Long-Term Treatment of Eosinophilic Esophagitis With Swallowed Topical Corticosteroids: Development and Evaluation of a Therapeutic Concept

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OBJECTIVES: **Swallowed topical corticosteroids (STCs) are efficacious in inducing and presumably maintaining remission in patients with active eosinophilic esophagitis (EoE). Hitherto, it has not been evaluated whether long-lasting remission can be achieved, and whether treatment can be stopped once patients have achieved this remission.**

METHODS: **Since 2007, EoE patients included into a large database at the Swiss EoE Clinics were put on STCs as induction/maintenance therapy. Disease activity was assessed on an annual basis. In patients who achieved long-lasting (≥6 months) clinical, endoscopic, and histological (=deep) remission, treatment was stopped. Data on all patients treated using this therapeutic strategy were analyzed retrospectively.**

RESULTS: **Of the 351 patients, 33 (9.4%) who were treated with STCs achieved deep remission. Median age of remitters at disease onset was 32.6 years (interquartile range (IQR) 19.1–49.3), and diagnostic delay was 5.4 years (IQR 1.2–11.4). Deep remission was achieved after 89.0 weeks (IQR 64.6–173.8). Female gender was the only independent prognostic factor for achieving deep remission (odds ratio (OR) 2.518, 95% confidence interval (CI) 1.203–5.269). Overall, STCs were stopped after 104.7 weeks (IQR 65.5–176.6). No mucosal damage was observed upon histological examination. In 27 of the 33 remitters (81.8%), a clinical relapse occurred after a median of 22.4 weeks (95% CI 5.1–39.7). Six remitters (18.2%) did not experience a clinical relapse during a follow-up of 35.1 weeks (IQR 18.3–44.9). Hence, a total of 1.7% (6/351) patients were able to discontinue STCs in the long term.**

CONCLUSIONS: **Long-term EoE treatment with STCs was well tolerated, but only a minority achieved deep remission. Female gender is the only prognostic factor for attainment of such remission. After treatment cessation, the majority experienced a clinical relapse.**

SUPPLEMENTARY MATERIAL is linked to the online version of the paper at http://www.nature.com/ajg

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INTRODUCTION

Eosinophilic esophagitis (EoE) is a chronic inflammatory disorder of the esophagus characterized histologically by an eosinophil-predominant mucosal inflammation and clinically by symptoms such as solid food dysphagia and bolus impaction that are consistent with esophageal dysfunction (1). Incidence and prevalence of EoE have been rapidly increasing since its first description in the early 1990s (2,3). Chronicity is a predominant feature of the disease, as observational studies and clinical experience show that both symptoms and eosinophilic inflammation persist over time in the vast majority of patients (1,4–6). If untreated, chronic eosinophilic inflammation leads to tissue remodeling that alters

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the structure of the esophagus and interferes with its proper functioning (7). These alterations put the patients at risk of suffering from acute food impactions that may lead to severe esophageal injury (8).

Current treatment options include topically acting corticosteroids, elimination of food allergens with diets, and endoscopic dilation, carried out in patients with advanced strictures (1,5). Topical corticosteroids have been shown to be efficacious in inducing remission in patients with active EoE (9–13). In addition, limited data suggest that topical corticosteroids are also efficacious for the maintenance of EoE remission (14,15). So far, topical corticosteroids are considered to be a first-line drug for EoE treatment. Unfortunately, many patients experience a clinical and histological relapse after cessation of such therapy (10,13). Even patients undergoing maintenance treatment with topical corticosteroids may experience a relapse (13). The relative paucity of data on long-term management of EoE with topical corticosteroids is such that even simple questions, including "*How long should patients be treated with this therapy*?", "*Does long-term administration of topical corticosteroids in the esophagus harbor a risk for mucosal atrophy*?", and "*Can EoE be cured following long-term administration of these drugs*?" remain unanswered. To date, no therapeutic strategy aimed at achieving long-term clinical and biologic remission in EoE patients has been evaluated. Similarly, we have yet to learn whether treatment with topical corticosteroids can be stopped for good once remission is achieved.

Thus, we developed a long-term swallowed topical corticosteroid (STC)-based therapeutic strategy for achieving remission and implemented this defined strategy prospectively in a large cohort of EoE patients who underwent esophagogastroduodenoscopy (EGD) with biopsy sampling during annual follow-up visits. The objective of this study was to evaluate whether this strategy is effective in bringing patients into clinical, endoscopic, and histological remission, and whether patients achieving such a remission for at least 6 months can discontinue the therapy.

METHODS

Study design

In this large observational single-center study, we retrospectively evaluated a therapeutic strategy for a long-term treatment of EoE using swallowed topical corticosteroids. The therapeutic strategy was used prospectively in EoE patients treated at the Swiss EoE Clinics in Olten, Switzerland. All patients had previously given their written informed consent for inclusion into the Swiss EoE database (SEED). The study is supported by the Swiss National Science Foundation and was approved by the local ethics committee (EKNZ 2015-388).

Patients and data collection

The SEED is a nationwide database into which EoE patients are prospectively included starting in 1989. Currently, the database contains data on 1091 EoE patients. Patients were included into SEED based on the following criteria: (i) presence of symptoms attributed to esophageal dysfunction (in accordance with the consensus recommendations (1)); (ii) presence of predominant eosinophilic esophageal mucosal inflammation (in accordance with consensus recommendations (1)); and (iii) absence of other diseases associated with esophageal eosinophilia, in particular absence of gastroesophageal reflux disease or eosinophilic gastroenteritis. Gastroesophageal reflux disease was excluded by any one of the following methods: (i) clinically, by lack of typical symptoms; (ii) endoscopically, by absence of hiatal hernia and signs of reflux esophagitis; (iii) lack of response (defined as peak eosinophil count ≥15 eosinophils per high-power field (HPF)) to treatment with proton-pump inhibitors; and/or (iv) negative 24 h pH monitoring study (optional).

For the purposes of this study, the patients on STCs with a baseline visit and at least one follow-up visit (follow-up time ≥1 year) were included provided that standardized assessment of symptoms as well as endoscopic and histologic findings (from the proximal and from the distal esophagus) was carried out and standardized documentation about treatment with swallowed topical corticosteroids was available. Patients were excluded if, during observation period, they were treated by either endoscopic dilation (within the last year of the observation period) or dietary therapy (anytime within the observation period). Data were collected by a thorough chart review using a standardized spreadsheet (**Supplementary Table S1** online). All data were anonymized. The following data were collected: patient characteristics (gender, age, family history of EoE, other atopic disease), baseline disease characteristics (symptom onset, year of diagnosis, symptom severity, endoscopic findings, peak eosinophil count, laboratory findings (full blood count, total IgE)), treatment characteristics (dosage and duration of treatment, side effects, such as mucosal atrophy or infection with *Candida* species), disease course (response to treatment, time to clinical, endoscopic and/or histological remission, disease complications), attainment of deep remission (rates of remission, time to remission, dosage of swallowed topical corticosteroids needed to achieve remission), and disease course after cessation of treatment (frequency of relapse, time to relapse, complications).

Assessment of symptoms (patient-reported outcomes)

To assess dysphagia frequency and severity, the previously published Straumann Dysphagia Index (SDI) was calculated (16). The score ranges between 0 and 9 (13).

Assessment of endoscopic alterations

EGD with esophageal biopsy sampling was performed in all patients by a single board-certified gastroenterologist (A.S.) on an annual basis. The following endoscopic alterations in accordance with Eosinophilic Esophagitis Endoscopic Reference Score (EREFS) classification and grading system were assessed (and following arbitrary values assigned in order to generate a nonvalidated score): (i) mucosal edema (absent=0; present=1), (ii) rings (absent=0; mild=1; moderate=2; severe=3), (iii) white exudates (absent=0; mild=1; severe=2), (iv) furrows (absent=0; mild=1; 2=severe) and (v) strictures (absent=0; present=1) (17). In addition, presence of esophageal fungal infection was recorded.

Assessment of histological alterations

For the annual histological assessment, four proximal and distal esophageal biopsies were taken using needle forceps. At least 10 5-µm sections of each esophageal biopsy sample were examined, and peak eosinophil count per HPF (Zeiss Axiophot, Oberkochen, Germany, Plan-Neofluar 40, ocular magnification ×10, area of microscopic field 0.3072 mm^2) was obtained. In addition, the severity of esophageal fibrosis was assessed using Van Gieson's staining. As described previously, a subepithelial tissue (~70 to 150 µm immediately beneath the epithelium) was assessed, and fibrosis severity was scored from 0 to 3 (no fibrosis=0; mild fibrosis=1; moderate fibrosis=2; severe fibrosis=3) based on the number of fibroblasts and density of collagen bundles (13,18). Mucosal atrophy—a potential side-effect of STC based on experience with long-term administration of topical corticosteroids for the skin—was defined as a reduction of the thickness of the epithelial layer that the pathologist regularly assesses semiquantitatively in patients under topical corticosteroids. All biopsies were examined by a single EoE pathologist (C.B.).

Definition of clinical, endoscopic, histological, and deep remission

For the purposes of this study, the following definitions were used:

- Long-term clinical remission: lack of any EoE-attributed symptoms (1) (dysphagia (as assessed by SDI), nonswallowing-associated retrosternal pain) under unrestricted nutritional habits for at least 6 months;
- Endoscopic inflammatory remission: complete absence of inflammatory signs, in particular white exudates, furrows, and edema (17);
- Histological inflammatory remission: peak eosinophil count <5 eosinophils/HPF;
- Deep remission: combination of clinical, endoscopic, and histological remission;
- Clinical response: improvement of EoE-attributed symptoms (1);
- Clinical relapse: reappearance of EoE-attributed symptoms (1).

Therapeutic concept involving the long-term use of STCs

Patients with clinically and/or endoscopically active EoE were treated with STCs. Treatment with STC was started after EGD had been performed (time point 0). Specifically, induction treatment with 1.0 mg b.i.d. of fluticasone or budesonide (until clinical response—usually 2 to 4 weeks) was followed by a maintenance therapy with 0.25 mg b.i.d. of the same medication. This therapeutic strategy was developed based on the data from prior studies (13,14). In case of EoE flare-ups, management included reinduction therapy with an increased dose of STC (1.0 mg b.i.d.) for 7–15 days. All patients had scheduled annual follow-up visits, during which symptom as well as endoscopic and histological disease activity was assessed as described above. Annual endoscopy was performed once per year regardless of symptoms. In addition, an endoscopy was performed 3 months after each major therapeutic adjustment because of symptomatic disease. After achieving long-lasting (≥6 months) "deep remission" (as defined on the above), treatment with STCs was discontinued. Patients then attended follow-up visits every 3 months (or more frequently in case of reappearance of EoE-related symptoms).

Statistical analysis

For all statistical analyses, IBM SPSS software (version 22.0.0, 2013 SPSS Science, Chicago, IL) was used. Metric data are presented as medians and interquartile range (IQR) in case these are nonnormal distributed or as means and s.d. in case these are normally distributed. Categorical data are depicted as percentage of the group total. For comparisons between continuous variables, two-sample *t*-test and Mann–Whitney *U*-test were used depending on whether data were normally distributed or not. Comparison between categorical data was performed using χ^2 test. Multivariate logistic regression modeling was performed to identify the prognostic factors for achieving "deep remission" by computing the odds ratio (OR) and 95% confidence intervals (CIs) with "deep remission" as an outcome and age, sex, length of diagnostic delay (log transformed), duration of follow-up (log transformed), total IgE (log transformed), eosinophilic counts at the time of treatment initiation, presence of other atopic disease, and family history of EoE as independent variables. Covariates that were significantly associated with "deep remission" (*P* value of <0.15) in the univariate analysis were incorporated into a multivariable logistic regression model using a stepwise process that involves removal of insignificant covariates and one-by-one addition of remaining covariates while checking for model significance and consistency at each step. For the purposes of this study, a *P* value of <0.05 was considered statistically significant.

RESULTS

Patient characteristics

Of the 1,091 patients currently included in the SEED, 351 patients (32.2%) were included in this study according to the above-mentioned inclusion and exclusion criteria (**Figure 1**). Of the 351 patients, 86 patients were female (24.5%), and mean age was 46.9 (s.d.±15.6) years. Median age of these patients at the time of symptom onset and at the time of EoE diagnosis was 28.5 IQR (17.0–43.0) years and 38.0 (IQR 28.0–50.2) years, respectively. Median diagnostic delay was 5.0 (IQR 2.0–13.7) years. Median follow-up time was 6.0 (IQR 4–9) years. Sixteen patients (4.6%) were diagnosed with EoE at <16 years of age. Only 3 patients were under the age of 12 years at the time of EoE diagnosis and study enrolment (1 patient was 10 years old at EoE diagnosis and study inclusion with a follow-up of 10 years, 1 patient was 5 years old at study enrolment with a follow-up of 5 years, and 1 patient was 9 years old at diagnosis with a follow-up of 9 years). Of the 351 patients, 297 (84.6%) initially responded to induction treatment with STC. **Table 1** shows characteristics of all 351 patients included into the study. Please refer to **Supplementary Table S2** for how gastroesophageal reflux disease was excluded in detail.

Of the 351 patients treated with STCs, 33 (9.4%) achieved deep remission (as defined on the above). Of the 33 patients, 14 patients

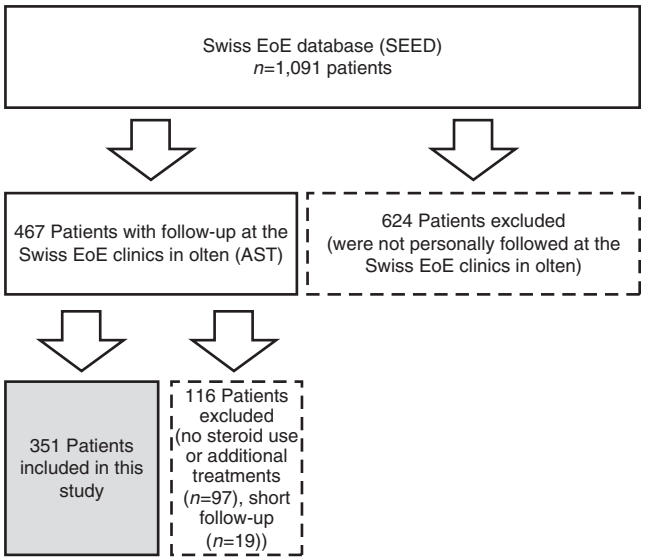

Figure 1. Flowchart regarding inclusion and exclusion of screened patients currently enrolled in the Swiss EoE database. EoE, eosinophilic esophagitis.

were female (42.4%). Mean age of patients was 50.8 (s.d.±14.7) years. All patients were Caucasians. Median age at the time of EoE symptom onset and at the time of EoE diagnosis was 32.6 (IQR 19.1–49.3) years and 42.2 years (IQR 33.2–50.4), respectively. The median diagnostic delay was 5.4 (IQR 1.2–11.4) years. Four patients reported a positive family history of diagnosed EoE (12.1%), whereas another 6 patients had first-line relatives with suspected EoE (18.2%). Twenty-two patients had atopic comorbidities, such as rhinoconjunctivitis, asthma, atopic dermatitis, food allergies, or a combination of these (66.7%). At the baseline visit, all patients were symptomatic (median SDI of 6 (IQR 6–8)) (13): 2 patients reported on dysphagia once per week, whereas 24 reported on dysphagia several times per week, 2 once per day, and 5 several times per day. The following intensity of dysphagia was reported: 8 patients reported on slight retching with delayed passage, 11 patients on short obstruction necessitating intervention, 10 patients on longer lasting period of obstruction, and 4 patients reported on endoscopic bolus removal. Upon EGD, endoscopic disease activity of median 4.0 (IQR 3–4.3) as detected by EREFS (17) was observed. Peak eosinophil count was 50.0 per HPF

Table 1. Patient demographics

	All patients (*n*=351)	Remitters (*n*=33)	Nonremitters (*n*=318)
Gender			
Female	86 (24.5%)	14 (42.4%)	72 (22.6%)
Male	265 (75.5%)	19 (57.6%)	246 (77.4%)
Age in years, mean (s.d.)	46.9 (15.6)	50.8 (14.7)	46.5 (15.7)
Age at EoE onset in years, median (IQR)	28.5 (17.0–43.0)	32.6 (19.1–49.3)	28.0 (17.0–42.0)
Age at EoE diagnosis in years, median (IQR)	38.0 (28–50.2)	42.2 (33.2–50.4)	38.0 (28.0–50.0)
Diagnostic delay in years, median (IQR)	5.0 (2.0–13.7)	5.4 (1.2–11.4)	5.0 (2.0–14.0)
Total IgE (kU/l), median (IQR)	145.0 (53.5–310.5)	87.0 (45.0–310.0)	147.5 (54.0–310.3)
Eosinophilic count (cell/mm^3), mean (s.d.)	308.6 (208.5)	264.2 (140.3)	315.1 (216.2)
Follow-up in years, median (IQR)	6 (4–9)	7 (5–8)	6 (4–9)
Family history of EoE			
None	241 (68.7%)	23 (69.7%)	218 (68.6%)
Proven	37 (10.5%)	4 (12.1%)	33 (10.4%)
Probably	34 (9.7%)	6 (18.2%)	28 (8.8%)
Unknown	39 (11.1%)	0 (0.0%)	39 (12.3%)
Atopic disorders			
None	95 (27.1%)	11 (33.3%)	84 (26.4%)
Yes	247 (70.4%)	22 (66.7%)	225 (70.8%)
Unknown	9 (2.6%)	0 (0.0%)	9 (2.8%)
Endoscopic outcome before treatment initiation			
Active EoE	351 (100.0%)	33 (100.0%)	318 (100.0%)
Inactive EoE	0 (0.0%)	0 (0.0%)	0 (0.0%)
Endoscopic dilation	76 (21.7%)	4 (12.1%)	72 (22.6%)

EoE, eosinophilic esophagitis; IQR, interquartile range.

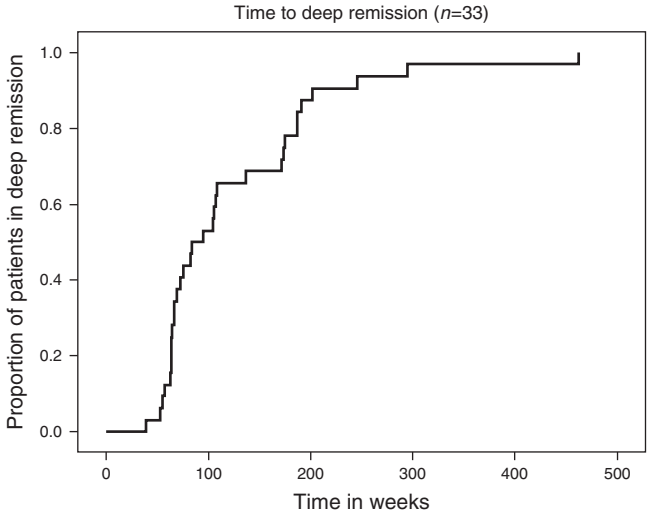

Figure 2. Kaplan–Meier curve showing time to deep remission in weeks.

(IQR 30.0–94.8). Deep remission was achieved after a median of 89.0 weeks (IQR 64.6–173.8). **Figure 2** shows Kaplan–Meier analysis for the time to deep remission (in weeks). **Supplementary Figure S1** in addition depicts an increasing proportion of patients in deep remission over time. STCs were stopped after 104.7 weeks (IQR 65.5–176.6). A cumulative dose of 297.5 mg (IQR 216.0–529.9) of STC was given before treatment was stopped. Only two patients were concomitantly treated with proton-pump inhibitors because of initially partial response despite absence of histological response (before initiation of STC). No mucosal damage, such as epithelial atrophy or dysplasia, was observed upon histological examination. Candida infection as a side effect of STC was reported in 7 patients (21.2%): 2 patients (6.1%) had oropharyngeal infection, and 5 patients (15.2%) had esophageal infection. All cases of esophageal candidiasis were asymptomatic.

Clinical remission

Clinical remission was achieved after a median of 26.0 weeks (IQR 4.3–77.0). In patients undergoing treatment with STC, clinical disease activity as assessed by SDI decreased from 6.6 to 1.9, 0.8, 0.8, and 0.4 after 1 (n=26), 2 (n=23), 3 (n=13), and 4 (n=9) years of STC treatment, respectively.

Endoscopic remission

First follow-up endoscopy was performed after a median of 321 days (IQR 95–433). The median time from initiation of STC treatment to attainment of endoscopic remission was 72.5 weeks (IQR 58.6–104.1). Over the period of EoE treatment, endoscopic disease activity as assessed by the EREFS dropped from 3.8 to 1.3 in the first year, to 1.0 in the second year, 0.4 in the third year, and 0.4 in the fourth year. For details including individual EREFS criteria see **Supplementary Table S3**. Examples of endoscopic disease activity for a subset of patients at baseline and at the time point, when endoscopic remission was detected, are shown in **Figure 3a**.

Histological remission

Histological remission was achieved after a median of 61.4 weeks (IQR 14.3–101.3). Following treatment, peak eosinophil count decreased from 64.5 to 15.3 in the first and second years, 5.0 in the third year, and 0.0 in the fourth year. The fibrosis score slowly decreased from 1.6 to 1.5, 1.1, and 1.0. Patients who achieved deep remission had either mild (n=18) or moderate (n=6) subepithelial fibrosis. Thus, a high proportion of patients (72.7%) showed relevant fibrotic alterations that appear to be partially irreversible. Examples of histological disease activity at baseline and at time point, when histological remission was achieved, are shown in **Figure 3b**. Box-and-whisker plots of time to clinical, endoscopic inflammatory, histological inflammatory, and deep remissions are shown in **Figure 4**.

Remitters vs. nonremitters

The proportion of female patients was higher in the group that achieved deep remission when compared with the group that did not (14/33 (42.4%) vs. 72/318 (22.6%), P=0.012). All 33 patients (100%) responded to induction treatment, whereas 54 of the 318 nonremitters (17.0%) did not show an adequate response to induction treatment with STC. Although 102 endoscopic bolus removals were reported in the nonremission group (102/318, 32.1%), none of the remitters experienced bolus impaction necessitating intervention during the observation period. No differences with regard to the age at the time of disease onset, length of diagnostic delay, family history of EoE, concomitant atopic diseases, and serum IgE levels at the time of treatment initiation between remitters and nonremitters were observed (**Table 1**). Female gender was the only independent prognostic factor for achieving deep remission (OR 2.518, 95% CI 1.203–5.269, P=0.014) (**Supplementary Table S4**).

Disease course after cessation of STCs

A clinical relapse occurred in 26 patients (78.8%) after the cessation of treatment, whereas 1 patient (3.0%) experienced a histological relapse without any clinical symptoms. Median time from treatment cessation to EoE relapse was 22.4 weeks (95% CI 5.1–39.7; **Figure 5**). In 8 of the 26 patients with a clinical relapse (30.8%), EGD was carried out. Histologically active disease was confirmed in 6 of these 8 patients (eosinophilic infiltration on esophageal biopsies of >15 eosinophils per HPF; biopsies were not available for 1 patient; another patient showed only 8 eosinophils per HPF despite experiencing clinical and endoscopic relapse). In all patients with EoE relapse, treatment with STC was reinitiated with a reachievement of disease remission. No severe complications, such as food impaction or strictures, were reported. To evaluate rate of reachievement of deep remission (>6 months)—however—follow-up was too short.

Six remitters (18.2%) did not experience a clinical, endoscopic, and/or histological relapse during a median follow-up of 35.1 weeks (IQR 18.3–44.9) after cessation of STCs. These 6 patients had a mean age of 50.2 years (±14.3), 3 were females (50%). Patients who did not relapse had a shorter diagnostic delay (median 1.1

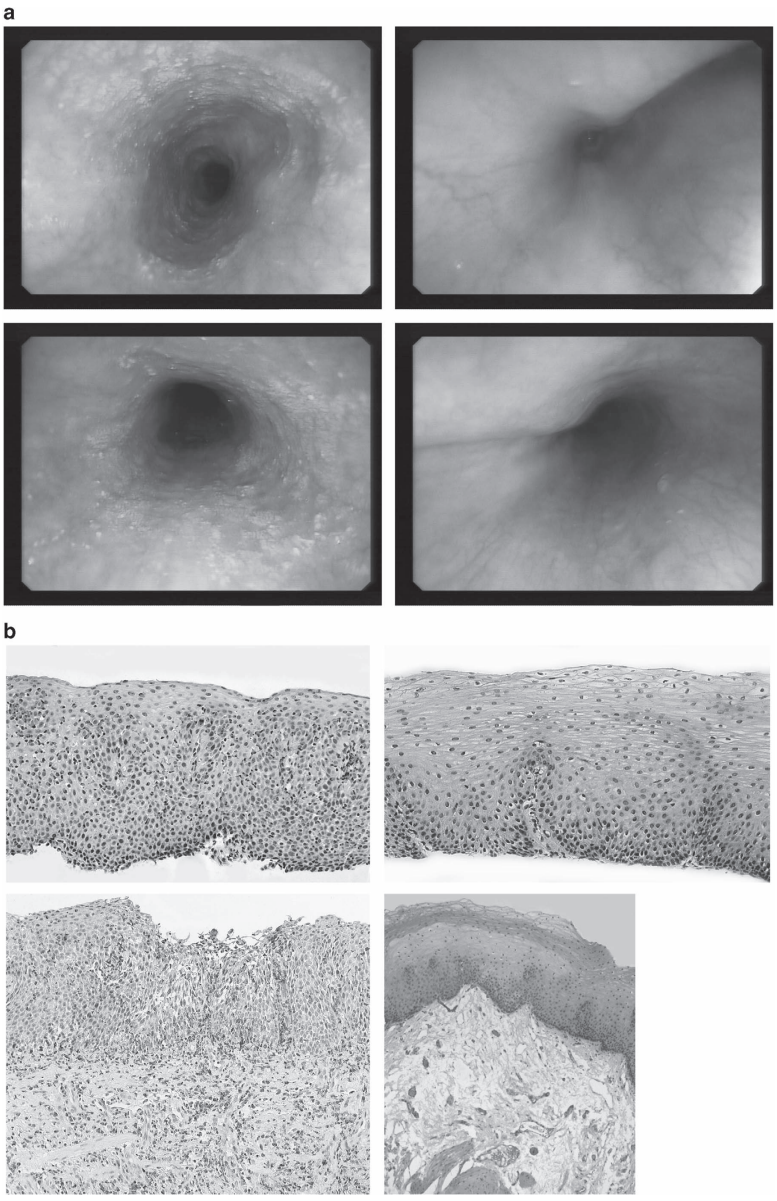

Figure 3. Representative endoscopic and histological findings in patients before treatment and in disease remission. (**a**) Examples of endoscopic disease activity for two patients at baseline (active disease with white exudates and furrows, upper and lower left) and at the time point when endoscopic remission was detected (upper and lower right). (**b**) Examples of histological disease activity for two patients at baseline (active disease, upper and lower left) and at the time point when histological remission was achieved (upper and lower right). Upper left picture shows eosinophil infiltration of the epithelium that is completely resolved in the upper right (under treatment). In the lower left picture, eosinophils infiltrate the epithelium and the subepithelial layer. Both infiltrates (epithelial and subepithelial) completely disappeared after successful treatment (lower right). Hematoxylin and eosin (HE) staining, original magnification ×100. A full color version of this figure is available at the *American College of Gastroenterology* journal online.

year (IQR 1.0–2.7) vs. 7.8 (1.4–13.5), P=0.045) and a trend toward a shorter time until achieving clinical remission (median 4.8 weeks (IQR 2.0–35.0) vs. 26.6 (IQR 7.7–80.9), P=0.093) when compared with those who did relapse. No other differences between patients experiencing a relapse and those who did not experience a relapse were observed when age, time from establishment of diagnosis to beginning of treatment, symptom severity at baseline as assessed by SDI, endoscopic disease severity at baseline as assessed by EREFS, total IgE assessed before treatment initiation, and blood eosinophilia assessed before treatment initiation were examined. Taken together, only 6 out of 351 patients (1.7%) were able to discontinue STCs in the long term.

DISCUSSION

The ability of STCs to bring active EoE in remission is well documented (10,13–15). However, EoE is a chronic inflammatory condition. As such, maintaining remission represents another important milestone of treatment. A therapeutic strategy for long-term management of EoE is urgently needed (4,19), but no such

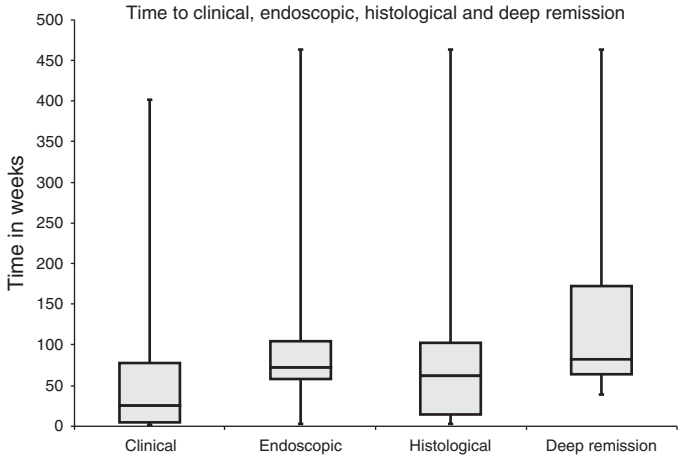

Figure 4. Time to clinical, endoscopic, and histologic remission in weeks.

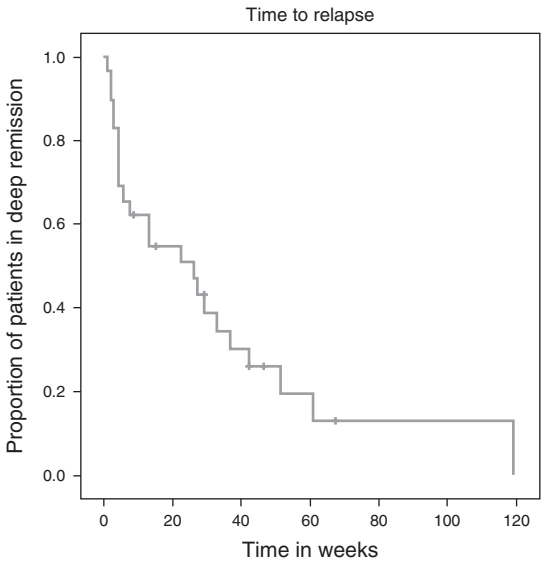

Figure 5. Kaplan–Meier curve showing time to clinical relapse after treatment cessation in weeks.

strategy has been proposed or evaluated (5). Therefore, we empirically developed a therapeutic concept that involves long-term use of STCs. We used this defined strategy prospectively with a goal of achieving a defined outcome, namely combined clinical, endoscopic inflammatory, and histologic inflammatory remission (deep remission). In addition, we report on the disease course after cessation of STC in patients who achieved deep remission.

Patients were treated with STCs for a median of 26.0, 72.5, 61.4, and 89.0 weeks to achieve clinical, endoscopic inflammatory, histological inflammatory, and deep remission, respectively. Although treatment with STC is very effective in inducing and to some extent in maintaining short-term remission in EoE, only a minority of patients treated at the Swiss EoE Clinics achieved a sustained clinical, endoscopic, and histological remission. The longer time until achievement of deep remission compared with our previous trial on topical steroids, where a high histological and clinical response was achieved within 2 weeks, is likely because of the herein used stringent definition of deep remission with the strong requirement of clinical, endoscopic, and histological remission for at least 6 months (13). In that trial—however—we reported on histologic and clinical response not related to the term deep remission (13). Methods used in the two trials were rather different. Besides the long time to deep remission, the remission rates in this study are considerably lower than the remission rates reported in two other maintenance studies (14,15). In a maintenance trial evaluating efficacy of swallowed topical budesonide in adults, Straumann *et al.* (14) reported that 9 out of 14 patients (64.3%) maintain clinical remission after 50 weeks of treatment, whereas complete histological remission was achieved in 5 of 14 patients (35.7%) (14). In the maintenance study evaluating the effectiveness of topical fluticasone in children, Andreae *et al.* (15) showed that histological remission was achieved in 58% of the patients after 24 months of maintenance treatment (a mean follow-up of 20.4 months, a maximum follow-up of 68 months) (15). In contrast to above-mentioned studies, the patient in the current study were followed over a much longer period (median 6 years). Another possible explanation for low remission rates observed in our study might be a rather low dose of STC (0.25 mg b.i.d.) that was used as a maintenance regimen. This low dose was chosen to minimize the risk of topical corticosteroid-induced side effects given the lack of long-term safety data on these compounds administered *per os* (15). However—with regard to the absence of systemic side effects and the low remission rates—a maintenance dose of 0.25 mg b.i.d. may be too low. Our results highlight the need for dose-finding trials aimed at identifying minimal STC dosage that would keep EoE in long-term histologic remission such as the currently ongoing randomized controlled EOS-2 trial (Maintenance of Remission With Budesonide Orodispersible Tables vs. Placebo in Eosinophilic Esophagitis). Despite the low rates of deep remission in our study, increasing proportion of patients with deep remission over time on the same steroid dose

highlights a possibly beneficial effect of long-term topical steroid exposure.

Female gender was an independent prognostic factor for achieving deep remission. Based on the results of recent studies, it appears that EoE presents with comparable clinical symptoms as well as endoscopic and histologic findings in women and men (20), although men report dysphagia and food impaction somewhat more frequently (21). In our study, we report that although women are less likely to be affected by EoE, they seem to have a better response rate to treatment with STC.

Patients with a shorter diagnostic delay were more likely to remain in remission even after cessation with STC. Hence, duration of the prediagnostic period without any treatment seems to influence the response to topical corticosteroid therapy. This finding can be partially explained by the fact that a longer diagnostic delay increases the risk of observing fibrotic EoE-associated features including esophageal rings and strictures upon EGD, and these fibrotic features are more difficult to treat when compared with EoE-associated inflammatory features (7,22). Therefore, early diagnosis and adequate treatment appear to be crucial for management of EoE as it has been shown for other chronic inflammatory gastrointestinal diseases such as inflammatory bowel disease.

Long-term treatment with STC appears to be safe, as no severe adverse events was observed in our cohort over fairly long exposure time. As such, our findings are consistent with those of two previously published maintenance studies (14,15). Given the lack of severe systemic side effects and the fact that application is only topical, there is no need for cortisol testing. Although deep remission patients in this study were treated with a median cumulative dosage of nearly 300 mg of STC for the median of at least 2 years (or longer), no case of mucosal atrophy was observed. In addition, no dysplasia was detected. Therefore, these side effects appear to be less of a concern in daily clinical practice (23,24). In contrast, the observed risk of esophageal candidiasis observed in our study (15%) was markedly higher than that (5.6%) in the cohort studied by Andreae *et al.* (15) This difference might be explained by the longer exposure to the drug in our study. Notably, all patients with esophageal candidiasis in the current study were asymptomatic.

Even after staying in deep remission for the duration of at least 6 months, the majority of patients experienced a relapse after cessation of the treatment with STCs. Although a relapse rate (week 50) in the placebo arm of a double-blind trial with STC was 64.3%, the rate observed following cessation of corticosteroid therapy in this study is higher still (80%) (14). There might be a number of reasons for the observed difference. First, the high rate of relapse in this study is likely to be the result of a long-term follow-up, as at least 4 (of 27) cases of relapse would not have been detected, if the patients were to be followed for 50 weeks. Second, data gathered in the setting of a randomized clinical trial and that obtained in the setting of a routine clinical practice cannot be directly compared. In addition, time from cessation of treatment to relapse was considerably longer in this study (median of 22.4 weeks) when compared with the duration of that period in a previously published maintenance study (median 13.6 weeks) (14). Therefore, patients who attained deep remission seem to stay longer in such a disease state when compared with patients who had just undergone induction treatment. Nonetheless, even those patients who attained such a remission are likely to experience a clinical relapse upon cessation of treatment. This finding highlights the chronic nature of this condition. Only a minority of patients remained symptom-free even after a median follow-up of 35.1 weeks. Particularly those with a short diagnostic delay and a faster clinical response were likely to experience sustained disease remission. Given the small sample size of nonrelapsing patients, more studies are needed to find out which patients might remain in remission despite discontinuation of STCs. Based on our findings, early treatment discontinuation cannot be recommended. However, at least in those patients with a short diagnostic delay and a fast clinical response, discontinuation of STCs may be discussed on an individual basis (including the lack of evidence). Close follow-up is required in case of early treatment discontinuation.

Our study has several strengths as well as limitations. This large cohort of EoE patients (351) was followed at a single center by a single EoE expert (A.S.), and all biopsies taken upon EGD of these patients were interpreted by single reference EoE pathologist (C.B.). The median follow-up of 6 years is the longest that has ever been reported for EoE cohort treated long term with STC. Nevertheless, retrospective study design limits the interpretation of factors influencing response to treatment and disease course after treatment cessation. However, potential sources of bias due to the retrospective nature of this study were minimized by a structured format of medical report summarizing various elements of clinical examinations and EGD, a thorough chart review, and an *a priori* defined therapeutic strategy, with which all patients were treated. The exclusion of those patients with endoscopic dilation within the last year of the observation period may limit the generalizability of our finding as a less severe phenotype may have been selected. However, the number of these patients was very low (n=12). If some of the patients adhered to an elimination diet without reporting during annual visits cannot be ruled out completely. However, follow-up by a single gastroenterologist (A.S.) makes it very unlikely. Another drawback of this retrospective study is the fact that our concept with one endoscopy per year cannot be transmitted 1:1 into clinical reality as the time to first endoscopy—for example—was 321 days (IQR 95–433) rather than exactly 1 year. Broad definition of gastroesophageal reflux disease is another clear limitation; however, such broad definition is more likely used in clinical practice compared with the stringent definitions in clinical trials. Only 2 of the 33 patients with deep remission reported on concomitant proton-pump inhibitor intake.

In summary, only a minority of EoE patients achieved deep remission despite a long-term treatment with STC. After cessation of the medication, the majority of patients experienced a relapse that is consistent with the chronic nature of this condition. However, at least in some patients, STC-free remission was observed. Based on our data, the current understanding of EoE, and the currently available medical treatment modalities, we can neither counsel our patients that EoE is curable nor that a lifetime treatment will be necessary. Therefore, we advocate for a long-term monitoring of EoE patients treated with STCs.

CONFLICT OF INTEREST

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Specific author contributions: Study concept and design: T.G. and A.S.; acquisition of data: T.G., C.B., E.S., A.M.S., L.B., S.R.V. and A.S.; analysis and interpretation of data: T.G., C.B., E.S., A.M.S., L.B., S.R.V. and A.S.; drafting of manuscript: T.G., A.M.S. and A.S.; critical revision of the manuscript for important intellectual content: T.G., C.B., E.S., A.M.S., L.B., S.R.V. and A.S; supervision: T.G. and A.S.

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Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Swallowed topical corticosteroids (STCs) are efficacious in inducing clinical, endoscopic, and histological remission in patients with active eosinophilic esophagitis (EoE). Limited evidence suggests that STCs are also able to maintain remission.
- ✓ It has not been evaluated whether long-lasting remission can be achieved following treatment with STC, and whether maintenance treatment can be stopped once patients have achieved such a remission.

WHAT IS NEW HERE

- ✓ Only a minority of EoE patients (9.4%) achieved clinical, endoscopic, and histological inflammatory remission despite long-term treatment with STCs.
- ✓ Deep remission was achieved after a median of 89.0 weeks of treatment.
- ✓ Female gender was the only prognostic factor for attainment of deep remission.
- ✓ After cessation of the STC the majority of patients (81.8%) experienced a clinical relapse that occurred after a median time of 22.4 weeks.
- ✓ In only 1.7% of EoE patients, STCs were discontinued in the long term.

REFERENCES

1. Liacouras CA, Furuta GT, Hirano I *et al.* Eosinophilic esophagitis: updated consensus recommendations for children and adults. J Allergy Clin Immunol 2011;128:3–20.e6.quiz 1-2.
2. Straumann A, Schoepfer A. Update on basic and clinical aspects of eosinophilic oesophagitis. Gut 2014;63:1355–63.
3. Attwood SE, Smyrk TC, Demeester TR *et al.* Esophageal eosinophilia with dysphagia. A distinct clinicopathologic syndrome. Dig Dis Sci 1993;38:109–16.
4. Straumann A, Spichtin HP, Grize L *et al.* Natural history of primary eosinophilic esophagitis: a follow-up of 30 adult patients for up to 11.5 years. Gastroenterology 2003;125:1660–9.
5. Furuta GT, Liacouras CA, Collins MH *et al.* Eosinophilic esophagitis in children and adults: a systematic review and consensus recommendations for diagnosis and treatment. Gastroenterology 2007;133:1342–63.
6. Alexander JA, Katzka DA. Eosinophilic esophagitis: it is here to stay. Clin Gastroenterol Hepatol 2011;9:370–2.
7. Schoepfer AM, Safroneeva E, Bussmann C *et al.* Delay in diagnosis of eosinophilic esophagitis increases risk for stricture formation in a time-dependent manner. Gastroenterology 2013;145:1230–6.e1-2.
8. Desai TK, Stecevic V, Chang CH *et al.* Association of eosinophilic inflammation with esophageal food impaction in adults. Gastrointest Endosc 2005;61:795–801.
9. Konikoff MR, Noel RJ, Blanchard C *et al.* A randomized, double-blind, placebo-controlled trial of fluticasone propionate for pediatric eosinophilic esophagitis. Gastroenterology 2006;131:1381–91.
10. Schaefer ET, Fitzgerald JF, Molleston JP *et al.* Comparison of oral prednisone and topical fluticasone in the treatment of eosinophilic esophagitis: a randomized trial in children. Clin Gastroenterol Hepatol 2008;6:165–73.
11. Dohil R, Newbury R, Fox L *et al.* Oral viscous budesonide is effective in children with eosinophilic esophagitis in a randomized, placebo-controlled trial. Gastroenterology 2010;139:418–29.
12. Peterson KA, Thomas KL, Hilden K *et al.* Comparison of esomeprazole to aerosolized, swallowed fluticasone for eosinophilic esophagitis. Dig Dis Sci 2010;55:1313–9.
13. Straumann A, Conus S, Degen L *et al.* Budesonide is effective in adolescent and adult patients with active eosinophilic esophagitis. Gastroenterology 2010;139:1526–37.37.e1.
14. Straumann A, Conus S, Degen L *et al.* Long-term budesonide maintenance treatment is partially effective for patients with eosinophilic esophagitis. Clin Gastroenterol Hepatol 2011;9:400–9.e1.
15. Andreae DA, Hanna MG, Magid MS *et al.* Swallowed fluticasone propionate is an effective long-term maintenance therapy for children with eosinophilic esophagitis. Am J Gastroenterol 2016;111:1187–97.
16. Dellon ES, Irani AM, Hill MR *et al.* Development and field testing of a novel patient-reported outcome measure of dysphagia in patients with eosinophilic esophagitis. Aliment Pharmacol Ther 2013;38:634–42.
17. Hirano I, Moy N, Heckman MG *et al.* Endoscopic assessment of the oesophageal features of eosinophilic oesophagitis: validation of a novel classification and grading system. Gut 2013;62:489–95.
18. Aceves SS, Newbury RO, Dohil R *et al.* Esophageal remodeling in pediatric eosinophilic esophagitis. J Allergy Clin Immunol 2007;119:206–12.
19. Arora AS, Yamazaki K. Eosinophilic esophagitis: asthma of the esophagus? Clin Gastroenterol Hepatol 2004;2:523–30.
20. Moawad FJ, Dellon ES, Achem SR *et al.* Effects of race and sex on features of eosinophilic esophagitis. Clin Gastroenterol Hepatol 2016;14:23–30.
21. Sperry SL, Woosley JT, Shaheen NJ *et al.* Influence of race and gender on the presentation of eosinophilic esophagitis. Am J Gastroenterol 2012;107:215–21.
22. Dellon ES, Kim HP, Sperry SL *et al.* A phenotypic analysis shows that eosinophilic esophagitis is a progressive fibrostenotic disease. Gastrointest Endosc 2014;79:577–85.e4.
23. Brazzini B, Pimpinelli N. New and established topical corticosteroids in dermatology: clinical pharmacology and therapeutic use. Am J Clin Dermatol 2002;3:47–58.
24. Lebrun-Vignes B, Chosidow O. Topical corticosteroids. Ann Dermatol Venereol 2004;131(1 Pt 1):39–48.