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Close follow-up is associated with fewer stricture formation and results in earlier detection of histological relapse in the long-term management of eosinophilic esophagitis

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Abstract

Background and aims: No recommendations exist regarding optimal follow-up schedule in patients with eosinophilic esophagitis (EoE) under maintenance treatment.

Methods: We retrospectively evaluated a long-term surveillance concept at the Swiss EoE clinic, where clinical, endoscopic and histological disease activity is assessed annually regardless of EoE symptoms. Data on 159 adult patients under maintenance steroid treatment with available follow-up were analyzed. Patients were classified as having close (duration between visits <18 months) or non-close follow-up (≥18 months).

Results: We analyzed a total of 309 follow-up visits of 159 patients (123 males, age at diagnosis 38.9 ± 15.4 years). 157 (51%) visits were within a close follow-up schedule (median duration between visits of 1.0 years (interquartile range (IQR) 0.9–1.2)), while 152 visits (49%) were not (median duration between visits 2.9 years (IQR 2.0–4.1)). There was no difference regarding ongoing clinical, endoscopic, and histological disease activity, and adherence to prescribed steroid treatment between the two groups. However, stricture formation was significantly less frequently observed at visits within a close follow-up schedule (22.9 vs. 33.6%, $p = 0.038$). Absence of close follow-up was a significant risk factor for stricture development in a multivariate regression model. Patients who achieved histological remission and were followed within a close-follow-up schedule had significantly earlier detection of histological relapse compared to patients not within such close follow-up.

Conclusion: Close follow-up is associated with fewer stricture formation and appears to result in earlier detection of histological relapse in patients with

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eosinophilic esophagitis. We advocate for regular assessment of disease activity (every 12–18 months) in order to detect relapsing disease as early as possible, and therefore potentially minimize the risk for EoE complications.

KEYWORDS
eosinophilic esophagitis, esophagus, long-term outcome, relapse, swallowed topical corticosteroids

INTRODUCTION

Eosinophilic esophagitis (EoE) is a chronic inflammatory disorder of the esophagus characterized clinically by symptoms of esophageal dysfunction – mainly dysphagia in adults – and histologically by an eosinophil-predominant infiltration of the esophageal mucosa.[1] Since its first description in the 1990s,[2,3] incidence and prevalence of EoE have been rapidly increasing.[4] In North America and Europe, it is currently estimated that 1 individual among 2000 inhabitants is affected by EoE. Chronicity is a predominant feature of the disease: observational studies and clinical experience accordingly show that in the vast majority of patients both symptoms and eosinophilic inflammation persist over years.[5] Delay in diagnosis and inadequate treatment may result in development of disease complications such as stricture formation and esophageal food bolus impactions necessitating endoscopic removal.[6,7]

A comprehensive care of patients with any chronic (inflammatory) disease requires both, an efficient and safe long-term treatment as well as an appropriate surveillance of symptoms and of disease-relevant biomarkers. For EoE, the two currently (and mostly) applied treatment modalities are either (empiric) elimination diet or swallowed topical corticosteroids (STC). While therapeutic interventions have proven efficacy in bringing active EoE into remission and maintaining clinical, endoscopic and histological remission, data on long-term treatment beyond 1 year in adults with EoE are still limited.[8–14] Our group has recently shown efficacy of topical steroids in the long run, which however was considerably lower than that seen for shorter treatment duration with histological relapse being a frequent problem despite ongoing treatment – both for low and high dose steroid regimens.[7,15–17] Regarding long-term surveillance strategies in EoE, the situation is worse as currently no data are available and therefore no evidence-based recommendations exist. Neither reasonable intervals for clinical visits nor schedules for the control of disease-relevant biomarkers have been evaluated.

Given this lack of knowledge and missing recommendations, we developed a long-term surveillance concept at a EoE referral center for adult patients (Swiss EoE Clinic).[18] This concept was launched in 2007 and aims to improve quality of care (e.g. control of symptoms) and to be cost-efficient (e.g. reduction of urgent endoscopies for bolus impactions, emergency room visits). However, implementation of such a concept in real life settings has its challenges. So far, we have neither evaluated whether our concept has been implemented to a sufficient extent nor whether close surveillance results in a better therapeutic outcome.

Key summary

What is known:

- Eosinophilic esophagitis is a chronic inflammatory disorder of the esophagus that requires long-term treatment and follow-up
- However, neither reasonable intervals for clinical visits nor schedules for the control of disease-relevant biomarkers have been evaluated

What is new:

- We retrospectively evaluated a long-term surveillance concept at the Swiss EoE clinic, where clinical, endoscopic and histological disease activity is assessed annually regardless of EoE symptoms
- Close follow-up is associated with fewer stricture formation and appears to result in earlier detection of histological relapse

The primary purpose of this study was to evaluate the impact of a close and predefined surveillance concept on disease course in a large cohort of adult EoE patients.

METHODS

Study design

In this observational study, we retrospectively evaluated a cohort of EoE patients under ongoing topical steroid maintenance treatment according to our previously published therapeutic concept consisting of an induction phase (1 mg bid) until clinical response (usually 2–4 weeks), followed by a long-term maintenance phase (0.25 mg bid).[15] All patients provided written informed consent prior to

inclusion into the Swiss EoE database (SEED). The study was approved by the local ethics committee (EKNZ 2015-388).

Patients and data collection

The SEED is a nation-wide database of patients with confirmed EoE diagnosis established in accordance with defined criteria.[1] Inclusion criteria for the SEED have been published elsewhere.[15] For the purpose of this study, we applied the following inclusion criteria: (1) availability of a baseline examination with at least one follow-up with standardized assessment of clinical, endoscopic and histological disease activity (= first visit of the maintenance phase); (2) ongoing (prescribed) maintenance treatment with topical steroids in the follow-up. Patients with clinical features and laboratory findings typical for eosinophilic gastroenteritis were excluded from this study. Patients without prescribed treatment or treatment with investigational drugs were excluded from this study. Patients with therapeutic changes such as STC taper or dietary restrictions were also excluded. In case STC taper or dietary restrictions occurred in the follow-up, last follow-up visit before therapeutic changes was eligible. Patients with an early follow-up within 0.5 years were excluded from analysis as those visits were most likely due to a symptomatic relapse and not based on a regular follow-up schedule. All documents were reviewed and data were extracted from patients' records by one physician (TG) under the close supervision of EoE experts (AS, AMS). Endoscopic disease activity was graded using the EoE Endoscopic Reference Score (EREFS) grading and classification system based on the available endoscopic pictures.[19] This EREFS-based score ranging from zero to eight has been described in detail elsewhere.[19] For endoscopic pictures taken before 2012, images were re-assessed in retrospect to assign an EREFS score. Structured data collection was performed by means of a standardized spreadsheet. All data were anonymized.

Long-term follow-up concept at the swiss eosinophilic esophagitis clinics

The following concept has been uniformely applied to all patients treated by AS at the Swiss EoE clinics as previously described:[15]

- Induction treatment with swallowed topical steroids (1 mg bid) until clinical response (usually 2–4 weeks, followed by a long-term maintenance phase (0.25 mg bid).
- Long-term treatment is continued regardless of achievement of clinical, endoscopic or histological remission.
- EoE flare ups are managed with re-induction therapy with increased doses of swallowed topical steroids (1 mg bid) for 1–2 weeks.
- Patients had scheduled annual follow-up visits regardless of presence of symptoms with assessment of clinical, endoscopic and histological disease activity during each follow-up visit.

Annual follow-up at an exact 12-month interval was aimed for, but deviation of +/− 6 months was allowed due to practical reasons such as capacity at the EoE clinics of AS, long distance to travel to the clinic (AS follows patients throughout Switzerland), and insurance related reasons such as bills cumulatively paid within 12-months periods.

Definition of follow-up schedule

Close follow-up was defined by a time period since last visit of less than 18 months (<18 months). Visits that were scheduled 18 months or more (≥18 months) after the last visit were considered as non-close follow-up. For per patient analysis, patients with a mean duration between "annual" follow-up visits with clinical and endoscopic assessment of disease activity of less than 18 months (<18 months) were considered to adhere to a close follow-up schedule. Patients where this mean duration was 18 months or more (≥18 months) were considered having a non-close follow-up. Patients with a follow-up within only 6 months were excluded from the study as those visits were not pre-scheduled, but rather due to early symptomatic relapse.

Study endpoints

Primary endpoints for per visit analyses were proportions of clinical and histological remission at respective visits (close vs. non-close follow-up). Further endpoints were proportions of endoscopic remission, adherence to steroid regimen and development of strictures. Primary endpoint for per patient analyses was the proportion of patients developing a histological relapse despite ongoing maintenance treatment (close vs. non-close follow-up). Further endpoints were proportions of patients of clinical and endoscopic remission, adherence to treatment and development of strictures (new stricture and worsening stricture requiring endoscopic dilation). Clinical remission was based on the single observer's assessment (AS).

Statistics

For statistical analyses, statistical package program STATA (version 16, College Station, Texas, USA) was used. Categorical data was compared using the Chi-square test; differences in quantitative data distributions were assessed using the unpaired Student's *t*-test (for normally distributed data) and the Wilcoxon rank-sum test (for non-normally distributed data). Multivariate logistic regression was performed by taking into account all covariates with a univariate *p*-value of <0.1. The following covariates were analyzed: sex (male vs. female), age at EoE onset in years, diagnostic delay in years, adherence to STC treatment in the follow-up (yes vs. no), prescribed proton pump inhibitor (PPI) therapy in the follow-up (yes vs. no), family history for EoE

(positive vs. negative), presence of allergic comorbidities (yes vs. no), histological activity at baseline (yes vs. no), and clinical activity at baseline (yes vs. no). For calculation of time from histological remission to relapse, Kaplan Meier curves were computed. In order to correct for confounding factors, multivariate Cox regression (for time to histological relapse) was performed. For the purpose of this study, a *p*-value of <0.05 was considered statistically significant.

RESULTS

Patient and disease characteristics

We analyzed a total of 309 follow-up visits of 159 patients (123 males, 77.4%). For a study flow chart including total patients within the SEED and treated at the Swiss EoE clinics, see Supplementary Figure 1. Mean age at diagnosis was 38.9 ± 15.4 years with a median of 5 years of symptoms (interquartile range (IQR) 2–11) prior to diagnosis. Family history for EoE was reported in 30 patients (18.9%), while 111 patients had atopic comorbidities (69.8%). 26 patients suffered from concomitant gastroesophageal reflux disease (GERD) (16.4%). Baseline disease characteristics are shown in Table 1. Of the 309 analyzed follow-up visits (median follow-up 5 years, IQR 4–8), we identified 251 with EoE-related symptoms (81.2%), 215 with endoscopic inflammatory features (69.6%), and 231 with histological disease activity defined by ≥15 eos/hpf (74.8%). Adherence to steroid treatment was 43.4% (134 visits), while co-treatment with PPI was present at 62 visits (20.1%). For details see Table 1.

Follow-up strategy

Of the 309 visits, 157 visits were within a close follow-up schedule (median of 1.0 years since last visit, IQR 0.9–1.2), while 152 were not within a close follow-up schedule (2.9 years after last visit, IQR 2.0–4.1). Disease characteristics for the two groups are shown in Table 2. Number of visits was the only significant predictor for adherence to a close follow-up schedule (OR 1.245, 95% confidence interval (CI) 1.098–1.411, $p = 0.001$) remaining significant in a multivariate model (OR 1.243, 95% CI 1.095–1.410, $p = 0.001$). For detail see Supplementary Table 1. So, the higher the number of visits, the less likely this visit was within a close follow-up. Female sex showed a trend towards higher rates of close follow-up (OR 1.583, 95% CI 0.932–2.690, $p = 0.089$), while neither clinical nor histological activity at baseline predicted follow-up schedule. Thus, presence of symptoms did not predict adherence to a close follow-up (Supplementary Table 1).

Visits within versus not within a close follow-up did not show any differences with regards to clinical (82.2 vs. 80.3%), endoscopic (68.8 vs. 70.4%), and histological disease activity (75.2 vs. 74.3%). Adherence rates to STC (44.6 vs. 42.1%) and co-treatment with PPI (23.6 vs. 16.4%) were also similar between the two groups (Table 2). However, strictures were significantly more often found at visits that were not within a close follow-up schedule (33.6 vs. 22.9%, $p = 0.038$), see Figure 1. Univariate logistic regression model for prediction of stricture formation identified both a longer diagnostic delay (OR 1.038, 95% CI 1.010–1.066, $p = 0.007$) and non-close follow-up (OR for close follow-up schedule 0.588, 95% CI 0.356–0.972, $p = 0.038$) as significant risk factors. Non-close follow-up remained a significant risk factor in a multivariate regression model (OR for close follow-up schedule 0.558, 95% CI 0.325–0.957, $p = 0.034$). For details, see Table 3.

Per patient data

We subsequently analyzed our data by patients and included a total of 74 subjects who achieved histological remission during follow-up and had at least one additional follow-up visit (with assessment of endoscopic and histological disease activity). Patients with a follow-up visit within 0.5 years were excluded from analyses as these patients most probably presented due to symptomatic relapse, but not due to a regular scheduled visit regardless of disease activity. We finally included 46 patients (for a study flow chart, see Supplementary Figure 2). Of these 46 patients, 40 were males (87.0%) with a mean age at EoE diagnosis of 38.8 ± 14.5 years (diagnostic delay 7.5 years, IQR 2.3–16.5). Family history for EoE was reported in 8 patients (17.4%), while 25 patients had atopic comorbidities (54.3%). Eight patients had concomitant GERD (17.4%). Baseline disease characteristics are shown in Supplementary Table 2. Patients where the average time between visits was <18 months were considered to be followed within a close follow-up schedule. 26 patients were considered to have such a close follow-up (duration between visits 13 months (IQR 11.1–15.0), number of visits 3 (IQR 1–4)), while the remaining 20 patients were not within a close follow-up schedule (duration between visits 25 months (IQR 19.3–33.6), number of visits 2 (IQR 2–3)).

The two groups did not show any difference with regards to baseline characteristics nor with regards to clinical, endoscopic and histological disease activity in the follow-up. Rates of ongoing clinical and endoscopic disease activity as well as histological relapse were high with 76.9 versus 75.0%, 61.5 versus 65.0%, and 61.5 versus 65%, respectively. In addition, adherence rates to STC in the long-term were inadequate in both groups with 61.5% and 45.0%, respectively. PPI co-treatment was prescribed in 30.8% and 15.0%. For details see Supplementary Table 3 and Figure 2a. However, when looking at time to histological relapse, we identified patients within a close follow-up schedule to experience such relapse significantly earlier than patients not within a close follow-up schedule. For a Kaplan Meier analysis, see Figure 2b (log-rank test $p = 0.004$). In fact, close follow-up was a significant predictor of early histological relapse in a multivariate cox regression model corrected for esophageal eosinophilia at the time of histological remission, clinical activity at the time of histological remission, adherence to STC, and co-treatment with PPI (Table 4). The corrected hazard ratio was 3.375, 95% CI 1.148–9.921, $p = 0.028$. Based on this, we conclude that frequent follow-up and testing (within a predefined schedule

TABLE 1 Patient and disease characteristics at baseline

Patient demographics and disease characteristics at study inclusion	**Frequency (*n* = 159 patients)**
Males	123 (77.4%)
Age at EoE diagnosis (mean, SD) (years)	38.9, 15.4
Diagnostic delay (median, IQR, range) (years)	5, 2–11, 0–40
Family history for EoE	30 (18.9%)
Symptoms leading to EoE diagnosis	
- Dysphagia	135 (84.9%)
- Chest pain	34 (21.4%)
- Reflux	8 (5.0%)
- Food bolus removal	37 (23.3%)
Concomitant atopic diseases (ever reported)	111 (69.8%)
Concomitant gastroesophageal reflux disease at baseline	26 (16.4%)
Endoscopic disease activity at study inclusion	
Endoscopic inflammatory signs	99 (62.3%)
Endoscopic fibrotic features	67 (42.1%)
Strictures	44 (27.7%)
EREFS-based score, median (IQR)	3, 1–4
Histological disease activity at study inclusion	
Peak eosinophil count per hpf, median (IQR)	40, 3–80
Subepithelial fibrosis	Assessed for 45 patients
- Mild to moderate	33 (73.3%)
- Severe	10 (22.2%)
Disease characteristics during follow-up	**Frequency (n = 309 visits)**
Follow-up, median (IQR) (years)	5, 4–8
Clinical characteristics	
Presence of EoE-related symptoms	251 (81.2%)
PPI Treatment	62 (20.1%)
Topical steroid treatment during visits (adherence)	134 (43.4%)
Endoscopic findings	
Endoscopic inflammatory signs	215 (69.6%)
Endoscopic fibrotic features	131 (42.4%)
Strictures	87 (28.2%)
EREFS-based score, median (IQR)	3, 2–5
Histologic findings	
Peak count of ≥15 eosinophils/hpf	231 (74.8%)
Subepithelial fibrosis	Assessed during 116 visits
- Mild to moderate	83 (71.6%)
- Severe	24 (20.7%)

Abbreviations: IQR, interquartile range; PPI, proton pump inhibitor.

TABLE 2 Comparison of visits within versus not within a close follow-up schedule

Disease characteristics	No close FU *N* = 152	Close FU *N* = 157	*p* Value
Time since last visit, median (IQR) (in years)	2.9, 2.0–4.1	1.0, 0.9–1.2	0.001
Clinical characteristics			
Presence of EoE-related symptoms	122 (80.3%)	129 (82.2%)	ns
Prescribed PPI treatment	25 (16.4%)	37 (23.6%)	ns
Adherence to topical steroid treatment during visits	64 (42.1%)	70 (44.6%)	ns
Endoscopic findings			
Endoscopic inflammatory signs	107 (70.4%)	108 (68.8%)	ns
Endoscopic fibrotic features	67 (44.1%)	64 (40.8%)	ns
Strictures	51 (33.6%)	36 (22.9%)	0.038
EREFS-based score, median (IQR)	3, 2–4	3, 1–5	ns
Histologic findings			
Peak count of ≥15 eosinophils/hpf	113 (74.3%)	118 (75.2%)	ns
Subepithelial fibrosis	Assessed during 66 visits	Assessed during 50 visits	ns
- Mild to moderate	46 (69.7%)	37 (74.0%)	
- Severe	17 (25.8%)	7 (14.0%)	

Abbreviations: FU, follow-up; IQR, interquartile range; PPI, proton pump inhibitor.

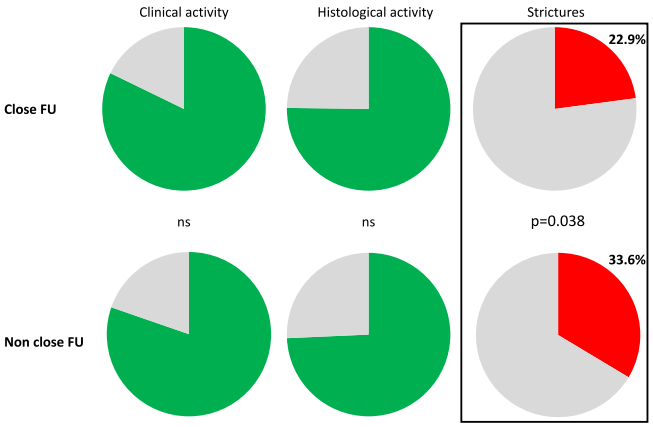

FIGURE 1 Proportion of patients with clinical and histological activity (green color) and stricture formation (red color) during follow-up with regards to follow-up schedule (close follow-up vs. non-close follow-up)

regardless of clinical disease activity) results in earlier detection of histological disease activity regardless of clinical symptoms.

DISCUSSION

In this observational study, we retrospectively analyzed adherence to a close follow-up schedule and its impact on disease activity and disease progression in adult EoE patients under indefinite topical steroid treatment. Based on our analysis more than 300 follow-up visits from 159 adult patients with EoE with a median follow-up of 5 years, our main findings are: (1) adherence to a close follow-up schedule is seen in 51% with lower adherence after a higher number of visits; (2) visits within a close follow-up schedule do not result in higher rates of clinical, endoscopic, histological remission nor higher adherence to treatment, but are associated with fewer stricture formation; and (3) close follow-up of patients in histological remission appears to result in earlier detection of histological relapse.

Despite our implemented therapeutic concept with annual assessment of clinical, endoscopic and histological disease activity, adherence to such a close follow-up is only seen in roughly 50% of our follow-up visits. Number of already attended visits was the only predictor for adherence to a close follow-up schedule – even after correction for confounding factors. Thus, the more visits a patient already had before, the lower was the likelihood that he or she will show up for a subsequent visit within an 18 months period. Such decreasing adherence to surveillance strategies with longer treatment duration over time has been shown for other allergic diseases.[20] Particularly for asthma, lack or insufficient follow-up appears to be a frequent problem despite the known efficacy of disease surveillance and education.[21] Interestingly, neither symptoms, disease activity at baseline nor adherence to treatment predicted adherence to a close follow-up schedule. Both patients and medical providers might get reluctant to the initially chosen follow-up strategy after several years of follow-up, although our retrospective chart review does not allow to find specific reasons for delaying follow-up beyond 18 months.

While a close follow-up schedule did not result in lower rates of disease activity or higher rates of adherence to steroid treatment, a significantly lower number of strictures was detected (22.9

TABLE 3 Univariate and multivariate logistic regression for prediction of stricture development at follow-up

Prediction of stricture at follow-up visit				
	Univariate model		Multivariate model	
Candidate risk factor	OR, 95% CI	*p*-value	Or, 95% CI	*p*-value
Sex				
- Male	Ref.			
- Female	0.711 (0.386–1.310)	0.274		
Age at onset in y	1.010 (0.994–1.026)	0.223		
Diagnostic delay in y	1.038 (1.010–1.066)	0.007	1.035 (1.007–1.065)	0.014
Adherence to topical steroids during visit				
- No	Ref.			
- Yes	1.090 (0.648–1.833)	0.745		
PPI Therapy				
- No	Ref.			
- Yes	0.584 (0.299–1.142)	0.116		
Family history				
- Negative	Ref.			
- Positive	1.493 (0.838–2.660)	0.173		
Allergic conditions				
- No	Ref.			
- Yes	0.878 (0.564–1.366)	0.564		
Close follow-up				
- No	Ref.		Ref.	
- Yes	0.588 (0.356–0.972)	0.038	0.558 (0.325–0.957)	0.034
Histological activity at baseline				
- No	Ref.		Ref.	
- Yes	1.823 (0.972–3.418)	0.061	1.810 (0.953–3.438)	0.070
Clinical activity at baseline				
- No	ref.			
- Yes	1.111 (0.496–2.487)	0.798		

Abbreviations: CI, confidence interval; PPI, proton pump inhibitor.

vs. 33.6%). Of note, close follow-up remained a significant protective factor with regards to stricture formation in a multivariate regression model such as seen for a shorter diagnostic delay. The identification of two independent predictors, diagnostic delay and follow-up schedule, in light of the previous data showing a clear association between diagnostic delay and stricture formation over time makes our data more robust.[6] Although adherence rates were similar between the two groups, adherence was only assessed based on whether or not patients were actually taking their drugs at the time of follow-up. Grading adherence, by steps of 10% or 25% on a scale from 0 to 100 for example, was not possible based on our retrospective chart review but could potentially explain our findings. Our group has recently shown that adherence to treatment indeed affects development of EoE complications such as bolus impactions.[7] It remains to be determined in future studies whether or not shorter follow-up triggers higher accuracy in the intake of topical steroids. Nevertheless, our data supports the implementation of a follow-up strategy with scheduled visits within an 18-month time frame regardless of initial disease presentation.

Even in patients with well-controlled disease defined by maintenance of histological remission (<15 eosinophils per hpf) under ongoing topical steroid treatment, close follow-up appears to have benefits. Patients within a predefined close follow-up schedule (with scheduled visits regardless of clinical disease activity) were detected significantly earlier as having a histological relapse, while overall histological relapse rates did not differ between the two groups. Thus, frequent follow-up and testing results in earlier detection of

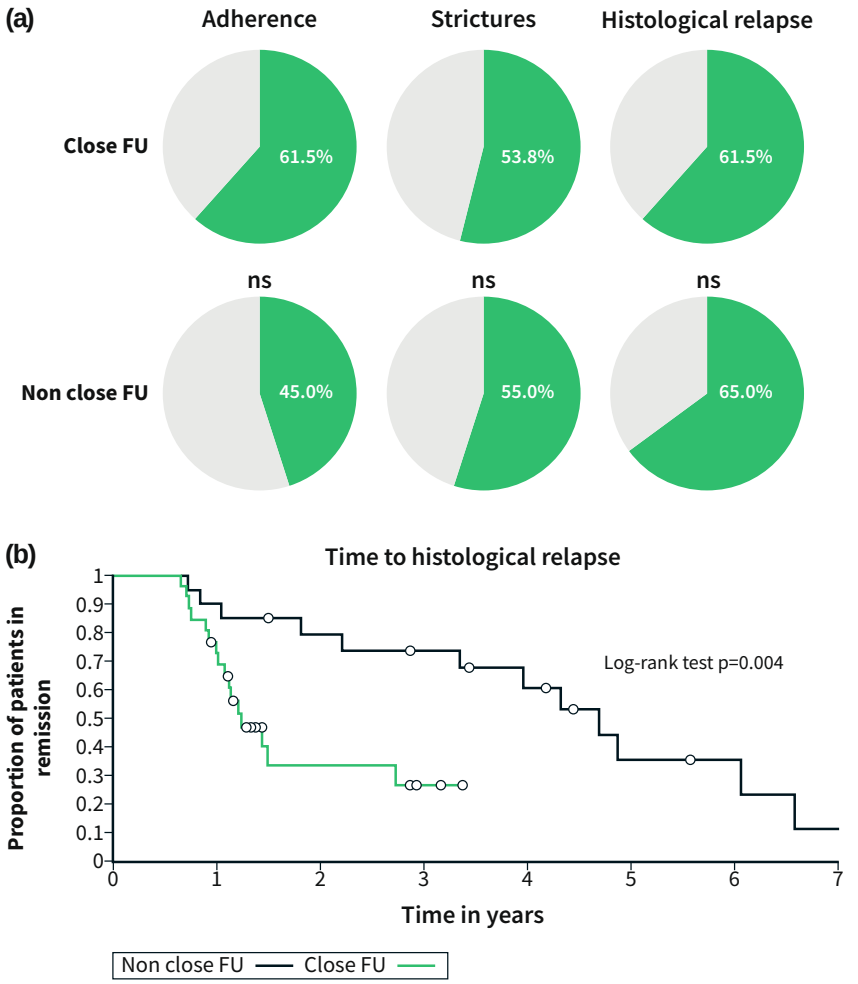

FIGURE 2 (a) Proportion of patients with adherence to swallowed topical corticosteroids (STC), stricture formation and histological relapse (green color) during follow-up with regards to follow-up schedule. (b) Kaplan Meier curves for time to histological relapse in patients with (green line) versus without close follow-up (blue line)

histological disease activity regardless of clinical symptoms allowing for potential interference with disease course due to ongoing inflammation, although the latter still has to be proven in further studies. High histological relapse rates despite ongoing maintenance treatment have been previously shown by our group, which were partly attributed to the low steroid regimen used in our cohort.[17] However, even higher steroid formulation resulted in a considerable proportion of disease relapse over time.[16] Thus, histological relapse is a frequent phenomenon in the follow-up of EoE patients underscoring the chronicity of EoE. As symptoms show only a moderate correlation with histological activity, esophageal biopsies – at least for now – are needed to adequately assess EoE activity. Disease often flares up (on a histological level) without patients noticing it. Earlier detection of relapse within a close follow-up schedule might allow both patients and medical providers to take necessary actions for optimizing disease control such as increasing adherence rates, changing steroid formulations, applying short courses of reinduction treatment, or switching treatment strategies. Ongoing undetected disease activity clearly has its clinical implications, as longer diagnostic delay has been previously associated with the development of stricture formation.[6] The latter was not shown in our per patient analysis for several reasons: 1) low number of patients due to rigorous inclusion criteria, 2) follow-up period limited to the time-point of histologic remission, and 3) ongoing steroid treatment which has been associated with a positive effect on fibrosis in previous studies.[8,22]

Our study has several limitations. The retrospective nature of the study did not allow to grade adherence in detail. Such grading would have possibly allowed to explain differences with regards to stricture formation for close versus non-close follow-up. Indirect measures such as prescription refills could not be tracked in this study. Furthermore, clinical disease activity was not assessed in a standardized manner with symptoms being reported in a binary fashion (present or not) only. The definition of clinical remission/activity was based on physician's interpretation in the charts. Mild to moderate disease activity might have been under-estimated. However, all patients were followed by a single EoE expert (AS) seeing >200 EoE patients per year minimizing such bias. Furthermore, our

TABLE 4 Multivariate Cox regression model for prediction of histological relapse in the follow-up

Multivariate cox regression, all patients (n = 46)	Hazard ratio (95% CI; p-Value)
Close follow-up	
- No	Ref.
- Yes	3.375 (1.148–9.921, p = 0.028)
Esophageal eosinophilia at baseline	
- No (0–1 eos/hpf)	Ref.
- ≥2 eos/hpf	0.934 (0.401–2.175, p = 0.872)
Clinical activity at baseline	
- No	Ref.
- Yes	3.742 (1.096–12.771, p = 0.036)
Prescribed PPI treatment during follow-up	
- No	Ref.
- Yes	0.849 (0.0.362–1.991, p = 0.700)
Adherence to topical steroids during follow-up	
- No	Ref.
- Yes	1.528 (0.597–3.912, p = 0.369)

Abbreviations: CI, confidence interval; PPI, proton pump inhibitor.

data only included adults and patients on long-term steroid treatment, as dietary regimens are infrequently prescribed at the EoE clinics (<9%). Therefore, our findings cannot be extrapolated neither to children nor to patients following dietary restrictions. Visits were still considered as "annual" even with a variation of +/− 6 months due to practical and insurance related reasons. Nevertheless, 75% of the patients within the close follow-up group had visits that were very close to "annual" defined as exactly 12 months (interquartile range of 11 to 14 months). Strictures were assessed in a binary fashion (yes or no). The small numbers of patients with a food bolus impaction necessitating endoscopic removal in the follow-up (n = 7) did not allow us to analyze the significance/severity of these strictures in more detail. An important limitation for the per patient analyses is the study sample size of only 46. Although the SEED comprises of a uniquely high number of patients followed by a single EoE expert, the current number was relatively small due to the rigorous inclusion criteria applied to our retrospective per patient analysis (histological remission, ongoing prescribed steroid treatment, available follow-up). In addition, we excluded patients with a follow-up visit within 0.5 years as such a visit would most probably be attributed to symptomatic relapse rather than to a visit within a pre-scheduled strategy. Finally, the steroid dose used in the SEED is rather low (0.25 mg bid). However, we have recently shown that in the long-term treatment of EoE both low and high dose steroid regimens are associated with high rates of histological relapse regardless of the chosen strategy.[16]

In conclusion, adherence to a close follow-up was seen in roughly half of the time with decreasing adherence after a higher number of visits. Despite no direct impact on disease activity, close follow-up was associated with fewer stricture formation. In addition, patients in histological remission and under ongoing topical steroid treatment were detected significantly earlier with a histological relapse. Based on these data, we advocate for implementation of a close follow-up schedule in adult patients with EoE where disease activity is regularly assessed (every 12–18 months), even in patients with ongoing treatment and well-controlled disease.

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CONFLICT OF INTEREST

Ekaterina Safroneeva is a consultant for Celgene Corp., Regeneron Pharmaceuticals Inc., and Novartis. Luc Biedermann has received consulting fees and/or speaker fees from Falk Pharma, Esocap, Sanofi-Aventis and Calypso Biotech. Philipp Schreiner received fees for consulting from Pfizer, Janssen and Takeda. Stephan R. Vavricka received consultant fees and unrestricted research grants from Vifor and Falk Pharma. Alain M. Schoepfer is a consultant for Falk Pharma, Adare Pharmaceuticals, Celgene-Receptos, and Sanofi-Regeneron. Hans-Uwe Simon is a consultant for AstraZeneca, GlaxoSmithKline, and Esocap. Alex Straumann has consulting contracts with Actelion, Celgene-Receptos, Falk Pharma, Roche-Genentech, GlaxoSmithKline, Novartis, Nutricia and Sanofi-Regeneron. Mirna Chehade received research support from Regeneron, Allakos, Shire/Takeda, AstraZeneca, Adare/Ellodi, Danone; and consulting fees from Regeneron, Allakos, Adare/Ellodi, Shire/Takeda, AstraZeneca, Sanofi, Bristol Myers Squibb, Phathom. Thomas Greuter has consulting contracts with Sanofi-Regeneron and Falk Pharma, received travel grants from Falk Pharma GmbH and Vifor, and an unrestricted research grant from Novartis. The other authors (Lorenz Bon, Christian Bussmann, Talaya McCright-Gill) have nothing to declare. No company representative was involved in conception, writing, or financing of this study.

AUTHOR CONTRIBUTION

Study concept and design: Alex Straumann, Mirna Chehade, Thomas Greuter; acquisition of data: Lorenz Bon, Ekaterina Safroneeva, Alain M. Schoepfer, Alex Straumann, Thomas Greuter; follow-up visits and endoscopic evaluation: Alex Straumann; histological examination: Christian Bussmann; analysis and interpretation of data: Lorenz Bon, Ekaterina Safroneeva, Alain M. Schoepfer, Alex Straumann, Mirna Chehade, Thomas Greuter; drafting of manuscript: Lorenz Bon, Mirna Chehade, Thomas Greuter; critical revision of the manuscript for important intellectual content: Ekaterina Safroneeva, Christian Bussmann, Luc Biedermann, Philipp Schreiner, Stephan R. Vavricka, Alain M. Schoepfer, Talaya McCright-Gill, Hans-Uwe Simon, Alex Straumann; supervision: Mirna Chehade, Thomas Greuter.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found in the online version of the article at the publisher's website.

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