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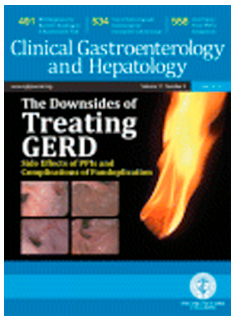

Maintenance Treatment of Eosinophilic Esophagitis With Swallowed Topical Steroids Alters Disease Course Over A 5-Year Follow-Up Period in Adult Patients

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MAINTENANCE TREATMENT OF EOSINOPHILIC ESOPHAGITIS WITH SWALLOWED TOPICAL STEROIDS ALTERS DISEASE COURSE OVER A 5-YEAR FOLLOW-UP PERIOD IN ADULT PATIENTS

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CONFLICT OF INTEREST

Guarantors of the article: Thomas Greuter, MD and Alex Straumann, MD

Specific author contributions: Study concept and design: TG, AMS, and AS; acquisition of data: TG, ES, AMS and AS; follow-up visits and endoscopic evaluation: AS; histological examination: CB; analysis and interpretation of data: TG, ES, AMS, and AS; drafting of manuscript: TG, AMS and AS; critical revision of the manuscript for important intellectual content: ES, CB, LB, SRV, and DAK; supervision: TG and AS.

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ABSTRACT

Background & Aims: Although swallowed topical corticosteroids (STCs) are effective in inducing remission of active eosinophilic esophagitis (EoE), there are few data on maintenance of long-term remission. We evaluated the long-term effectiveness of STC therapy for adults with EoE.

Methods: We performed a retrospective study using the Swiss EoE database. We analyzed data on 229 patients with EoE treated with STCs (175 male; mean age at diagnosis, 39±15 years; median time until diagnosis, 6 years) from 2000 through 2014. Patients were followed for a median 5 years (interquartile range [IQR], 3–7 years). We collected data from 819 follow-up visits on clinical, endoscopic and histological disease characteristics. The primary endpoint was proportions of clinical, endoscopic, and histological remission in all patients and groups, based on the status and duration of STC treatment.

Results: Patients were taking STCs at 336 of the follow-up visits (41.0% of visits). The median duration of STC use before a follow-up visit was 347 days (IQR, 90–750 days) corresponding to 677 doses (IQR, 280–1413 doses) of 0.25 mg each. At the visits, higher proportions of patients who were still taking STCs were in clinical remission (31.0%) compared to patients not taking STCs (4.5%) (*P*<.001), as well as endoscopic remission (48.8% vs 17.8%; *P*<.001), histologic remission (44.8% vs 10.1%; *P*<.001), and complete remission (16.1% vs 1.3%; *P*<.001). Higher cumulative doses of STCs and longer durations of treatment were associated with higher proportions of clinical and complete remission. No dysplasia or mucosal atrophy was detected. Esophageal candidiasis was observed at 2.7% of visits in patients taking STCs.

Conclusion: In an analysis of data from the Swiss EoE database, we found maintenance therapy with STCs to achieve complete remission at 16.1% of follow-up visits, which was higher than in patients receiving no treatment (1.3%). Given the good safety profile of low-dose STC, we advocate for a prolonged treatment. Dose-finding trials are needed to achieve higher remission rates.

KEY WORDS: esophagus; long-term outcome; predictive factors; response to therapy

INTRODUCTION

Short-term treatment with swallowed topical corticosteroids (STC) has proven efficacy in inducing clinical, endoscopic, and histological remission in adult patients with eosinophilic esophagitis (EoE) and has been recently approved by the European Medicines Agency.[1-3] In contrast, data on long-term maintenance treatment are sparse. To date, one randomized-controlled trial that included 28 adult patients has been conducted evaluating 1-year remission rates only.[4]

Beyond the time frame of one year, the impact of STC treatment on disease course in adults with EoE has not been rigorously studied. In the observational study by Kuchen *et al.* long-term use of STC was associated with a reduced risk of long-lasting food impactions.[5] Using data from the same population, our group has shown that deep remission, which we defined as clinical, endoscopic, and histological remission for at least 6 months, was achieved by 9% of the patients.[6] Almost all of these patients experienced symptomatic relapse after discontinuation of STC. Over 90% needed long-term therapeutic management and displayed some degree of disease activity when treated with a low dose of 0.5mg STC per day.[6] Nevertheless, we showed that patients benefit from ongoing STC treatment with slightly increasing deep remission rates and a reduced risk of long-lasting food impactions over time.[5,6] In spite of these recent findings, the general course of EoE under long-term STC management has not been well explored and a comprehensive picture of STC maintenance treatment is still missing. It has yet to be determined whether patients clearly benefit from a long-term treatment with regards to the rates of clinical, endoscopic, and histological remission.

Potential side-effects of corticosteroids are a matter of concern for patients undergoing long-term treatment. Short-term STC trials have shown that *Candida albicans* infections occur with a frequency of up to 22%, but the risk of infections associated with lower maintenance doses has not been rigorously assessed.[1,2,4,6] In addition, it is well established that topical application of corticosteroids to the skin results in epithelial atrophy and disruption of epithelial integrity.[7,8] Since the skin and the esophagus share many similarities regarding their histo-morphological structure, this potential side-effect requires careful exploration. The data on safety of STC use in 33 patients analyzed in our previous study are of some value, but larger studies are needed to assess these safety concerns.[6]

The purposes of this study were elucidation of the effectiveness as well as assessment of the safety profile of long-term use of STC in adult EoE patients.

METHODS

Study design

In this single-center observational study, we retrospectively evaluated a cohort of EoE patients, who received an induction treatment with STC 1.0mg b.i.d. (2-4 weeks until clinical response), followed by an infinite maintenance treatment of 0.25mg b.i.d. according to our previously published therapeutic concept (**Supplementary Methods**).[6] This concept has been rigorously applied to all our patients since 2007. Disease activity was assessed clinically, endoscopically and histologically on annual basis regardless of presence or absence of EoE symptoms. All patients were seen by a single EoE expert (AS). Patients had 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

Set up in 1989, SEED is a nation-wide database of patients with confirmed EoE diagnosis established in accordance with defined criteria.[9] At the time of study analysis, the SEED contained data on 783 EoE patients. Inclusion criteria for the SEED have been published elsewhere.[6] For the purpose of this study, the following inclusion criteria were applied: i) patients underwent baseline examination and ≥ 1 follow-up examinations (≥ 1 year) with standardized assessment of symptoms, endoscopic, and histological findings; ii) patients showed clinical response to STC induction treatment within 2-4 weeks; iii) patients were treated with a maintenance regimen (0.25mg b.i.d.) after induction of clinical response; and iv) the documentation related to the effectiveness of this treatment regimen was available. Patients, who followed food elimination diet were excluded from analysis. 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 a EoE Endoscopic Reference Score (EREFS) grading and classification system based on the available endoscopic pictures.[10] This EREFS-based score ranges from zero to eight by assigning the values of 1 and 2 to mild and severe exudates; 1, 2 and 3 to mild, moderate and severe rings; 1 to edema; 1 to furrows; and 1 to strictures. Absence of these features was scored with 0. For endoscopic pictures taken before 2012, images were re-assessed in retrospect to assign an EREFS score.

Definitions used in this study

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

- Clinical remission: Absence of any EoE-attributed symptoms,[9] in particular dysphagia, retrosternal pain and heart burn, in patients with unrestricted nutritional habits;
- Endoscopic remission: No endoscopic signs of inflammation detectable, in particular white exudates, furrows and edema,[10] mild rings may be present;
- Histological remission: Peak eosinophil count < 15 eos/ hpf;
- Complete remission: Combination of clinical, endoscopic, and histological remission.
- Number of days under STC: consecutive days of STC treatment at the time of follow-up visit
- Cumulative doses of STC: multiples of 0.25mg STC that were cumulatively taken until the time of follow-up visit

Study Endpoints

As primary endpoint, we determined the proportions of clinical, endoscopic, and histological remission in all patients and in patient groups stratified based on the status and duration of STC treatment. As secondary endpoints, we examined: i) factors associated with attainment of remission, ii) factors associated with presence of symptoms despite endoscopic and histological remission, iii) the relationship between clinical, endoscopic, histological, and laboratory findings, and iv) STC side-effects.

Statistical Analysis

For all statistical analyses, IBM SPSS software (version 22.0.0, 2013 SPSS Science, Chicago, IL) was used. Briefly, categorical data was compared using χ^2 test; differences in quantitative data distributions were assessed using the unpaired Student's t-test and the Mann-Whitney-Wilcoxon test; multivariate logistic regression was performed by taking into account all covariates with a univariate p-value of < 0.1 (**Supplementary Methods**). For the purpose of this study, a p-value of < 0.05 was considered statistically significant.

RESULTS

Patient and disease characteristics at baseline and follow-up visits

Of a total of 783 eligible patients enrolled in the Swiss EoE database, 229 were included in this analysis (175 males, mean age at diagnosis 39±15 years, median diagnostic delay 6 years [IQR 2-13], **Table 1**). **Figure 1** depicts the flow-chart for patients` selection in this study as well as missing data. In total, 819 follow-up visits (median of 3 visits [IQR 2-5], median follow-up time of 5 years [IQR 3-7]) were analyzed (**Table 1**). Median time between follow-up visits was 11 months (IQR 3-20).

Remission during follow-up visits

The remission proportions for all visits are shown in **Figure 2**. At the time of the 62 follow-up visits, when patients were in complete remission (1.2 years [IQR 0.5-3.7] after enrolment), higher use of STC (90.0% of visits vs. 37.9% of visits, p<0.001), longer duration of STC treatment (403 [IQR 98-695] vs. 0 days [IQR 0-192], p<0.001), and higher number of STC doses of 0.25mg (863 [IQR 361-1301] vs. 0 [IQR 0-430], p<0.001) were observed compared to the 757 visits, when patients were not in such remission (1.9 years [IQR 0.7-4.4] after enrolment). No differences with regards to the age at disease onset, diagnostic delay, gender or atopic history of patients were seen when visits in complete remission were compared with visits without such remission. Treatment with STC and a negative family history of EoE were independent positive predictors for presence of complete remission at the time of follow-up (OR 16.98 [6.69-43.09] and OR 4.02 [1.41-11.47], **Table 2**).

Treatment with swallowed topical corticosteroids

During 336/819 visits (41.0%, 2.1 years [IQR 0.8-4.5] after enrolment), patients were undergoing treatment with STC, while during 468 visits (57.1%, 1.7 years [IQR 0.7-4.1] after enrolment), patients were without any treatment. For 15 visits, intake of STC could not be clearly verified (1.8%). When we compared visits with STC treatment and those without STC, no differences with regards to gender and disease characteristics, such as age at diagnosis, disease onset, and diagnostic delay, were observed. At visits under STC treatment, median peak eosinophil counts (5 vs. 40/hpf, p<0.001) and EREFS-based score (2.0 vs. 4.0, p<0.001) were lower than at visits without such treatment. At visits, when patients were treated with STC, clinical (31.0 vs. 4.5%, p<0.001), endoscopic (48.8 vs. 17.8%, p<0.001), histological (44.8 vs. 10.1%, p<0.001), and complete remission (16.1 vs. 1.3%, p<0.001) was more likely to be observed compared to visits, when patients were not under STC treatment (**Figure 2**). If

patients had received endoscopic dilation within one year before the visit, the difference regarding clinical remission between STC-treated and non-treated patients was less pronounced (**Supplementary Figure 1**). When analyzing remission proportions per patient after three follow-up visits (corresponding to the median number of follow-up visits), these proportions were higher for patients treated with STC compared to those without treatment: 32.2 vs. 6.6% (clinical remission, p<0.001), 45.8 vs. 23.7% (endoscopic remission, p=0.007), 49.2 vs. 9.2% (histological remission, p<0.001), and 16.9 vs. 2.6% (complete remission, p=0.004, **Table 3**).

At visits under STC, median reported treatment duration was 347 days of past STC use (IQR 90-750) corresponding to 677 doses (IQR 280-1413) of 0.25mg of STC. During 144 visits, patients reported STC treatment duration of one year or longer (median 785 days, IQR 510-1112, range 370-3780), while during 192 visits, we observed treatment duration of shorter than 1 year (median 90 days, IQR 16-194, range 7-364). When examining the number of STC doses (in multiples of 0.25mg doses of budesonide or fluticasone, classified into 4 groups) and the duration of STC treatment (in days, classified into 4 groups) leading to follow-up visit, both of these were associated with higher clinical and complete remission proportions observed at a given visit (**Figure 3**).

Predictive factors for achieving clinical, endoscopic, histological and complete remission in patients treated with swallowed topical corticosteroids

Using first a univariate model for prediction of clinical remission at the time of follow-up visit, we identified age at EoE onset (OR 1.02 [1.00-1.03]), longer STC intake (OR 2.68 [1.67-4.32]), blood eosinophilia (0.37 [0.11-1.19]) and PPI treatment (OR 0.50 [0.27-0.96]) as predictive factors with a p-value of <0.10 **(Supplementary Table 1).** Indeed, at 62/104 of visits with clinical remission (59.6%) patients reported long-term use of STC (≥ 1 year), while this proportion was significantly lower for visits with no such remission (82/231, 35.5%, p<0.001). However, in a multivariate model only age at disease onset and absence of PPI treatment remained significant; Patients without clinical remission despite steroid treatment were more likely to be treated with PPI. For prediction of endoscopic and histological remission, see **Supplementary Table 2 and 3**. Longer STC intake and a negative family history of EoE were independent positive predictive factors for achieving complete remission at a given visit (2.02 [1.12-3.64] and OR 5.06 [1.53-16.75], respectively, **Table 2**). Indeed, during visits of patients in complete remission, higher proportions of long-term STC use and

lower proportions of positive family history of EoE were observed when compared to visits of patients without such remission (57.4% vs. 40.1%, p=0.02, and 5.7 vs. 32.3%, p=0.004). These factors remained significant in a multivariate analysis (**Table 2**). When cumulative doses of STC – instead of treatment duration – were assessed as co-variable, higher doses (>600 x 0.25mg) compared to lower STC doses (≤600 x 0.25mg) were an independent predictor for achieving complete remission in both the univariate and multivariate regression model (corrected for positive family history) to a similar extent of what was seen for treatment duration (OR 1.89, p=0.046, and OR 1.90, p=0.049, respectively).

Per-patient data for maintenance of histological remission

To further investigate the effect of low-dose STC on maintenance of disease remission, we analyzed all patients who achieved histological remission at one of their follow-up visits and computed Kaplan Meier curves for time to histological relapse. Patients were stratified into STC treatment (defined as under STC treatment at at least one of the following two visits) vs. no such STC treatment. 74 patients were identified with achievement of histological remission in the follow-up (who were under STC treatment at the time of histological remission) and at least 1 second follow-up endoscopy. Time to histological relapse was significantly longer in the STC group (1.5 [0.44-2.55] vs. 0.7 years [0.33-1.11], log-rank p=0.047, **Supplementary Figure 2**).

Clinical activity despite endoscopic and histological remission

Over the course of 120 visits (120/182, 65.9%, 1.8 years [IQR 0.9-3.5] after enrolment), patients presented with EoE-attributed symptoms despite being in endoscopic and histological disease remission. When compared to visits of patients in complete remission (n=62), visits of patients in endoscopic and histologic but ongoing disease activity (n=120) were more likely to be associated with less frequent treatment with STC at the time of follow-up visit (62.3 vs. 90%, p<0.001), shorter STC treatment duration (18 vs. 403 days, p<0.001) corresponding to a lower number of cumulative STC doses (120 vs. 863, multiples of 0.25mg, p<0.001), higher number of strictures (36.5 vs. 6.8%, p<0.001) and endoscopic fibrotic features (59.1 vs. 29.1%, p<0.001). No differences between the two groups were observed, when gender, atopic history, age at disease onset, and diagnostic delay were examined. In a multivariate analysis, lack of STC treatment (OR 7.63 [1.98-29.42]) and presence of strictures (OR 12.03 [2.26-63.96]) were the main independent prognostic factors

for persisting symptoms despite endoscopic and histological remission during a visit (**Supplementary Table 4**).

Safety concerns associated with swallowed topical corticosteroid use

In biopsy samples obtained during 310 visits, for which past STC use was reported (2.0 years [IQR 0.7-4.5] after enrolment, 26 visits without histological evaluation), no dysplasia and no mucosal atrophy were detected. Histologically and endoscopically confirmed, symptomatic esophageal candidiasis warranting antifungal treatment was found at 9/336 of visits under STC (2.7%).

DISCUSSION

Swallowed topical corticosteroids have been demonstrated to reliably bring active EoE into clinical, endoscopic and histological remission. In contrast, data on long-term management and maintenance of remission are sparse. In this study, we comprehensively analyzed our Swiss EoE cohort in order to obtain an overview of effectiveness and safety of medical maintenance treatment in adult EoE patients.

The most important finding of our analysis is that STC are more effective than no treatment in long-term EoE management. When follow-up visits were performed with ongoing medication use the proportion of remission was 16.1%, whereas at visits during periods without STC ("drug-holidays") this proportion was significantly lower (1.3%). This is a strong argument that EoE patients – after a successful induction therapy – should be considered for maintenance treatment. However, despite this optimistic data, patients frequently reported periods without STC use; in fact STC were taken at only 40% of the visits. Adherence to treatment seems to be an important issue. However, the periods of medication abstinence are comparable with other long-term treatments of chronic gastrointestinal diseases, such as inflammatory bowel disease.[11] With a significant benefit from STC over no treatment, but high proportions of patient-initiated medication cessation, we advocate for a close monitoring of STC-treated patients including visits more often than once a year. Upcoming tools for assessment of histological disease activity such as the cytosponge or esophageal string test might facilitate more comprehensive follow-up in the future.[12,13]

Maintenance remission proportions are much lower than those seen after short-term induction treatment, leaving considerable room for improvement. Complete remission was only seen in 7.6% of 819 analyzed visits. The high proportions of ongoing disease activity, whether clinical, endoscopic or histological, shed light on the chronic nature of EoE and question the STC doses currently used in long-term management.[14] Dose-finding trials with higher STC doses are definitely needed. Compared to the conducted maintenance trial – with remission proportions of 64% (clinical) and 35% (histological) in the adult population – clinical and complete remission proportions at visits with patient STC treatment (31 and 16.1%) were considerably lower in our study.[4] This might be due to the following reasons: i) recall period for symptoms was longer in our study compared to the 1-week recall in the maintenance trial, ii) patients in the maintenance trial had closer follow-up visits (every 3

months) and more frequent assessment of their symptoms (every 1 week), while our study represents real-life conditions, and iii) follow-up was considerably longer in our study. Compared to our previously published deep remission study, proportions of complete remission (= clinical, endoscopic and histological remission) were however higher (16.1% at visits under STC treatment vs. 9.4%), which is most probably due to the less stringent histologic definition than that used to define deep remission.[6]

Despite these low maintenance remission proportions, longer duration of steroid treatment and higher cumulative doses were associated with higher proportions of complete remission compared to shorter treatment duration and lower doses. In fact, treatment for more than one year was an independent positive predictor for achievement of complete remission. When four classes of cumulative STC doses and treatment duration were compared, significant associations between complete remission, and higher doses and longer duration of STC were found. This is consistent with our previous data showing increasing, albeit modestly, rates of deep remission over time and lower rates of bolus impactions with higher frequency of STC intake.[5,6] However, in the latter study we reported on adherence rather than exact duration and cumulative doses of treatment. Indeed, we were able to show associations between treatment duration and doses, and treatment outcome in a follow-up maintenance study for the first time. Interestingly, this association was only seen between treatment duration and complete remission, and partially clinical remission, but not with endoscopic and histological remission. It has yet to be determined if this is the result of STC dose accumulation or more due to partial disease regression and therefore more treatable disease over time. Either or, treating physicians and some patients might anticipate a longer course of low-dose STC maintenance to be effective. It remains unclear, why a small subset of patients achieved endoscopic and histological disease remission without STC treatment. We cannot rule out that some patients adhered to self-initiated dietary restrictions or under-reported STC use. Based on our previous study, ongoing disease remission without any treatment is very unlikely.[6]

It is well established that long-term use of corticosteroids poses risk for side-effects. For instance the administration of topical corticosteroids to the skin results in epithelial atrophy and disruption of epithelial integrity.[7,8] Since the skin and the esophagus share many similarities regarding their histo-morphological structure, this potential side-effect requires careful exploration, because it may further facilitate antigen and fungal entry. In EoE, STC in

the applied dose of 0.25mg b.i.d. appear to be safe and well-tolerated. Esophageal candida infections occur in a negligible proportion. In addition, our finding that no single case of mucosal atrophy, dysplasia was detected is reassuring. A dose of 0.25mg b.i.d. – even in the long-term – is not harmful to the esophageal epithelial layer. This is consistent with our previous study,[6] but the biopsy number examined for the purposes of this study is considerably higher.

Since PPI responsiveness was an exclusion criteria, our study does not account for PPI-responsive EoE (PPI-REE). However, this reflected the state of the art, when the treatment concept was launched. PPI-REE and PPI as treatment for EoE have been included in the guidelines only very recently.[15] A clear limitation of this study is that the applied dose of STC was most probably too low to achieve adequate drug levels in the esophageal mucosa. Thus, the high proportion of refractory cases most likely resulted from inadequate dosing. This is supported by our finding that higher cumulative doses of STC are associated with a higher probability of disease remission. This apparently suboptimal dose was chosen as side-effects were an important concern when determining the therapeutic dose to be used. Furthermore, 0.25mg b.i.d had shown a benefit over placebo in the only maintenance trial conducted in adults so far.[4] Since our concept with low-dose STC is rigorously applied in our EoE cohort, a comparison to patients with higher maintenance doses was not possible, but would be of particular interest in the future. Further limitations were the use of a non-validated symptom score, the reliance on patient-reported STC intake, and the considerable amount of missing data, which could have biased our results. Since almost all patients were treated with fluticasone, stratification by STC compound was not feasible.

In conclusion, EoE patients benefit from a long-term treatment with STC. This regimen has an excellent safety profile and the potential to alter the course of the disease. Of note, our data show that longer treatment and higher cumulative doses of STC are associated with higher proportions of disease remission. Based on this data, we advocate for indefinite long-term EoE treatment with STC. Given that patients rarely achieved complete remission with the STC doses used for the purposes of their clinical care, prospective long-term trials comparing different doses are needed in the future.

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LEGENDS

Table 1: Patient, disease characteristics at baseline, during follow-up.

Table 2: Logistic regression model for predicting complete remission in all patients and STC-treated patients.

Table 3: Patient follow-up and per-patient remission data after the median number of follow-up visits (=3 visits). *for 3 patients STC treatment could not be verified.

Figure 1: Flow-chart of included, excluded patients

Figure 2: Clinical, endoscopic, histological, and complete remission at the time of all follow-up visits, and stratified into visits, during which STC treatment or no treatment was undertaken. Darker shade represents remission.

Figure 3: Clinical and complete remission in patients stratified into groups based on STC treatment duration (in days [d]) and cumulative number of doses (in multiples of 0.25mg).

Patient demographics and disease characteristics at baseline	**Frequency (n=229 patients)**
Males	175 (76.4%)
Age at EoE diagnosis (mean, SD) (years)	39, 15
Diagnostic delay (median, IQR, range) (years)	6, 2 - 13, 0 - 40
Family history for EoE - proven - suspected	 27 (11.8%) 16 (7.0%)
Symptoms leading to EoE diagnosis - Dysphagia - Chest pain - Reflux - Abdominal pain	 216 (94.3%) 81 (35.4%) 16 (7.0%) 4 (1.7%)
Concomitant atopic diseases (ever reported)	144 (62.9%)
Concomitant gastroesophageal reflux disease at baseline	27 (11.8 %)
Endoscopic disease activity	
Strictures	81 (35.4 %)
Corrugated rings	145 (63.3 %)
White exudates	115 (50.2 %)
Edema	164 (71.6%)
Furrows	146 (63.8 %)
Histological disease activity	
Peak eosinophil count per hpf, median (IQR)	37, 22-65
Active histological disease	217 (94.8%)
Subepithelial fibrosis - Mild to moderate - Severe	 67 (29.3 %) 15 (6.6 %)
Disease characteristics during follow-up	**Frequency (n=819 visits)**
Follow-up, median (IQR) (years)	5 (3-7)
Number of follow-up visits per patient, median (IQR)	3 (2-5)
Endoscopic dilation at the time of follow-up	125 (15.3%)
Prior endoscopic dilation (within 1 year) at the time of follow-up	47 (5.7%)
Clinical characteristics	
Presence of EoE-related symptoms	684 (83.5%)
PPI treatment	163 (19.9%)
STC treatment during visits	336 (41.0%)
Endoscopic findings	
Endoscopic inflammatory signs	539 (65.8%)
Endoscopic fibrotic features	392 (47.9%)
Strictures	245 (29.9%)
EREFS-based score, median (IQR)	3 (1-4)
Histologic findings	
Peak eosinophil count per hpf, median (IQR)	25 (1.0-65.0)
Peak count of ≥ 15 eosinophils/hpf	539 (65.8%)
Subepithelial fibrosis - mild to moderate	Assessed during 277 visits 200 (72.2%)

- severe	58 (20.9%)
Dysplasia	0 (0.0%)

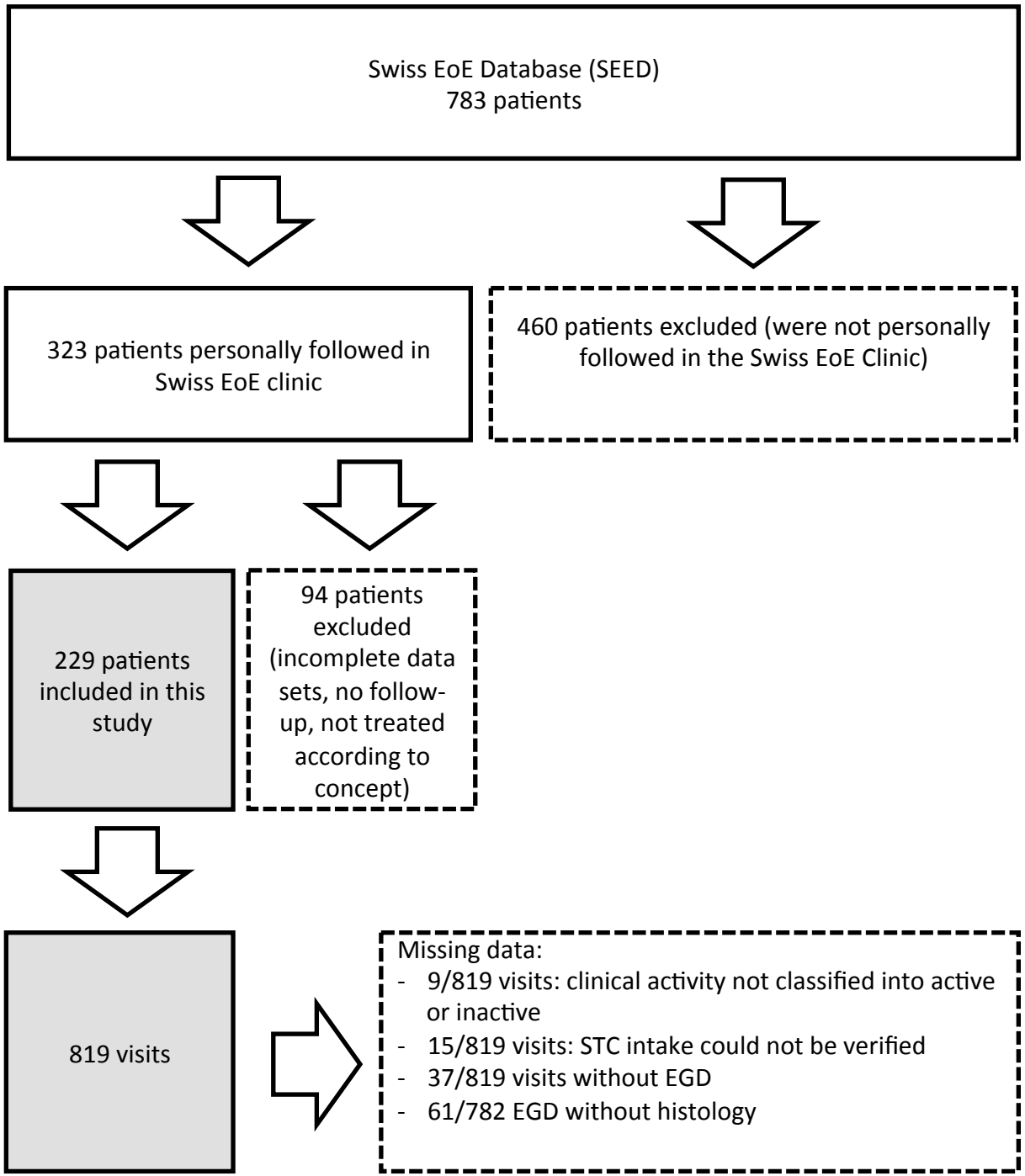
Table 1: Patient and disease characteristics at baseline and during follow-up. Abbreviations: EREFS, endoscopic reference score; hpf, high-power field; IQR, interquartile range; PPI, proton-pump inhibitor; SD, standard deviation

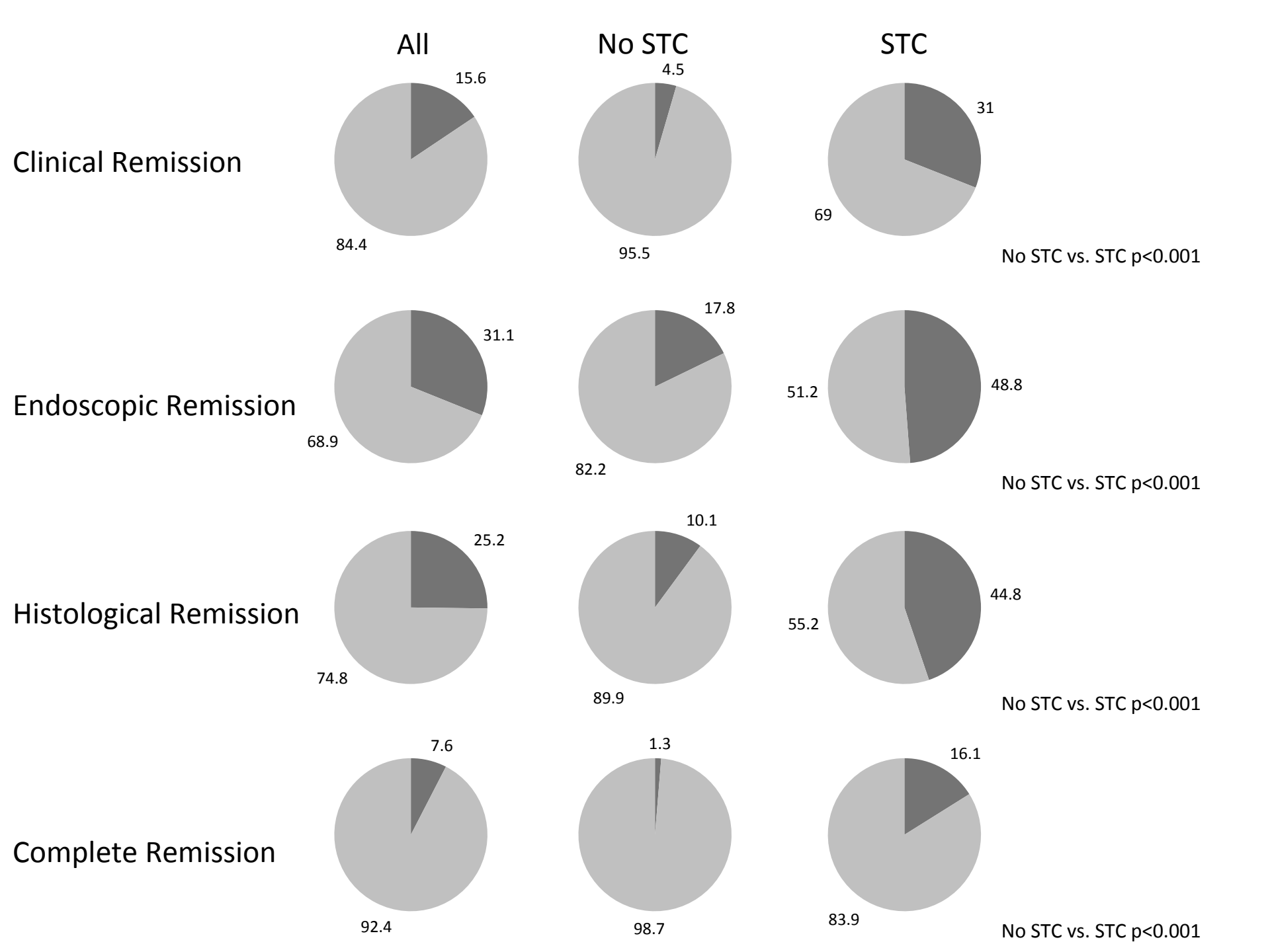
Prediction of complete remission in all patients				
	Univariate model		Multivariate model	
Candidate risk factor	OR, 95% CI	P-value	OR, 95% CI	P-Value
Gender				
- Male	ref.			
- Female	0.870 (0.469-1.614)	0.660		
Age at onset	1.002 (0.989-1.016)	0.746		
Diagnostic delay	0.989 (0.957-1.023)	0.528		
Blood eosinophilia				
- Absent	ref.			
- Present	0.497 (0.129-1.913)	0.309		
Elevated IgE levels				
- Absent	ref.			
- Present	1.020 (0.291-3.575)	0.975		
Therapy with STC				
- No	ref.		ref.	
- Yes	14.745 (6.262-34.717)	**<0.001**	16.983 (6.694-43.090)	**<0.001**
PPI therapy				
- No	ref.			
- Yes	0.954 (0.495-1.838)	0.887		
Family history				
- Positive	ref.		ref.	
- Negative	4.060 (1.451-11.365)	**0.008**	4.021 (1.410-11.466)	**0.009**
Allergic conditions				
- No	ref.			
- Yes	0.762 (0.438-1.324)	0.335		
Prediction of complete remission in STC treated patients				
	Univariate model		Multivariate model	
Candidate risk factor	OR, 95% CI	P-value	OR, 95% CI	P-Value
Gender				
- Male	ref.			
- Female	1.080 (0.545-2.139)	0.825		
Age at onset	1.008 (0.989-1.028)	0.412		
Diagnostic delay	0.997 (0.964-1.032)	0.866		
Blood eosinophilia				
- Absent	ref.			
- Present	0.918 (0.221-3.818)	0.907		
Elevated IgE levels				
- Absent	ref.			
- Present	0.764 (0.199-2.940)	0.696		
Long duration of STC use				
- No (<1 year)	ref.		ref.	
- Yes (≥1 year)	2.016 (1.118-3.635)	**0.020**	1.976 (1.082-3.610)	**0.027**
PPI therapy				
- No	ref.			
- Yes	0.867 (0.411-1.828)	0.708		
Family history				
- Positive	ref.		ref.	
- Negative	5.055 (1.525-16.753)	**0.008**	5.103 (1.534-16.976)	**0.008**
Allergic conditions				
- No	ref.			
- Yes	0.805 (0.432-1.500)	0.495		

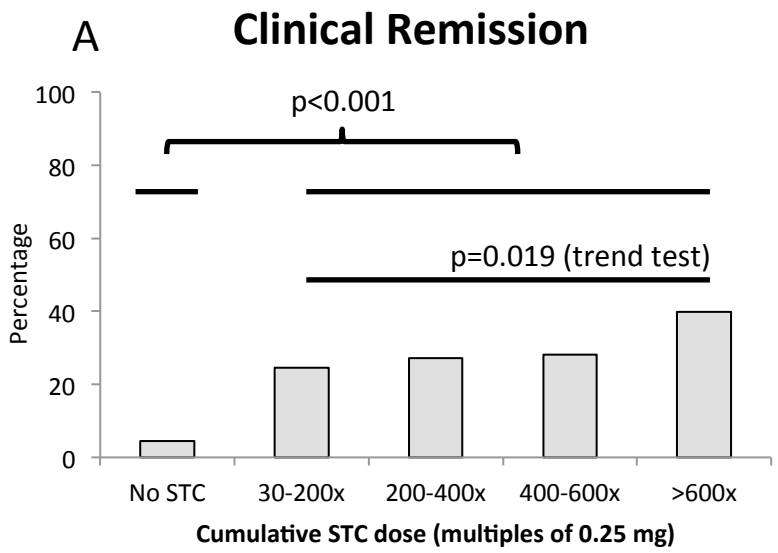
Table 2: Logistic regression model for predicting complete remission in all patients and STC-treated patients at the time of follow-up. Abbreviations: PPI, proton-pump inhibitor; STC, swallowed topical corticosteroids.

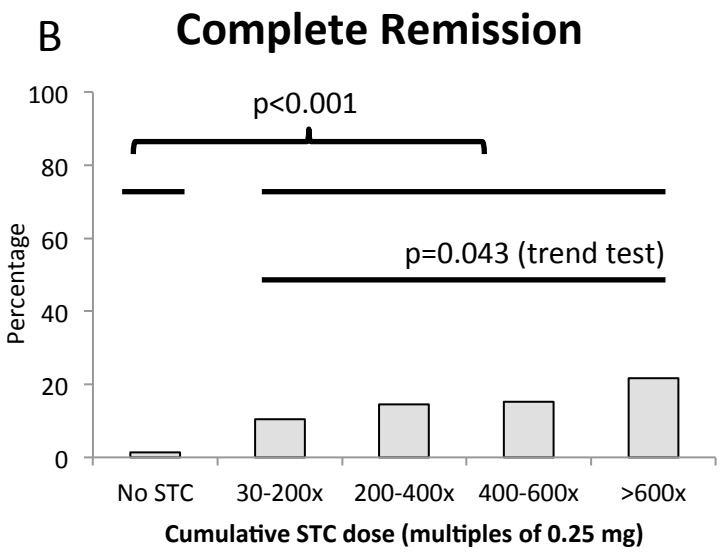
Follow-up of patients	**Frequency (n=229)**
Follow-up visits - 1 follow-up visit - 2 follow-up visits - 3 follow-up visits - 4 follow-up visits - 5 follow-up visits - >5 follow-up visits	 34 (14.8%) 57 (24.9%) 39 (17.0%) 39 (17.0%) 28 (12.2%) 32 (14.0%)
Remission rates for patients at Visit 3	**n=138**
Patients in clinical remission	24 (17.4%)
Patients in endoscopic remission	45 (32.6%)
Patients in histological remission	36 (26.1%)
Patients in complete remission	12 (8.7%)
Remission rates for patients without STC treatment at Visit 3	**n=76**
Patients in clinical remission	5 (6.6%)
Patients in endoscopic remission	18 (23.7%)
Patients in histological remission	7 (9.2%)
Patients in complete remission	2 (2.6%)
Remission rates for patients under treatment with STC at Visit 3	**n=59***
Patients in clinical remission	19 (32.2%)
Patients in endoscopic remission	27 (45.8%)
Patients in histological remission	29 (49.2%)
Patients in complete remission	10 (16.9%)

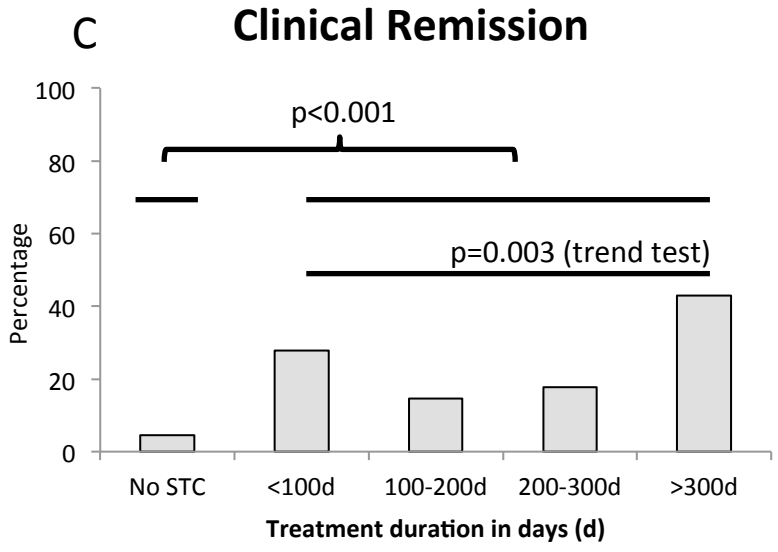
Table 3: Patient follow-up and per-patient remission data after the median number of follow-up visits (=3 follow-up visits). *For 3 patients STC treatment at visit 3 could not be verified. STC, swallowed topical corticosteroids

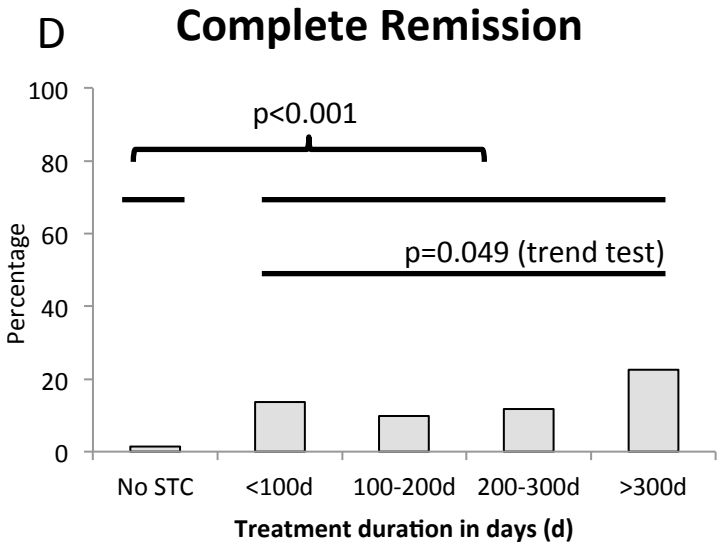

Swiss EoE Database (SEED)
783 patients
323 patients personally followed in Swiss EoE clinic
460 patients excluded (were not personally followed in the Swiss EoE Clinic)
229 patients included in this study
94 patients excluded (incomplete data sets, no follow-up, not treated according to concept)
819 visits
Missing data:
- 9/819 visits: clinical activity not classified into active or inactive
- 15/819 visits: STC intake could not be verified
- 37/819 visits without EGD
- 61/782 EGD without histology


All
No STC
STC
Clinical Remission
15.6
84.4
4.5
95.5
31
69
No STC vs. STC p<0.001
Endoscopic Remission
31.1
68.9
17.8
82.2
51.2
48.8
No STC vs. STC p<0.001
Histological Remission
25.2
74.8
10.1
89.9
44.8
55.2
No STC vs. STC p<0.001
Complete Remission
7.6
92.4
1.3
98.7
16.1
83.9
No STC vs. STC p<0.001


A
Clinical Remission
100
80
60
40
20
0
Percentage
p<0.001
p=0.019 (trend test)
No STC
30-200x
200-400x
400-600x
>600x
Cumulative STC dose (multiples of 0.25 mg)


B
Complete Remission
100
80
60
40
20
0
Percentage
p<0.001
p=0.043 (trend test)
No STC
30-200x
200-400x
400-600x
>600x
Cumulative STC dose (multiples of 0.25 mg)


C
Clinical Remission
100
80
60
40
20
0
Percentage
p<0.001
p=0.003 (trend test)
No STC
<100d
100-200d
200-300d
>300d
Treatment duration in days (d)


D
Complete Remission
100
80
60
40
20
0
Percentage
p<0.001
p=0.049 (trend test)
No STC
<100d
100-200d
200-300d
>300d
Treatment duration in days (d)

SUPPLEMENTARY TABLES

	Univariate model		Multivariate model	
Candidate risk factor	OR, 95% CI	P-value	OR, 95% CI	P-Value
Gender				
- Male	ref.			
- Female	1.074 (0.617-1.870)	0.800		
Age at onset	1.018 (1.002-1.034	**0.026**	1.054 (1.012-1.098)	**0.012**
Diagnostic delay	0.981 (0.953-1.009)	0.185		
Blood eosinophilia				
- Absent	ref.		ref	
- Present	0.366 (0.113-1.190)	**0.095**	0.671 (0.186-2.423)	0.543
Elevated IgE levels				
- Absent	ref.			
- Present	1.306 (0.471-3.622)	0.608		
Long duration of STC use				
- No (<1 year)	ref.		ref.	
- Yes (≥1 year)	2.682 (1.667-4.315)	**<0.001**	0.733 (0.213-2.519)	0.622
PPI therapy				
- No	ref.		ref.	
- Yes	0.503 (0.265-0.955)	**0.036**	0.083 (0.009-0.755)	**0.027**
Family history				
- Negative	ref.			
- Positive	0.594 (0.316-1.115)	0.105		
Prior dilation (within 1 year)				
- No	ref.			
- Yes	1.283 (0.520-3.161)	0.589		
Allergic conditions				
- No	ref.			
- Yes	1.061 (0.640-1.759)	0.818		

Supplementary Table 1: Logistic regression model for predicting clinical remission in patients treated with swallowed topical steroids at the time of follow-up visit. PPI, proton-pump inhibitor; STC, swallowed topical corticosteroids.

	Univariate model		Multivariate model	
Candidate risk factor	OR, 95% CI	P-value	OR, 95% CI	P-Value
Gender				
- Male	ref.			
- Female	0.727 (0.432-1.222)	0.229		
Age at onset	1.007 (0.992-1.022)	0.351		
Diagnostic delay	1.003 (0.978-1.029)	0.812		
Blood eosinophilia				
- Absent	ref.		ref.	
- Present	0.219 (0.080-0.604)	**0.003**	0.246 (0.087-0.696)	**0.008**
Elevated IgE levels				
- Absent	ref.			
- Present	0.731 (0.305-1.755)	0.484		
Long duration of STC use				
- No (<1 year)	ref.			
- Yes (≥1 year)	1.172 (0.758-1.814)	0.475		
PPI therapy				
- No	ref.			
- Yes	1.178 (0.693-2.004)	0.545		
Family history				
- Negative	ref.			
- Positive	0.651 (0.375-1.132)	0.129		
Allergic conditions				
- No	ref.		ref.	
- Yes	0.570 (0.353-0.918)	**0.021**	0.547 (0.218-1.375)	0.200

Supplementary Table 2: Logistic regression model for predicting endoscopic remission in patients treated with swallowed topical steroids at the time of follow-up visit. PPI, proton-pump inhibitor; STC, swallowed topical corticosteroids.

	Univariate model		Multivariate model	
Candidate risk factor	OR, 95% CI	P-value	OR, 95% CI	P-Value
Gender				
- Male	ref.			
- Female	0.836 (0.488-1.433)	0.515		
Age at onset	0.997 (0.982-1.012)	0.683		
Diagnostic delay	1.009 (0.983-1.035)	0.518		
Blood eosinophilia				
- Absent	ref.		ref	
- Present	0.266 (0.096-0.734)	**0.011**	0.265 (0.085-0.828)	**0.022**
Elevated IgE levels				
- Absent	ref.			
- Present	0.559 (0.230-1.358)	0.199		
Long duration of STC use				
- No (<1 year)	ref.			
- Yes (≥1 year)	0.859 (0.547-1.348)	0.509		
PPI therapy				
- No	ref.			
- Yes	1.365 (0.789-1.362)	0.266		
Family history				
- Negative	ref.		ref.	
- Positive	0.540 (0.302-0.965)	**0.038**	0.328 (0.083-1.293)	0.111
Allergic conditions				
- No	ref.		ref.	
- Yes	0.534 (0.327-0.870)	**0.012**	1.510 (0.552-4.129)	0.422

Supplementary Table 3: Logistic regression model for predicting histological remission in patients treated with swallowed topical steroids at the time of follow-up visit. PPI, proton-pump inhibitor; STC, swallowed topical corticosteroids.

	Univariate model		Multivariate model	
Candidate risk factor	OR, 95% CI	P-value	OR, 95% CI	P-Value
Gender				
- Male	ref.			
- Female	1.043 (0.503-2.166)	0.909		
Age at onset	0.997 (0.978-1.017)	0.787		
Diagnostic delay	1.023 (0.985-1.063)	0.230		
Blood eosinophilia				
- Absent	ref.			
- Present	0.513 (0.100-2.633)	0.424		
Elevated IgE levels				
- Absent	ref.			
- Present	0.615 (0.146-2.602)	0.509		
Strictures				
- Absent	ref.		ref.	
- Present	7.911 (2.677-23.380)	**<0.001**	12.033 (2.264-63.955)	**0.004**
Endoscopic fibrosis				
- Absent	ref.		ref.	
- Present	3.521 (1.713-7.237)	**0.001**	1.437 (0.542-3.810)	0.466
Therapy with STC				
- Yes	ref.		ref.	
- No	5.451 (2.162-13.740)	**<0.001**	7.631 (1.980-29.418)	**0.003**
PPI therapy				
- No	ref.			
- Yes	1.314 (0.614-2.814)	0.482		
Family history				
- Negative	ref.		ref.	
- Positive	3.128 (1.021-9.579)	**0.046**	7.817 (1.580-38.673)	**0.012**
Prior dilation (within 1 year)				
- No	ref.			
- Yes	1.188 (0.296-4.770)	0.808		
Allergic conditions				
- No	ref.			
- Yes	0.819 (0.427-1.571)	0.548		

Supplementary Table 4: Logistic regression model for predicting ongoing clinical activity despite endoscopic and histological remission. PPI, proton-pump inhibitor; STC, swallowed topical corticosteroids.

SUPPLEMENTARY METHODS

Inclusion criteria for the Swiss EoE database

Briefly, patients with active disease based on presence of typical EoE-associated symptoms, endoscopic features, and esophageal eosinophilia, defined as a peak count of ≥ 15 eosinophils (eos) per high power field (hpf) were included. Patients were excluded, if other diseases associated with esophageal eosinophilia were present. Underlying gastro-esophageal reflux disease (GERD) was excluded based on any one of the following: lack of typical symptoms (heartburn and acid regurgitation), absence of hiatal hernia and signs of reflux esophagitis, non-response to PPI trial, or a positive 24-hour pH monitoring study (optional). Patients with persistent dysphagia and eosinophil inflammation, whose symptoms and signs of GERD resolved following PPI treatment, were considered to have EoE and concomitant GERD and were not excluded from the SEED.

Therapeutic concept of maintenance treatment with STC

Based on our clinical experience and the findings of a maintenance treatment study, the following long-term concept was developed, and patients of the Swiss EoE Clinic have been treated according to the following principles:

- Clinically and histologically active EoE was considered to be a clear indication for treatment;
- STC (fluticasone or budesonide) was used as first line treatment for induction and maintenance of EoE remission;
- The following treatment schedule was used: Induction treatment with fluticasone or budesonide at the dose of 1.0 mg b.i.d. (2.0 mg per day) was administered until clinical response (defined as 50-70% reduction from baseline symptoms on a 10-point scale [non-validated symptom assessment]) was achieved (usually following 2-4 weeks of treatment); a maintenance treatment with fluticasone or budesonide at the dose of 0.25 mg b.i.d. (=0.5 mg per day) followed;
- Clinical, endoscopic and histological examination was performed once a year. During each visit, the patients were asked about the presence and the severity of EoE- and GERD-related symptoms, their eating habits, and their treatment regimen (cumulative dose and duration of treatment). Endoscopic findings were described in detail in a written report and documented with pictures. Four biopsies were taken from each the proximal and

distal esophagus (total of eight biopsies). As previously described, 'distal' was defined as the section of the esophagus 5 cm above the gastro-esophageal junction, whereas 'proximal' was defined as the section spanning the top half of the esophagus. All biopsies were examined by an EoE reference pathologist (CB) or pathologist under his supervision. For the histologic examination, 4-µm sections were cut from the paraffin blocks. They were stained with Hematoxylin & Eosin and van Gieson stain. In all cases, a standard pathology microscope (Zeiss Axiophot, Plan-Neofluar 40, ocular magnification 10 ×, area of microscopic field 0.3072 mm^2) was used. At least 10 sections of each esophageal biopsy sample were examined, and the peak eosinophil count was reported;

- As long as a disease activity was documented clinically, endoscopically, and/or histologically, the treatment with STC was continued for another year;
- In case of deteriorating clinical, endoscopic, and/or histological disease activity, patients underwent a second induction treatment for a period of 2-4 weeks.

Type of STC and drug formulations

At our Swiss EoE Clinic, two STC formulations are prescribed for long-term maintenance treatment: 1) fluticasone powder from a metered-dose inhaler for asthma (one blister containing 0.25mg of fluticasone applied orally and swallowed twice a day); and 2) budesonide respules dissolved in syrup with a sucrose concentration of 64% (1ml syrup = 0.03mg budesonide, swallowed at a dose of 0.25mg b.i.d.). For practical reasons – syrup needs to be individually prepared by a pharmacy, while fluticasone inhalers are readily available – fluticasone is the treatment of choice for most of the patients.

Additional statistical analyses

For all statistical analyses, IBM SPSS software (version 22.0.0, 2013 SPSS Science, Chicago, IL) was used. Data distribution was analyzed using Normal-QQ-Plots. Results of quantitative data are presented as either mean ± standard deviation (SD, for normally distributed data) or median plus interquartile range (IQR) in case of non-normal distribution. Categorical data are summarized as the percentage of the group total. Differences in quantitative data distributions between two groups were assessed using the unpaired Student's t-test (for continuous variables with normal distribution) and the Mann-Whitney-Wilcoxon test (for non-parametric data or continuous, but non-normally distributed data). Comparison between categorical data was performed using χ^2 test. Multivariate logistic regression was

performed by first taking into account all covariates with univariate p-value of < 0.1, removing insignificant covariates, and then adding remaining covariates one by one, checking the model for significance and consistency. For prediction of remission (clinical, endoscopic, histological and complete remission as dependent variables), the following factors were analyzed: gender (coded as male or female), age at disease onset, diagnostic delay, blood eosinophilia (coded as present [>350 eos/µL] or absent [≤350 eos/µL]), elevated IgE levels (coded as present [>100 kU/L] or absent [≤100 kU/L]), treatment with STC (coded as yes or no) or duration of STC treatment (coded as long [≥1 year] or short [<1 year]), treatment with PPI (coded as yes or no), family history of EoE (coded as positive or negative), and presence of allergic conditions (coded as yes or no). To evaluate the factors, that might be associated with ongoing clinical activity despite endoscopic, histological remission (ongoing symptoms as dependent variable), we additionally analyzed the following co-variables: strictures (coded as present or absent), endoscopic fibrotic signs (coded as present or absent), and prior endoscopic dilation (within one year before the examined visit, coded as yes or no). The linear-by-linear association test for trend was used to assess the association between duration of STC treatment (< 100 days, 100 - < 200 days, 200 - 300 days, and > 300 days) and frequency of disease remission, and to the assess association between cumulative doses of steroids (< 200, 200 - < 400, 400 - 600, > 600 $\times$ 0.25 mg) and disease remission. For the purpose of this study, a p-value of < 0.05 was considered statistically significant.

Editor`s notes: MAINTENANCE TREATMENT OF EOSINOPHILIC ESOPHAGITIS WITH SWALLOWED TOPICAL STEROIDS ALTERS DISEASE COURSE OVER A 5-YEAR FOLLOW-UP PERIOD IN ADULT PATIENTS

Background: Data on long-term management of eosinophilic esophagitis (EoE) with swallowed topical corticosteroids are limited.

Findings: Swallowed topical corticosteroids are more effective than no treatment in the long-term management of EoE. Maintenance remission proportions are lower than those seen after short-term induction treatment. Nonetheless, longer duration of steroid treatment and higher cumulative doses are associated with higher proportions of complete remission compared to shorter duration and lower doses. An applied dose of 0.25mg b.i.d is safe and well-tolerated.

Implications for patient care: Indefinite long-term EoE treatment with swallowed topical corticosteroids should be considered. Given that patients rarely achieve complete remission with the steroid doses used for the purposes of their clinical care, prospective long-term trials comparing different doses are needed in the future.