0 months
- 93 patients with disease control (61.6%) vs 58 patients (38.4%) without control
- Complications in 108 patients (71.5%)
- more often in patients with ongoing histological activity (89.7 vs 60.2, p<0.001)



Conclusions

- Ongoing histological disease activity predicts development of complicating disease course in EoE patients

- Current treatment strategies should aim at controlling both clinical and histological disease activity to prevent disease complications

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Abbreviations used
CI- Confidence interval
EoE- Eosinophilic esophagitis
FED- Food elimination diet
GERD- Gastroesophageal reflux disease
hpf- High-power field
HR- Hazard ratio
IQR- Interquartile range
PPI- Proton pump inhibitor
SEECS- Swiss EoE Cohort Study
STRIDE-II- Selecting Therapeutic Targets in Inflammatory Bowel Disease II

BACKGROUND: Eosinophilic esophagitis (EoE) is a chronic type 2 inflammatory disease of the esophagus that progresses to a fibrotic phenotype when left untreated. Current treatment options aim to control clinical, endoscopic, and histological disease activity. However, as of yet, it remains elusive if achieving disease control, particularly the long-term control of histological disease activity, can prevent the development of disease complications.
OBJECTIVE: We aimed to assess the impact of ongoing histological disease activity on the development of disease complications in adult patients with EoE.
METHODS: We evaluated prospectively included patients in the Swiss EoE cohort. Data on all patients with ongoing maintenance treatment, and at least 2 follow-up visits, but without concomitant gastroesophageal reflux or strictures at baseline, were analyzed. We compared patients with ongoing histological disease activity versus patients with disease control, with regard to development of disease complications over time (strictures, bolus impactions, and need for treatment escalation). Histological disease activity was defined by a peak eosinophil count of ≥15 eosinophils during all follow-up visits.
RESULTS: We included a total of 151 patients with a median follow-up of 56.0 months (70.9% male, median age 39.0 years). A total of 93 patients (61.6%) were classified as having disease control during follow-up, whereas 58 patients (38.4%) showed ongoing histological disease activity. Development of complications occurred in a total of 108 patients (71.5%), significantly more often in patients with ongoing histological activity compared with patients with disease control (89.7% vs 60.2%, $P < .001$). This difference was mainly due to higher rates of stricture formation and the need for treatment escalation. Multivariate Cox regression models revealed ongoing histologic disease activity as a significant predictor of the development of complications in the follow-up (hazard ratio [HR]: 2.45, $P < .001$), particularly for the need for treatment escalation (HR: 2.63, $P < .001$) and development of strictures (HR: 3.16, $P = .025$).
CONCLUSIONS: Ongoing histological disease activity predicts development of complicating disease course in patients with EoE. Current treatment strategies should aim to control both clinical and histological disease activity to prevent disease complications. **(J Allergy Clin Immunol Pract 2026;■:■-■)**

Key words: *Eosinophilic esophagitis; Histologic disease activity; Eosinophils; Complications; Anti-inflammatory treatment*

Eosinophilic esophagitis (EoE) is a chronic relapsing type 2 inflammatory disease of the esophagus. It is well known that if untreated it progresses from an inflammatory phenotype toward a combined inflammatory-fibrotic phenotype over time.[1] A long diagnostic delay, leading to ongoing disease activity due to the absence of treatment, is one of the best studied risk factors for such progression with the development of esophageal strictures.[2] In addition, several studies have shown ongoing inflammatory disease activity in the long-term follow-up of patients with EoE.[3,4] Therefore, long-term treatment of EoE has been propagated by current guidelines.[5] In the context of available treatment, progression to a fibrostenotic phenotype appears to be minimal. In fact, improvement of strictures can occur, but such improvement is modest and likely occurring over years.[6] Probably, there is also an impact of treatment on prevention and eventually reversion of disease progression, although firm data are lacking. At least, longer treatment with higher cumulative doses of topical steroids has been associated with a better long-term outcome.[4,7] Currently, a control of both symptomatic and histological disease activity is aimed for in clinical practice.[5] Control of histological disease activity is usually defined by a peak eosinophil count of <15 eosinophils/high-power field (hpf), although treating to levels of less than 5 eosinophils/hpf appears to have additional benefits.[8]

Recently, a treat-to-target concept has been proposed for the management of EoE.[9] Such treat-to-target concepts are well known for other chronic inflammatory diseases such as inflammatory bowel disease (Selecting Therapeutic Targets in Inflammatory Bowel Disease II [STRIDE-II] guidelines).[10] The EoE treat-to-target concept aims to control all aspects of disease

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Conflicts of interest: A. M. Schoepfer has received consulting fees, speaker fees, and/or research support from Dr Falk Pharma GmbH, Adare Pharmaceuticals Inc, Celgene-Receptos-BMS, Domain Therapeutics, Esocap, GSK, and Sanofi-Regeneron. L. Biedermann has received consulting fees and/or speaker fees from Falk Pharma GmbH, Esocap AG, Sanofi-Aventis AG, and Calypso Biotech SA. A. Straumann has consulting contracts with Actelion, Celgene-Receptos, Dr Falk Pharma GmbH, Roche-Genentech, GSK, Novartis, Nutricia, and Sanofi-Regeneron. T. Greuter has consulting contracts with Sanofi-Regeneron and Falk Pharma GmbH, and received a research grant from Sanofi-Regeneron and Falk Pharma GmHb. The rest of the authors declare that they have no relevant conflicts of interest.

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activity in the long-term follow-up, including symptoms, endoscopy, and histology. With the availability of highly efficacious treatment options, such aims appear more realistic than in the past. However, as of yet, it remains elusive if such a disease control, particularly the long-term control of histological disease activity with peak eosinophil counts of less than 15 eosinophils/hpf, can actually prevent the development of disease complications, especially stricture formation, long-lasting bolus impactions with the necessity of endoscopic intervention, and the need for treatment escalation.

Given these uncertainties, we aimed to investigate in a large EoE cohort whether long-term control of histological disease activity is associated with a favorable outcome compared with ongoing histological disease activity.

METHODS

Study design

This study was an analysis of prospectively obtained data from the Swiss EoE Cohort Study (SEECS).[11] Enrollment into the SEECS started in 2015 with patient recruitment from all regions across Switzerland. All patients had been previously diagnosed with EoE according to international guidelines.[5,12] Institutional review board approval has been obtained from the local ethics committee of each participating center (EKNZ 2015-388/CER-VD 148-14). All patients had provided written informed consent before inclusion into the SEECS. For the current study, the primary outcome measure was development of complicated disease course stratified by disease activity during follow-up (composite outcome: stricture formation/need for dilation, bolus impaction, and need for treatment escalation). Secondary outcomes were development of each complication separately. Further measures of interest were baseline demographics, baseline disease activity, duration of follow-up, activity during last follow-up visit, and EoE treatment.

Study population and data collection

All patients included in the Swiss EoE cohort by May 8, 2025 (n = 926) were eligible. For the current study, the following inclusion criteria were applied: (1) ongoing stable anti-inflammatory EoE treatment such as proton pump inhibitors (PPI), swallowed topical corticosteroids, dupilumab, or stable dietary restrictions (food elimination diet [FED]); and (2) availability of at least 2 follow-up visits including patient-reported outcomes, endoscopy, and histology reports. Patients were excluded for the following reasons: (1) the presence of strictures at baseline, (2) concomitant gastroesophageal reflux disease (GERD), (3) use of investigational drugs or patients included in a randomized controlled trial, and (4) patients treated with changes in dietary restrictions during follow-up. Patients with changes in dietary restrictions during follow-up were excluded as changes in dietary habits potentially lead to histological activity necessitating adaptation of treatment regimens (thus, these patients would be falsely misclassified as reaching the outcome "need for treatment escalation"). Patients with GERD were excluded as low-grade distal esophageal eosinophilia in the context of GERD could be falsely interpreted as ongoing histological disease activity. Baseline visit was the visit at the time of inclusion into the SEECS.

Definitions

All included patients were classified into 2 predefined subgroups, patients with controlled disease during follow-up versus patients without control of their disease activity. These 2 groups were defined as follows:

- Controlled group: Achievement of histological remission during at least 1 follow-up visit (<15 eosinophils/hpf)
- Ongoing active disease group: Histologically active disease at all follow-up visits (≥15 eosinophils/hpf)

For additional analyses, these groups were further divided into completely controlled disease (histological remission at all follow-up visits), on-off disease (at least 1 follow-up visit with histologically active disease and 1 follow-up visit with histological remission), and continuously active disease (histologically active disease at all follow-up visits).

The outcomes were defined as follows:

- Development of new strictures: Notion of any stricture during follow-up visit and/or need for endoscopic dilation
- Long-lasting food bolus impaction: Need for urgent endoscopy with bolus removal during follow-up
- Treatment escalation: Dose increase or re-induction treatment or switch out of class due to ongoing disease activity after initially successful treatment

Study objectives and central hypothesis

The objective of the study was to assess whether ongoing histological disease activity has a negative impact on disease progression, mainly development of disease complications. Our central hypothesis was that patients with ongoing esophageal eosinophilia despite anti-inflammatory treatment show a worse outcome with increased rates of disease progression, particularly development of fibrostenotic features.

Statistical analyses

For statistical analyses, R (R Foundation for Statistical Computing, Vienna, Austria) version 4.4.1 was used. For time to development of complications, Kaplan-Meier curves and Cox regression models were computed. These Cox regression models were adjusted for the following confounding factors: age, sex, diagnostic delay, active disease at baseline, and EoE treatment. For the purpose of this study, a P value of <.05 was considered statistically significant.

RESULTS

Patient and baseline disease characteristics

From the total number of patients included in the SEECS (n = 926), 151 subjects (107 male, 70.9%) met our inclusion criteria, with a median of 3 available follow-up visits (median observation time 56.0 months, interquartile range [IQR]: 36.3-76.2 months). The median age at study inclusion was 39.0 years (IQR: 31.0-48.0 years) with a median age at diagnosis of 34.0 years (IQR: 27.0-41.0 years). Diagnostic delay was considerable with 5.0 years (IQR: 1.9-10.2 years). All patients had pure EoE without any overlapping esophageal disease, particularly without concomitant GERD. A total of 117 patients (81.3%) had atopic comorbidities, particularly rhinoconjunctivitis (61.6%) or asthma (31.1%). At the time of study inclusion, 72 patients (47.7%) had histologically active disease, whereas 79 patients (52.3%) were in biological disease remission. The median peak eosinophil count was 12.0 eosinophils/hpf (IQR: 0-60.0 eosinophils/hpf), whereas the median endoscopic reference score (EREFS) was 2.0 (IQR: 1.0-3.0). A total of 124 patients were treated with topical steroids (82.1%), 26 with PPI (17.2%), and

TABLE I. Baseline demographics and disease characteristics

Characteristic	Overall (N = 151)	Controlled disease (N = 93)	Ongoing active disease (N = 58)	*P* value*
Sex, n (%)				
Male	107 (70.9)	69 (74.2)	38 (65.5)	.3
Female	44 (29.1)	24 (25.8)	20 (34.5)	
Median age at inclusion (y) [Q1; Q3]	39.00 [31.00; 48.00]	40.00 [32.00; 48.00]	37.00 [30.00; 43.00]	.1
Median age at EoE diagnosis (y) [Q1; Q3]	34.00 [27.00; 41.00]	35.50 [28.00; 43.00]	31.00 [26.00; 41.00]	.063
Median diagnostic delay from first symptoms (y) [Q1; Q3]	4.96 [1.91; 10.16]	3.83 [1.25; 9.83]	7.33 [2.46; 10.62]	.15
Atopic comorbidities, n (%)				
No	27 (18.8)	17 (18.7)	10 (18.9)	>.9
Yes	117 (81.3)	74 (81.3)	43 (81.1)	
Missing data	7	2	5	
Family history of EoE, n (%)				
Absent	99 (65.6)	61 (65.6)	38 (65.5)	>.9
Present	10 (6.6)	7 (7.5)	3 (5.2)	
Proven	4 (2.6)	2 (2.2)	2 (3.4)	
Suspected	15 (9.9)	9 (9.7)	6 (10.3)	
Unknown	23 (15.2)	14 (15.1)	9 (15.5)	
Disease activity at baseline, n (%)				
Controlled disease	79 (52.3)	56 (60.2)	23 (39.7)	.019
Active disease	72 (47.7)	37 (39.8)	35 (60.3)	
Median physician global assessment of symptom severity 7-day recall at baseline [Q1; Q3]	2.00 [0.00; 4.00]	2.00 [0.00; 3.00]	2.50 [1.00; 4.00]	.14
Median EREFS score at baseline [Q1; Q3]	2.00 [1.00; 3.00]	2.00 [0.00; 3.00]	3.00 [1.00; 4.00]	.004
Median peak eosinophil count/hpf at baseline [Q1; Q3]	12.00 [0.00; 60.00]	5.00 [0.00; 48.00]	21.50 [2.00; 78.00]	.035
Median patient-reported symptom severity 7-day recall at baseline [Q1; Q3]	1.00 [0.00; 3.00]	1.00 [0.00; 3.00]	2.00 [0.00; 4.00]	.5
Treatment at inclusion, n (%)				
PPI	13 (8.6)	6 (6.5)	7 (12.1)	
FED only	12 (7.9)	8 (8.6)	4 (6.9)	
PPI + FED	2 (1.3)	2 (2.2)	0 (0.0)	
STC	108 (71.5)	66 (71.0)	42 (72.4)	
STC + FED	5 (3.3)	2 (2.2)	3 (5.2)	
STC + PPI	11 (7.3)	9 (9.7)	2 (3.4)	
Median number of follow-up visits [Q1; Q3]	3.00 [2.00; 4.00]	3.00 [2.00; 4.00]	3.00 [2.00; 4.00]	.6
Median maximum follow-up time (mo) [Q1; Q3]	55.95 [36.34; 76.19]	55.43 [37.26; 74.45]	56.72 [30.36; 76.58]	>.9

EoE, Eosinophilic esophagitis; *EREFS*, endoscopic reference score; *FED*, food elimination diet; *hpf*, high-power field; *PPI*, proton pump inhibitor; *STC*, swallowed topical corticosteroids.
*Fisher's exact test.

12 with FED only (7.9%). None of the patients were treated with dupilumab. For details, see Table I.

Controlled disease versus ongoing disease during follow-up

Of the 151 patients, 93 (61.6%) were classified as having disease control during follow-up, whereas 58 patients (38.4%) showed ongoing histological disease activity. Patients with ongoing disease activity had a higher endoscopic (EREFS 3.0 vs 2.0, $P = .004$) and histological disease activity (peak eosinophil count 21.5 vs 5.0, $P = .035$) at baseline compared with patients with controlled disease during follow-up. However, the number of follow-up visits and the total time of follow-up did not differ between the groups. The groups were also comparable with regard to other baseline demographics, disease characteristics (particularly clinical disease activity at baseline), and treatment. For details, see Table I.

Outcome stratified by biological disease control during follow-up

The primary outcome (composite outcome of complicated disease) occurred in a total of 108 patients (71.5%). In patients

TABLE II. Cox proportional hazard model examining the time to first complication in relation to the stage of disease control (controlled disease vs ongoing active disease)

Covariates	Hazard ratio	95% CI	*P* value
Ongoing active disease (vs controlled disease)	2.45	[1.61, 3.73]	<.001
Sex = female (vs male)	1.25	[0.81, 1.91]	.308
Age at baseline	0.99	[0.97, 1.00]	.107
Active disease at baseline (vs inactive)	0.81	[0.54, 1.23]	.327
Treatment at baseline = FED only (vs PPI)	0.49	[0.19, 1.27]	.143
Treatment at baseline = PPI + FED (vs PPI)	3.72	[0.78, 17.77]	.099
Treatment at baseline = STC (vs PPI)	0.46	[0.25, 0.87]	.017
Treatment at baseline = STC + FED (vs PPI)	0.52	[0.14, 1.91]	.327
Treatment at baseline = STC + PPI (vs PPI)	0.57	[0.20, 1.66]	.304

CI, Confidence interval; *FED*, food elimination diet; *PPI*, proton pump inhibitor; *STC*, swallowed topical corticosteroids.

with controlled disease, complicated disease occurred in 56 cases (60.2%), whereas in individuals with ongoing active disease, complications were seen in 52 subjects (89.7%, $P < .001$). Complicated disease was mainly defined by the development of strictures (20.7% vs 7.5%, $P = .023$) or by the need for treatment escalation (67.2% vs 34.4%, $P < .001$), whereas bolus impactions were extremely rare (2 patients), both in patients with and without control of disease activity (1 episode each). The mean number of strictures per patient across all follow-up visits was significantly higher (0.34 vs 0.14, $P = .020$), as were the mean number of treatment escalations per patient (0.74 vs 0.43, $P < .001$) and the number of complications of any kind per patient (2.69 vs 1.83, $P = .005$). For details, see Table E1, available in this article's Online Repository at www.jaci-inpractice.org. At the last follow-up visit available for analysis, patients with ongoing disease activity showed significantly higher clinical (physician global assessment of symptom severity 2.0 vs 1.0, $P < .001$), endoscopic (EREFS 2.0 vs 1.0, $P < .001$), and histological disease activity (peak eosinophil count 50.0 vs 1.0 eosinophils/hpf, $P < .001$) compared with patients with controlled disease; see Table E2 in this article's Online Repository at www.jaci-inpractice.org.

Time to disease complications stratified by biological disease control during follow-up

To assess time to disease complications, Kaplan-Meier curves and confounder-adjusted Cox proportional odds models were computed. Cox models were adjusted for sex, age, disease activity at baseline, and treatment. Patients with continuously active disease during follow-up showed a higher likelihood of developing complications (hazard ratio [HR]: 2.45, 95% confidence interval [CI]: 1.61-3.73, $P < .001$) compared with patients with disease control. For details, see Table II. Of note, treatment with topical steroids was associated with a more favorable outcome compared with PPI therapy (HR: 0.46, $P = .017$). This negative effect of continuously active disease was particularly seen for the outcome of treatment escalation (HR: 2.63, $P < .001$) and stricture formation (HR: 3.16, $P = .025$). Again, treatment with topical steroids was associated with a more favorable outcome in these analyses compared with PPI. See Tables E3 to E5 in this article's Online Repository at www.jaci-inpractice.org. The median time to complicated disease (50%) was 17.3 months in patients with continuously active disease compared with 39.3 months in patients with controlled disease in the follow-up (Figure 1).

Development of disease complications stratified by 3 disease control groups

In a second step, patients in the controlled disease group were further divided into 2 groups depending on whether or not they were in continuous histological remission (completely controlled disease group: histological remission at all follow-up visits; on-off disease group: at least 1 follow-up visit with histological remission and 1 follow-up visit with active histological disease). These 2 groups were compared with patients with continuously active disease. Same primary (development of any complication) and secondary outcomes (stricture formation/need for dilation, treatment escalation, and bolus impaction) were analyzed. Patients with on-off remission were less likely to develop complications in the follow-up compared with patients with completely controlled disease (HR: 0.36, $P < .001$). However, this result was mainly driven by the increased likelihood of undergoing dilation in patients with controlled disease. For details, see Tables E6 to E9 and Figure E1 in this article's Online Repository at www.jaci-inpractice.org. To further investigate this finding, we stratified these patients based on their symptom severity (ongoing symptoms defined as visual analog scale >2 on a scale from 0 to 10, with 10 indicating most severe disease). Using this approach, we were able to detect a significantly increased likelihood of dilation in patients with histologically controlled disease, but ongoing symptoms, as a surrogate marker for fibrostenotic disease compared with patients without symptoms (HR: 3.46, $P = .002$). No significant differences were seen with regard to the other secondary outcomes.

DISCUSSION

Untreated EoE almost uniformly leads to the formation of strictures over time. However, data about EoE's natural history under efficacious treatment remain scarce. In this cohort study, we evaluated the frequency of complicated disease in the follow-up of patients with EoE under treatment and compared the outcome of patients with controlled disease versus ongoing active disease. Our main findings are as follows: (1) in an era of efficacious treatment options for EoE, complicated disease course still occurs relatively frequently; (2) bolus impactions necessitating endoscopic removal are rare when patients receive EoE treatment; and (3) patients with controlled disease activity show a significantly better outcome than patients with ongoing disease activity.

It is well documented that longer disease duration without treatment is associated with increased risk of stricture

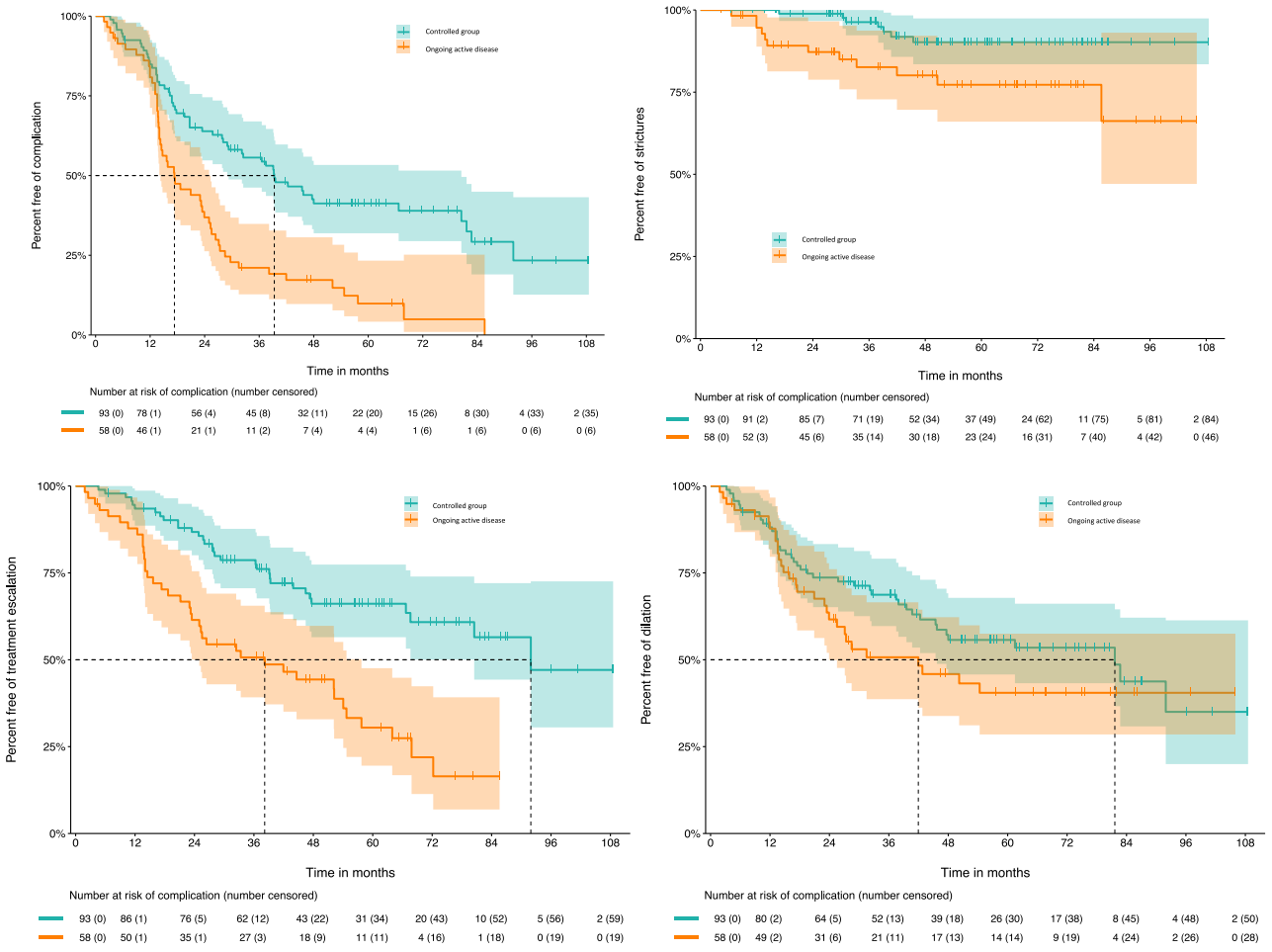

FIGURE 1. Kaplan-Meier curves for time to any complication, time to strictures, time to treatment escalation, and time to dilation, in relation to the stage of disease control (controlled disease vs ongoing active disease).

formation.[2,13] In fact, after 20 years of active disease, 87.5% of patients present with fibrotic features and 70.8% with an esophageal stricture.[2] Newer data suggest an increase in stricture risk of 9% with each additional year of undiagnosed EoE.[14] Moreover, the likelihood of fibrostenotic disease increases with age. The odds ratio for fibrostenosis for each 10-year increase in age has been shown to be 2.1 (95% CI: 1.7-2.7).[15] In contrast, real-world data including 613 patients suggest a disease progression of only 13.9%. Nevertheless, 3 years after index endoscopy, still many patients present with endoscopic abnormalities (62.3%) and histological activity (51.2%), probably due to a high rate of treatment discontinuation (44.0%).[16] It has been previously shown that a gap in clinical care is a risk factor for disease progression.[17,18] Our data suggest that even in the era of efficacious therapies, the occurrence of complications remains frequent, questioning the disease-modifying effects of currently available treatment options, particularly PPI and topical steroids. However, no conclusions can be made with regard to dupilumab (as none of our patients received the drug) or dietary approaches (due to the small sample size). Topical steroids were associated with some antifibrotic properties in the past, at least when investigating surrogate markers such as lamina propria fibrosis.[19] In our large cohort study, however, such an effect cannot be observed. Nevertheless, it is important to note that SEECS was initiated in 2015, at a time when most patients were being treated with off-label steroid formulations; thus our data cannot be applied 1:1 to the recently approved budesonide orodispersible tablet.[20,21] Taken together, our results highlight the urgent need for drugs that prevent tissue remodeling.

In contrast, current treatment modalities appear to do well with regard to the prevention of bolus impactions. In fact, the occurrence of bolus impaction events is extremely rare. In addition, the majority of patients achieve disease control in the follow-up, highlighting the anti-inflammatory efficacy of the currently available treatment options. These data go in line with randomized-controlled trials and large observational studies about the efficacy of PPI and topical steroids for the treatment of active EoE.[22,23] Low rates of bolus impactions have been previously reported in our cohort.[18] Thus, there appears to be a mismatch between the anti-inflammatory efficacy of EoE drugs and prevention of bolus impactions on one hand, and the ongoing risk for development of strictures on the other hand. Based on these data, it can also be suggested that increased stricture rates do not translate to an increased risk for bolus impactions. It remains to be determined whether the absence of edematous swelling of the mucosa (inflammation) is the reason

for the low rates of bolus impactions or if detected strictures are too subtle to cause severe complications. A major drawback is that endoscopy has limitations in accurately assessing strictures, particularly their diameter. EndoFLIP would overcome this limitation, but the technique is not yet universally applied in patients with EoE.

Although bolus impactions are rare, other complications are still frequently seen in patients with EoE. Achieving disease control leads to clear benefits during follow-up, including a reduction in complications, particularly a lower incidence of esophageal strictures. Chronicity and relapsing disease course of EoE have been well described in the seminal paper by Straumann et al published in 2003.[24] An 11.5-year follow-up of 30 patients revealed that dysphagia almost universally persists, with esophageal eosinophilia present in all symptomatic patients, though peak eosinophil counts fluctuate.[24] A systematic review and meta-analysis by Shaheen et al[25] further showed that most patients have stable or worsening disease after diagnosis, with most patients maintaining their inflammatory or combined inflammatory-fibrostenotic phenotype in the follow-up. On the other hand, disease course and a natural history of EoE under treatment is less clear. Particularly, it is unknown whether or not development of strictures remains a problem and whether this can be attributed to ongoing disease activity. In other chronic gastrointestinal diseases, particularly inflammatory bowel disease, we aim to obtain control of biological disease activity to interfere with disease progression. Currently, many EoE specialists advocate for regular assessment of disease activity, but it remains elusive whether such an approach translates to better disease outcomes once patients are under treatment. Our results suggest that control of biological activity has its value and is associated with better outcomes. Thus, a strategy similar to the STRIDE-II guidelines in inflammatory bowel disease[10] seems reasonable when aiming for clinical, endoscopic, and histological remission in the follow-up.

Our study has several strengths and limitations. It is one of the largest cohort studies systematically analyzing disease progression in treated patients. Patients within the Swiss EoE cohort adhere to a strict standard follow-up protocol with annual visits including endoscopic and histological assessment. A major limitation is the lack of a standardized definition of stricture diameter in the absence of EndoFLIP use. Thus, our data about complications appear to be mainly driven by increased rates of endoscopic dilation but not the presence of stricture. However, it is well known that endoscopy underestimates the presence of strictures, particularly in the proximal part of the esophagus.[26] Such strictures could be detected by a barium swallow, which is rarely performed in our cohort. The best modality to measure esophageal diameter and therefore to detect strictures is EndoFLIP. However, EndoFLIP has only been recently introduced and only at few centers in Switzerland. In addition, most EndoFLIP protocols include measurement of the distal but not proximal esophagus. Thus, we included endoscopic dilation as a surrogate marker for fibrostenotic disease. This outcome has been previously used as a disease complication in our cohort.[18] Nevertheless, we cannot exclude that some patients did not have fibrostenosis but underwent dilation for other reasons as motility studies are rarely performed in the Swiss EoE cohort. Furthermore, compliance of drug intake is difficult to assess in a cohort study, and compliance rates might be overestimated based on patients' feedback. Thus, higher adherence rates might result in lower risk of stricture formation. Because of its design, our study is looking at associations and correlations, which does not necessarily imply causation. Finally, our data cannot be applied to newer steroid formulations or dupilumab.

Taken together, development of complications is still frequently seen in patients with EoE despite efficacious treatment. Ongoing histological disease activity predicts development of complicating disease course, particularly stricture formation. Current treatment strategies should aim to control both clinical and histological disease activity to prevent disease complications.

DATA AVAILABILITY

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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Alain M. Schoepfer contributed to supervision, study design, data collection, data analysis, data interpretation, illustrations, and drafting of the manuscript, and provided funding. Sofia Asikainen design the study, analyzed and interpreted the data, and drafted the manuscript. Catherine Saner collected and interpreted the data, and reviewed the manuscript. Jean-Benoit Rossel designed the study, curated, analyzed, and interpreted the data, and reviewed the manuscript. Fritz Murray, Luc Biedermann, and Alex Straumann designed the study, collected and interpreted the data, and reviewed the manuscript. Anne Godat designed the study, analyzed and interpreted the data, and reviewed the manuscript. Fabian Luca Meichtry interpreted the data and revised the manuscript. Thomas Greuter supervised the study, designed, collected, analyzed, and interpreted the data, and drafted the manuscript, and provided funding.

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ONLINE REPOSITORY

TABLE E1. Development of complications in the follow-up (overall and stratified by biological disease control)

Outcome	Overall (N = 151)	Controlled disease (N = 93)	Ongoing active disease (N = 58)	*P* value*
Primary outcome: complications (any) (yes/no), n (%)				
No	43 (28.5)	37 (39.8)	6 (10.3)	<.001
Yes	108 (71.5)	56 (60.2)	52 (89.7)	
Escalation of treatment (yes/no), n (%)				
No	80 (53.0)	61 (65.6)	19 (32.8)	<.001
Yes	71 (47.0)	32 (34.4)	39 (67.2)	
Strictures (yes/no), n (%)				
No	132 (87.4)	86 (92.5)	46 (79.3)	.023
Yes	19 (12.6)	7 (7.5)	12 (20.7)	
Dilation (yes/no), n (%)				
No	80 (53.0)	52 (55.9)	28 (48.3)	.4
Yes	71 (47.0)	41 (44.1)	30 (51.7)	
Bolus impaction (yes/no), n (%)				
No	149 (98.7)	92 (98.9)	57 (98.3)	>.9
Yes	2 (1.3)	1 (1.1)	1 (1.7)	

*Fisher's exact test.

TABLE E2. Disease activity at last follow-up (overall and stratified by biological disease control)

Disease activity	Overall (N = 151)	Controlled disease (N = 93)	Ongoing active disease (N = 58)	*P* value*
Histologic disease activity at last visit, n (%)				
Active disease	64 (43.0)	24 (26.1)	40 (70.2)	<.001
Controlled disease	85 (57.0)	68 (73.9)	17 (29.8)	
Missing	2	1	1	
Median EEsAI-PRO at last visit [Q1; Q3]	12.00 [0.00; 33.00]	12.00 [0.00; 27.00]	12.00 [0.00; 36.00]	.13
Median physician global assessment of symptom severity 7-day recall at last visit [Q1; Q3]	1.00 [0.00; 3.00]	1.00 [0.00; 2.00]	2.00 [1.00; 4.00]	<.001
Median EREFS score at last visit [Q1; Q3]	1.00 [0.00; 3.00]	1.00 [0.00; 2.00]	2.00 [1.00; 4.00]	<.001
Median peak eosinophil count/hpf at last visit [Q1; Q3]	7.00 [0.00; 52.00]	1.00 [0.00; 15.50]	50.00 [8.00; 107.00]	<.001
Median patient-reported symptom severity 7-day recall at last visit [Q1; Q3]	1.00 [0.00; 3.00]	1.00 [0.00; 3.00]	1.50 [0.00; 3.00]	.3

EEsAI-PRO, eosinophilic esophagitis activity index - patient-reported outcome; EREFS, endoscopic reference score.
*Fisher's exact test.

TABLE E3. Treatment escalation—Cox proportional hazard model examining the time to treatment escalation in relation to the stage of disease control (controlled disease vs ongoing active disease)

Covariates	Hazard ratio	95% CI	*P* value
Ongoing active disease (vs controlled disease)	2.63	[1.57, 4.42]	<.001
Sex = female (vs male)	1	[0.59, 1.69]	1
Age at baseline	0.96	[0.94, 0.98]	<.001
Active disease at baseline (vs inactive)	1.18	[0.71, 1.97]	.518
Treatment at baseline = PPI (vs PPI)	0.5	[0.16, 1.51]	.219
Treatment at baseline = PPI + FED (vs PPI)	1.07	[0.13, 8.63]	.95
Treatment at baseline = STC (vs PPI)	0.25	[0.12, 0.51]	<.001
Treatment at baseline = STC + FED (vs PPI)	0.33	[0.07, 1.51]	.152
Treatment at baseline = STC + PPI (vs PPI)	0.28	[0.08, 1.04]	.057

CI, Confidence interval; *FED*, food elimination diet; *PPI*, proton pump inhibitor; *STC*, swallowed topical corticosteroids.

TABLE E4. Strictures—Cox proportional hazard model examining the time to strictures in relation to the stage of disease control (controlled disease vs ongoing active disease)

Covariates	Hazard ratio	95% CI	*P* value
Ongoing active disease (vs controlled disease)	3.16	[1.09, 9.17]	.025
Sex = female (vs. male)	1.4	[0.49, 4.00]	.515
Age at baseline	1	[0.95, 1.04]	.831
Active disease at baseline (vs inactive)	1.24	[0.41, 3.73]	.687
Treatment at baseline = PPI (vs PPI)	0.49	[0.06, 3.78]	.438
Treatment at baseline = PPI + FED (vs PPI)	1.56	[0.05, 46.28]	.787
Treatment at baseline = STC (vs PPI)	0.28	[0.08, 1.01]	.052
Treatment at baseline = STC + FED (vs PPI)	2.1	[0.32, 13.67]	.417
Treatment at baseline = STC + PPI (vs PPI)	2.64	[0.49, 14.27]	.234

CI, Confidence interval; *FED*, food elimination diet; *PPI*, proton pump inhibitor; *STC*, swallowed topical corticosteroids.

TABLE E5. Dilation—Cox proportional hazard model examining the time to dilation in relation to the stage of disease control (controlled disease vs ongoing active disease)

Covariates	Hazard ratio	95% CI	*P* value
Ongoing active disease (vs controlled disease)	1.4	[0.86, 2.31]	.18
Sex = female (vs male)	1.56	[0.92, 2.66]	.097
Age at baseline	1	[0.98, 1.02]	.807
Active disease at baseline (vs inactive)	0.78	[0.47, 1.29]	.337
Treatment at baseline = PPI (vs PPI)	0.32	[0.08, 1.28]	.108
Treatment at baseline = PPI + FED (vs PPI)	0.94	[0.11, 8.19]	.956
Treatment at baseline = STC (vs PPI)	0.64	[0.28, 1.45]	.28
Treatment at baseline = STC + FED (vs PPI)	0.52	[0.10, 2.63]	.429
Treatment at baseline = STC + PPI (vs PPI)	1.19	[0.37, 3.85]	.771

CI, Confidence interval; *FED*, food elimination diet; *PPI*, proton pump inhibitor; *STC*, swallowed topical corticosteroids.

TABLE E6. Cox regression analyses: primary outcome—Cox proportional hazard model examining the time to complication in relation to the stage of disease control (completely controlled disease vs on-off disease vs continuously active disease)

Covariates	Hazard ratio	95% CI	*P* value
On-off disease (vs. completely controlled disease)	0.36	[0.20, 0.66]	<.001
Continuously active disease (vs completely controlled disease)	1.49	[0.91, 2.42]	.11
Sex = female (vs male)	1.29	[0.84, 1.99]	.246
Age at baseline	0.98	[0.97, 1.00]	.059
Active disease at baseline (vs inactive)	0.95	[0.62, 1.44]	.793
Treatment at baseline = FED only (vs PPI)	0.47	[0.18, 1.22]	.121
Treatment at baseline = PPI + FED (vs PPI)	2.56	[0.53, 12.34]	.241
Treatment at baseline = STC (vs PPI)	0.53	[0.28, 0.99]	.048
Treatment at baseline = STC + FED (vs PPI)	0.82	[0.22, 3.05]	.767
Treatment at baseline = STC + PPI (vs PPI)	0.65	[0.22, 1.89]	.43

CI, Confidence interval; *FED*, food elimination diet; *PPI*, proton pump inhibitor; *STC*, swallowed topical corticosteroids.

TABLE E7. Cox regression analyses: secondary outcome—Cox proportional hazard model examining the time to treatment escalation in relation to the stage of disease control (completely controlled disease vs on-off disease vs continuously active disease)

Covariates	Hazard ratio	95% CI	*P* value
On-off disease (vs completely controlled disease)	0.89	[0.42, 1.91]	.773
Continuously active disease (vs completely controlled disease)	2.48	[1.29, 4.78]	.007
Sex = female (vs male)	1	[0.59, 1.69]	.991
Age at baseline	0.96	[0.94, 0.98]	<.001
Active disease at baseline (vs inactive)	1.21	[0.71, 2.05]	.486
Treatment at baseline = FED only (vs PPI)	0.5	[0.16, 1.51]	.219
Treatment at baseline = PPI + FED (vs PPI)	1.03	[0.13, 8.43]	.979
Treatment at baseline = STC (vs PPI)	0.25	[0.12, 0.52]	<.001
Treatment at baseline = STC + FED (vs PPI)	0.34	[0.07, 1.59]	.169
Treatment at baseline = STC + PPI (vs PPI)	0.28	[0.08, 1.05]	.059

CI, Confidence interval; *FED*, food elimination diet; *PPI*, proton pump inhibitor; *STC*, swallowed topical corticosteroids.

TABLE E8. Cox regression analyses: secondary outcome—Cox proportional hazard model examining the time to strictures in relation to the stage of disease control (completely controlled disease vs on-off disease vs continuously active disease)

Covariates	Hazard ratio	95% CI	*P* value
On-off disease (vs completely controlled disease)	1.23	[0.26, 5.87]	.781
Continuously active disease (vs completely controlled disease)	3.35	[0.85, 13.25]	.055
Sex = female (vs male)	1.43	[0.50, 4.11]	.494
Age at baseline	1	[0.95, 1.04]	.823
Active disease at baseline (vs inactive)	1.2	[0.39, 3.72]	.745
Treatment at baseline = FED only (vs PPI)	0.48	[0.06, 3.80]	.437
Treatment at baseline = PPI + FED (vs PPI)	1.63	[0.05, 53.70]	.774
Treatment at baseline = STC (vs PPI)	0.28	[0.08, 1.02]	.051
Treatment at baseline = STC + FED (vs PPI)	1.95	[0.28, 13.77]	.481
Treatment at baseline = STC + PPI (vs PPI)	2.58	[0.47, 14.06]	.248

CI, Confidence interval; *FED*, food elimination diet; *PPI*, proton pump inhibitor; *STC*, swallowed topical corticosteroids.

TABLE E9. Cox regression analyses: secondary outcome—Cox proportional hazard model examining the time to dilation in relation to the stage of disease control (completely controlled disease vs on-off disease vs continuously active disease

Covariates	Hazard ratio	95% CI	*P* value
On-off disease (vs completely controlled disease)	0.22	[0.10, 0.48]	<.001
Continuously active disease (vs completely controlled disease)	0.76	[0.44, 1.31]	.324
Sex = female (vs male)	1.65	[0.97, 2.82]	.066
Age at baseline	0.99	[0.97, 1.01]	.554
Active disease at baseline (vs inactive)	0.94	[0.57, 1.55]	.806
Treatment at baseline = FED only (vs PPI)	0.30	[0.07, 1.21]	.090
Treatment at baseline = PPI + FED (vs PPI)	0.59	[0.07, 5.16]	.631
Treatment at baseline = STC (vs PPI)	0.78	[0.35, 1.75]	.544
Treatment at baseline = STC + FED (vs PPI)	0.93	[0.18, 4.73]	.927
Treatment at baseline = STC + PPI (vs PPI)	1.53	[0.47, 4.97]	.477

CI, Confidence interval; *FED*, food elimination diet; *PPI*, proton pump inhibitor; *STC*, swallowed topical corticosteroids.

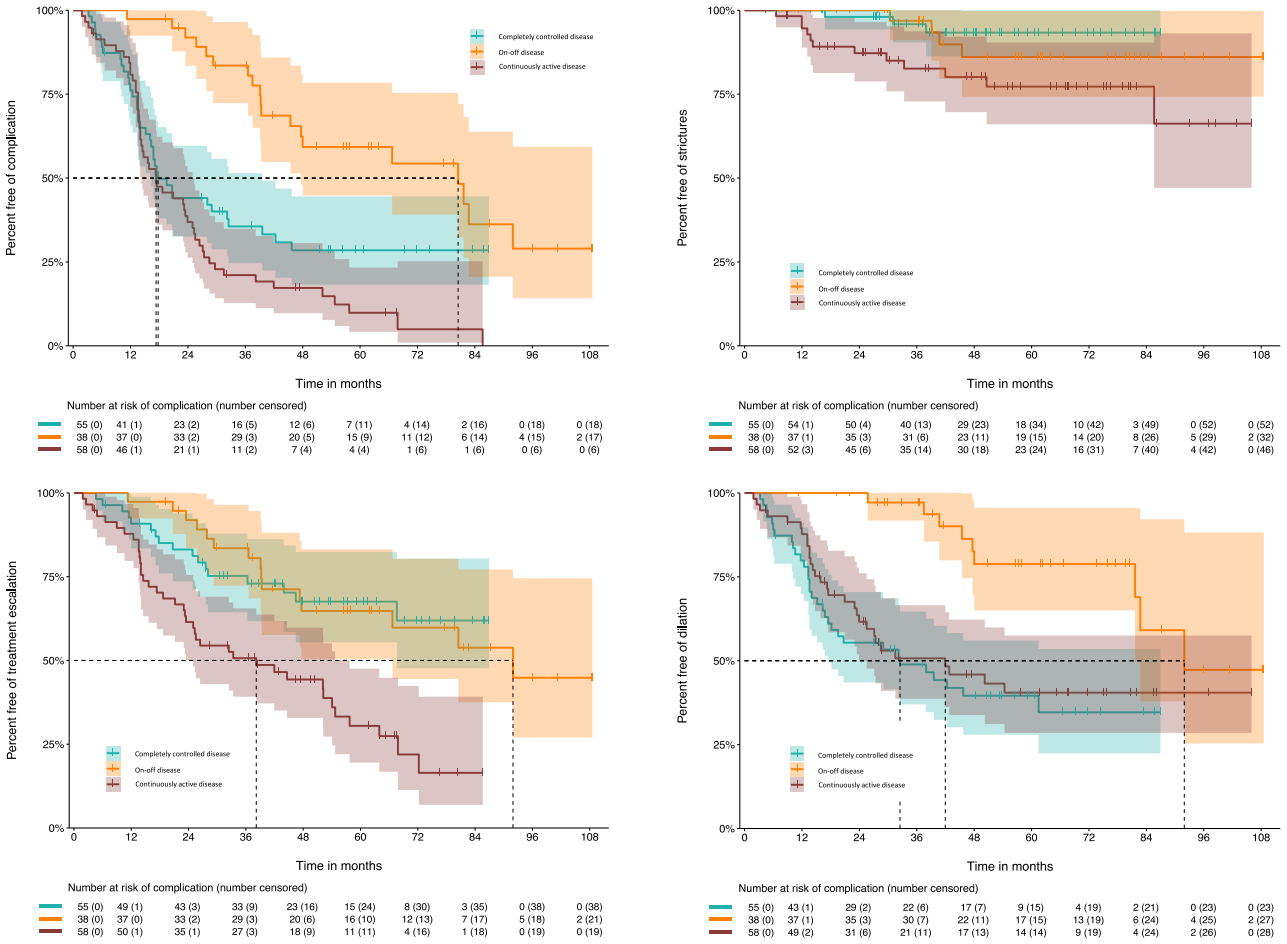

FIGURE E1. Kaplan-Meier curves for time to any complication, time to strictures, time to treatment escalation, and time to dilation, in relation to the stage of disease control (completely controlled disease vs on-off disease vs continuously active disease).