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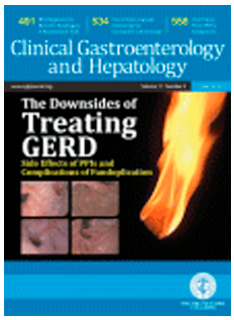

EFFeCtiveness AND SAFETY OF High versus low dose swallowed TopICal STEROIDs for Maintenance Treatment of Eosinophilic Esophagitis: A Multi-Center Observational Study

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EFFECTIVENESS AND SAFETY OF HIGH VERSUS LOW DOSE SWALLOWED TOPICAL STEROIDS FOR MAINTENANCE TREATMENT OF EOSINOPHILIC ESOPHAGITIS: A MULTI-CENTER OBSERVATIONAL STUDY

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CONFLICT OF INTEREST

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Specific author contributions: Study concept and design: TG, AS, and DAK; acquisition of data: AR, HAS, DS, GM, TM, ESD, IH, JA, MC, ES, CB, LB, PS, AMS; analysis and interpretation of data: TG, AG, AS, and DAK; drafting of manuscript: TG and AG; critical revision of the manuscript for important intellectual content: AR, HAS, DS, GM, TM, ESD, IH, JA, MC, ES, CB, LB, PS, AMS, AS, and DAK; supervision: TG, AS, and DAK.

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ABSTRACT

Background & Aims: Data evaluating efficacy of different doses of swallowed topical corticosteroids (STC) in the long-term management of eosinophilic esophagitis (EoE) are lacking. We assessed long-term effectiveness and safety of different STC doses for adults with EoE after achievement of histological remission.

Methods: We performed a retrospective multicenter study at five EoE referral centers (US and Switzerland). We analyzed data on 82 patients with EoE in histological remission and ongoing STC treatment with therapeutic adherence of ≥75% (58 males; mean age at diagnosis, 37.2±14.4 years). Patients were followed for a median of 2.2 years (interquartile range [IQR], 1.0-3.8 years). We collected data from 217 follow-up endoscopy visits. The primary endpoint was time to histological relapse.

Results: Histological relapse occurred in 67% of patients. Relapse rates were comparable in patients taking low dose (≤0.5 mg per day, n=58) and high dose STC (>0.5mg per day, n=24) with 72 vs. 54% (ns). However, histological relapse occurred significantly earlier with low dose STC (1.0 vs. 1.8 years, p=0.030). There was no difference regarding rates of and time to stricture formation for low vs. high dose STC. Esophageal candidiasis was observed in 6% of patients (5% for low dose, 8% for high dose, ns). No dysplasia or mucosal atrophy was detected.

Conclusion: Histological relapse frequently occurs in EoE despite ongoing STC treatment regardless of STC doses. However, relapse develops later in patients on high dose STC without an increase in side-effects. Doses higher than 0.5mg/day may be considered for EoE maintenance treatment, but advantage over lower doses appears to be small.

KEY WORDS: esophagus; long-term outcome; response to therapy; swallowed topical corticosteroids; relapse

Word count: 249 words (limit 250 words)

INTRODUCTION

Eosinophilic esophagitis (EoE) is a chronic inflammatory disorder of the esophagus that is defined clinically by symptoms of esophageal dysfunction (mainly dysphagia in adults) and histologically by an eosinophil-predominant infiltration of the esophageal squamous epithelium.[1] Swallowed topical corticosteroids (STCs) are considered the mainstay in EoE treatment by many EoE specialists.[2,3] STCs have proven efficacy in inducing clinical, endoscopic and histological remission in patients with active EoE.[4-6] Fluticasone and budesonide appear to be equally and highly effective when given by an optimized delivery system.[7-8]

In contrast to the plethora of available studies on short-term induction STC treatment, data on STCs' efficacy in the long-term are limited. STCs show a benefit over placebo, but remission rates are considerably lower in the long- compared to the short-term.[9-11] Cessation of treatment and dose reduction have been associated with disease relapse.[12,13] Most long-term data is from the Swiss EoE cohort, where patients were treated with 0.25mg STC b.i.d., which is a safe, well-tolerated and partly efficacious treatment regimen.[10] This dose maintains complete or partial histological remission in only 50% of patients after 1 year.[9] Thus, 0.25mg STC b.i.d. may be overall inadequate and higher doses could result in higher success rates. Indeed, longer treatment and higher cumulative doses have been associated with fewer EoE complications and higher rates of remission in retrospective studies.[10,11] As of yet, there is no study fully published that evaluated and compared efficacy and safety of different STC doses in the long-term management of EoE.

With this multicenter study in adults with EoE, we compared the effectiveness of two STC maintenance doses with regard to their ability to maintain histological remission and prevent development of disease complications, examined whether we could observe a STC dose threshold to maintain remission, and compared the safety of two doses of maintenance treatment.

METHODS

Study design

We performed a multicenter retrospective observational study comparing low dose and high dose STC long-term regimens in adult EoE patients who achieved histological disease remission and continued STC treatment. All patients provided written informed consent (general informed consent) prior to inclusion in the study. The study was approved by the local ethics committee of each of the participating centers.

Subjects and data collection

Patients were recruited at five EoE referral centers in the US and Switzerland (**Supplementary Methods**). The following criteria were applied for patients to be included into the study: 1) Diagnosis of EoE according to international guidelines;[1,14] 2) achievement of histological remission defined as a peak eosinophil (eos) count of <15eos per high power field (hpf) on treatment with STC (=baseline remission visit);[15-17] 3) ongoing STC treatment after achievement of histological remission; 4) availability of at least one follow-up endoscopy visit with esophageal biopsies to evaluate maintenance of histological remission; and 5) detailed documentation of the treatment regimen. Patients were excluded from the study when the following conditions were satisfied: 1) EoE that previously responded to PPI treatment; 2) treatment with investigational drugs; 3) treatment with systemic steroids or higher than standardly used STC doses ($\geq$2500µg per day) in the follow-up period;[18] 4) documented low adherence to STC of <75% based on patient self-reporting; 5) treatment with dietary restrictions during the follow-up period; and 6) age <16years at baseline remission visit. Presence of concomitant gastro-esophageal reflux disease (GERD) was not an exclusion criterion. PPI co-treatment was allowed if EoE was not considered PPI-responsive or if PPIs were used for GERD symptoms. For details on data collection, see **Supplementary Methods.**

Outcomes and definitions

Primary outcome of the study was time to histological relapse. Secondary outcomes were time to endoscopic bolus removal, time to stricture formation (new stricture and worsening stricture requiring endoscopic dilation) and development of local side effects of STC, particularly esophageal candidiasis and mucosal atrophy (**Supplementary Methods**).[19]

Endoscopic disease activity was graded using the EoE Endoscopic Reference Score (EREFS) grading and classification system as previously described.[20] The following definitions were used: Histological remission: <15eos/hpf; Deep histological remission: 0-1eos/hpf; Histological relapse: ≥15eos/hpf.

Steroid maintenance doses

STC maintenance doses were classified into two groups according to the lowest prescribed dose during the follow-up: patients receiving doses of ≤0.5mg per day (low dose STC) and patients being maintained on a dose of >0.5mg per day (high dose STC).

Statistical analyses

For statistical analyses, statistical package program STATA (version 16, College Station, Texas, USA) and GraphPad Prism software (version 8.3.0, La Jolla, CA) were used (**Supplementary Methods**).

RESULTS

Patient and disease characteristics

A total of 82 patients (58 males, 71%) were included in this study (**Figure 1**). Mean age at diagnosis was 37.2±14.4 years with a median of 7.3y of symptoms (IQR 3.0-17.8) prior to diagnosis. Mean age at first visit with disease remission under STC (baseline remission visit) was 38.2±14.5y. Patients were mostly of Caucasian descent (94%, 1 patient of Asian descent, 4 patients without data on ethnic background). Family history for EoE was reported in 14 patients (17%), while 52 patients had atopic comorbidities (63%). Twenty-three patients had concomitant GERD (28%). Fifty-one patients had no response to PPI (62%), while 27 never received PPI treatment (33%), and 3 reported improved GERD symptoms (acid regurgitation, heart burn) without EoE response (4%, 1 patient without information about PPI treatment). A total of 217 follow-up endoscopy visits with biopsies were available for analysis (median number of follow-up visits 2, IQR 1-3). Median follow-up time was 2.2y (IQR 1.0-3.8), with a median average time between follow-up visits of 11.4 months (IQR 6.8-14.0). For details, see **Table 1**.

Per inclusion criteria, all patients achieved histological remission under treatment with STC (22 budesonide, 60 fluticasone). Most of the patients were treated with STC twice daily at the time of remission (76 patients, 93%) with a median dose of 0.5mg per day (IQR 500-2000ug, baseline remission visit), see **Table 1**. Fifty-four patients received low dose steroid treatment at baseline remission visit (66%), while 28 patients were on high dose STC (34%). Co-treatment with PPI was reported in 33 patients (40%). Median peak eosinophil count was 0 (IQR 0-3, range 0-12) at the start of the maintenance period (baseline remission visit). Fifty-four patients (66%) were in deep histological remission. EREFS score at baseline was 1 (IQR 0-2). Despite histological remission, 45 patients reported ongoing EoE-specific symptoms such as dysphagia and bolus impactions (55%); 9 patients were symptomatic because of stricturing disease, 11 patients underwent endoscopic dilation due to ongoing symptoms. The number of patients with ongoing clinical activity was not lower in patients with deep histological remission (59%, ns).

After achievement of histological remission, 58 patients continued STC treatment with doses of 0.5mg per day or lower (71%, low dose group), while 24 patients received STC at doses

higher than 0.5mg per day (29%, high dose group). Dose groups varied by practice site: Swiss EoE Clinic and Mount Sinai 100% low dose, Northwestern University 67% low dose, Mayo Clinic 89% high dose, and University of North Carolina 68% high dose. For details, see **Supplementary Table 1**. The two STC dose groups were comparable for peak eosinophil counts, endoscopic activity, presence of strictures and PPI co-treatment at baseline remission visit (**Table 2**). However, initial diagnostic delay was longer in the high dose group (median 11.0 vs. 5.6 years, p=0.003); and patients in the high dose group more frequently reported a positive family history for EoE (33% vs. 10%, p=0.012). In addition, those in the high dose group were less likely to be in deep histological remission at baseline (50% vs. 72%), although this difference did not reach statistical significance (p=0.051). While longer diagnostic delay might be a reason why patients received higher doses, lower numbers of deep remission rates were not, as only few patients were switched from a low to high dose regimen at the time of remission (baseline remission visit) or vice versa. Median number of follow-up visit was similar and total follow-up time did not differ significantly between the two groups. Furthermore, time to first follow-up visit and average time between follow-up visits were not different between the two groups (**Table 2**).

Histological relapse rates

Histological relapse was detected in 55 patients (67%). Median time to histological relapse was 1.1y Stratification by STC doses revealed histological relapse in 42 patients within the low dose group (72%) compared to 13 patients within the high dose group (54%, ns). Degree of relapse was considerable with median peak eosinophil counts of 47.5eos/hpf (IQR 25.0-74.3) and concomitant endoscopic activity with median EREFS score of 3 (IQR 1-4). Histological relapse occurred significantly earlier in patients treated with low dose STC (1.0 vs 1.8y, p=0.030 **Figure 2a**). Dose reduction was more often undertaken in the high dose group (21/24 vs. 8/58, p<0.001). Reduction of the STC dose that brought patients into histological remission did not *per se* result in a worse outcome suggesting that maintaining a dose above a certain cut-off (0.5mg) is more important than the actual dose level (**Supplementary Figure 1a**). Of note, once daily dosing was associated with a longer time to histological relapse (**Supplementary Figure 1b**). Although once daily dosing was the preferred strategy in the high

dose group (18/24 vs. 11/58 in the low dose group), subgroup analyses revealed that once daily dosing is indeed associated with a better outcome even in the low dose group (**Supplementary Figure 1c**).

Bolus impaction and stricture formation

Bolus impactions occurred infrequently during follow-up. Endoscopic removal was not needed in patients treated with high dose of STC and was carried out in 3 of the patients in the low dose STC group (**Figure 2b**). Overall need for endoscopic bolus removal under STC was significantly reduced compared to before treatment (4 vs. 13%, p=0.025). Rates of and time to stricture formation were not significantly different between the two groups (43% vs. 63%, ns). Results of the Kaplan Meier analyses are shown in **Figure 2c.** Clinical activity in the follow-up was not systematically assessed at all of our centers. Based on physician's global assessment, clinical activity was higher in patients on low compared to high dose steroids (85 vs. 43%, p=0.01).

Patients in deep histological remission at baseline

Of the 54 patients who achieved deep histological remission at baseline remission visit under STC treatment, 37 developed a histological relapse (69%). This relapse rate was not different from patients without deep histological remission (64%, ns). Of those patients in deep histological remission, 42 patients continued with low dose (78%), while 12 patients received high dose STC (22%). There was no significant difference between the two groups with regards to duration of follow-up. However, relapse occurred significantly earlier in patients treated with low dose STC (0.8 vs 4.0y, p=0.012, **Figure 3a**). Rates of and time to stricture formation were comparable in the two groups (**Figure 3b**).

Side effects

Esophageal candida infections were rarely observed. In a total of 5 patients, treated esophageal candidiasis was reported (6%). There were no differences when comparing patients with low dose to patients under high dose steroid treatment (3/58, 5% vs. 2/24, 8%, ns). No single case of mucosal atrophy or dysplasia was observed.

Multivariable Cox regression models

Given possible confounding effects, we computed multivariable Cox regression models for prediction of histological relapse adjusted for average time between follow-up visits (in months), peak eosinophil count at baseline remission visit (in eos/hpf), dilation before maintenance phase, sex, diagnostic delay (in years) and steroid type (fluticasone vs. budesonide). In this multivariable model, high STC dose was identified as an independent predictor for longer time to histological relapse (Hazard ratio (HR) 0.35, 95%CI 0.12-0.99, p=0.048). Specifically examining patients in deep remission at baseline, high STC dose remained significantly associated with longer maintenance of histological remission with an HR of 0.20 (95%CI 0.05-0.82, p=0.026) for development of histological relapse (**Table 3**).

DISCUSSION

In this multicenter observational study, we comparatively analyzed effectiveness and safety of low dose (≤0.5mg per day) and high dose STC treatment regimens (>0.5mg per day) in maintaining histological remission at five EoE centers. Our main findings are: 1) histological relapses are frequently observed regardless of the specific STC dose with recurrent disease activity in 67%; 2) histological relapse occurs significantly earlier in patients under low dose STC, even in those with well-controlled disease activity at baseline (deep histological remission); 3) both low dose and high dose STC regimens are safe and well-tolerated with an esophageal candidiasis incidence of 5 and 8%, respectively; and 4) Despite histological relapse in more than 60% of patients, ongoing STC treatment is still able to maintain disease remission in 28 (low dose) and 46% (high dose) with a potentially superior effectiveness for once daily dosing.

Histological relapses are frequent regardless of the therapeutic regimen and specific STC doses. In our study, histological relapse was observed in 67% of all patients. This rate was comparable in patients treated with low dose (72%) and high dose STC (54%). These findings contrast the high remission rates with STC induction treatment, which have been reported at up to 93% after 6 weeks.[21] In the long-term management of EoE, histological relapses are a considerable problem. Our data are similar to the few available steroid long-term studies in EoE. Straumann and colleagues reported 50% ongoing remission in adults after 50 week of 0.25mg bid treatment.[9] Andreae and colleagues showed histological remission of 59% after 24 months in children.[22] So, 40 and 50% of the studied patients experienced a histological relapse despite ongoing steroid treatment. Similar rates were found in a retrospective study on 229 patients, where recurrent histological disease activity was seen at 55% of follow-up visits despite treatment,[10] and another study on 33 patients with relapse rates of 61% after achievement of histological remission.[12] Our finding of frequent histological relapse is particularly noteworthy as low adherence and treatment cessation during follow-up were exclusion criteria, so we can assume that these are true steroid failure rates. Based on these data and poor correlation of symptoms to histological activity,[23] regular assessment of esophageal eosinophilia should be recommended. This is particularly true as ongoing disease activity potentially results in disease progression and stricture formation.[24] We currently do not

know if all of these patients can be considered steroid refractory requiring changes of treatment modality (switch to dietary restrictions or step-up to biological treatment) or if they can still benefit from re-introduction treatment.[25]

Despite similar rates, histological relapse occurs significantly earlier in patients on low dose STC compared to high dose STC regimens. So far, no dose finding STC long-term trial has been published in EoE. It had been speculated that the dose of 0.25mg bid, which had been best studied in EoE long-term management, is too low and not adequate to maintain remission. Here, we show that both low dose and high dose regimens result in histological relapse rates of more than 50%. Nonetheless, a higher dose can keep patients longer in disease remission. Intriguingly, this positive effect of higher doses was even observed in patients with deeply controlled histological disease activity (peak eos count 0-1eos/hpf) at baseline remission visit. One might assume that these are the patients that could maintain remission on lower doses. However, based on our data, very low peak eosinophil counts at the time of histological remission is not an indication to use lower doses of STC to maintain histologic remission. A negative effect of reduced steroid doses has first been suggested by Eluri and colleagues, where dose reduction was significantly associated with a worse outcome.[12] We herein show that more important than keeping the dose steady, STC dose should be maintained above a certain level (0.5mg) in adults with EoE. The recently finished, but not yet fully published EOS2 trial (NCT02493335) comparing budesonide maintenance doses of 2mg/d vs. 1mg/d suggest that there is no additional benefit of daily doses higher than 1mg (1y remission rates of 75.0 and 73.5%, respectively).[26] However, it should be kept in mind that most of the relapses appear to occur beyond a one year follow-up, which will not be captured by this one-year trial. In addition, despite keeping patients longer in disease remission, higher STC doses were not more potent regarding prevention of stricture formation in our study. Furthermore, severe bolus impactions appear to be effectively prevented by both low and high dose STC.

There was no significant increase in side effects with high dose steroids compared to low dose STC regimens. Our rate of esophageal candidiasis (6%) is higher than those reported in the Swiss long-term studies,[9,10] but in accordance with the prospective study in children and the recently published EOS1 trial.[21,22] In addition, there was no single case of mucosal atrophy.

Based on these data, we conclude that STC are safe and that the risk of esophageal candida infection is low, even with maintenance doses above 0.5mg per day. Still, no statement can be made about doses of >2500ug, as these patients were excluded from our analyses. In addition – as we did not systematically assess serum cortisol levels – we cannot rule out the possibility of subclinical adrenal insufficiency.

Our study has several limitations. Clinical activity during follow-up was not systematically analyzed as retrospective assessment would have been inaccurate given different reporting at our five institutions. However, our cut-off of <15eos/hpf to define histological remission has been shown to identify most patients with symptom improvement.[16] At least, physician's global assessment shows a benefit of high compared to low dose steroids. An important limitation is the study sample size of 82. Although most of the patients at our centers are treated with topical steroids also in the long-term, this number is relatively small due to the rigorous inclusion criteria applied to our retrospective analysis (histological remission at baseline, ongoing treatment, available follow-up, and high adherence without intermittent cessation of treatment). Particularly low adherence and cessation of treatment have previously been associated with inferior outcomes and high rates of disease relapse. Thus, inclusion of these patients would have led to a considerable bias. A further limitation is that our two steroid groups showed differences in terms of diagnostic delay, family history and proportion of deep histological remission at baseline. Longer diagnostic delay and lower numbers of deep histological remission rates in the high dose group may have diminished the effect size. With equal distribution of these characteristics, the positive effects of high doses might have been even higher. Another limitation is that we did not follow our patients after occurrence of disease relapse. So, no conclusions can be made about effectiveness of re-induction treatment or steroid dose increases in these cases. Finally, comparison between budesonide vs. fluticasone and different formulations was not feasible as most of the patients in the high dose group were on budesonide, while patients in the low dose group more often received fluticasone. However, medication choice was not a significant factor in our multivariable analysis, and there is evidence to suggest that these STC compounds have similar

efficacy at the same doses despite different potency (likely related to clinical delivery) based on a recently published trial by Dellon et al.[7]

In conclusion, histological relapse frequently occurs in EoE despite ongoing STC treatment regardless of STC doses. However, relapse develops later in patients on high dose STC without an increase in side-effects. Long-term treatment with doses higher than 0.5mg per day may be considered for EoE maintenance treatment, but advantage over lower doses appears to be small.

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FIGURE LEGENDS

Table 1: Patient and disease characteristics

Table 2: Low dose vs. high dose steroid group comparison

Table 3: Multivariable Cox regression models for prediction of histological relapse in all patients and patients in deep histological remission at baseline (peak eosinophil count 0-1 eos/hpf)

Figure 1: Study flow chart

Figure 2: Kaplan Meier curves for time to histological relapse (A), time to bolus removal (B) and time to stricture formation (C) in all patients stratified by steroid dose groups.

Figure 3: Kaplan Meier curves for time to histological relapse (A) and time to stricture formation (B) in patients with deep histological remission at baseline stratified by steroid dose groups.

Supplementary Figure 1: Kaplan Meier curves for time to histological relapse stratified by dose reduction strategy (A) and application mode (B: all doses; C: low dose STC).

Supplementary Table 1: Steroid regimens in the follow-up stratified by low vs. high dose.

TABLES

Patient demographics and disease characteristics	N=82 patients
Males	58 (70.7%)
Age at EoE diagnosis (mean, SD) (years)	37.2, 14.4
Diagnostic delay (median, IQR, range) (years)	7.3, 3.0-17.8, 0-47
Ethnic background	
- Caucasian	77 (93.9%)
- Asian	1 (1.2%)
- unknown	4 (4.9%)
Positive family history for EoE	14 (17.1%)
Previous PPI Treatment	
- PPI treatment without response	51 (62.2%),
- PPI treatment with GERD response	3 (3.7%)
- No PPI treatment	27 (32.9%)
- Missing data	1 (1.2%)
Concomitant atopic diseases	52 (63.4%)
- Allergic rhinitis/rhinoconjunctivitis	40 (48.8%)
- Asthma	20 (24.4%)
- Oral allergy syndrome/food allergy	22 (26.8%)
- Atopic dermatitis	9 (11.0%)
Concomitant gastroesophageal reflux disease	23 (28.0%)
Baseline visit (histological remission)	
Age at baseline visit (mean, SD) (years)	38.2, 14.5
EREFS (median, IQR, range)	1, 0-2, 0-7
Peak eos count (median, IQR, range) (eos/hpf)	0, 0-3, 0-12
Deep histological remission	54 (65.9%)
STC treatment dose at baseline remission visit (median, IQR, range) (ug per day)	500, 500-2000, 220-6000
STC treatment at baseline remission visit	
- Low dose	54 (65.9%)
- High dose	28 (34.1%)
PPI co-treatment	33 (40.2%)
Follow-up	
Follow-up (median, IQR, range) (years)	2.2, 1.0-3.8, 0.1-10
Number of follow-up visits (median, IQR, range)	2, 1-3, 1-10
STC treatment during follow-up	
- Low dose	58 (70.7%)
- High dose	24 (29.3%)
STC treatment dose (median, IQR, range) (ug per day)	500, 500-880, 220-2250
Histological relapse	55 (67.1%)
Stricture formation	40 (48.8%)
Endoscopic bolus removal	3 (3.6%)
Esophageal candida infection	5 (6.1%)
Mucosal atrophy or dysplasia	0 (0%)

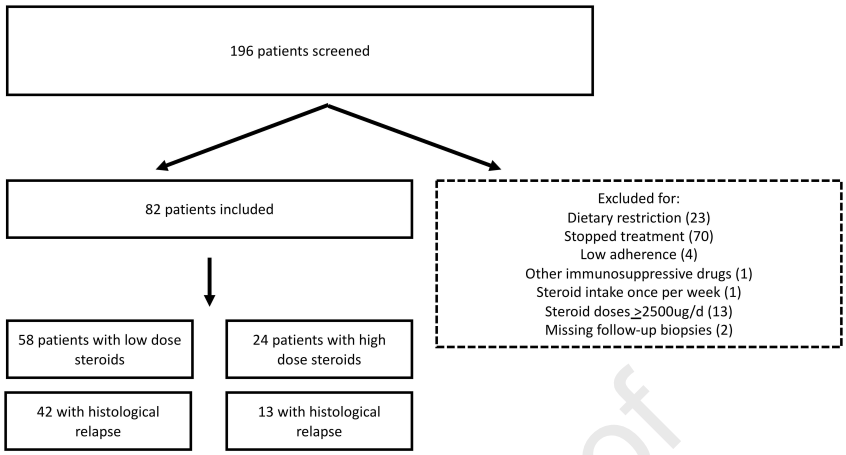
Table 1: Patient and disease characteristics

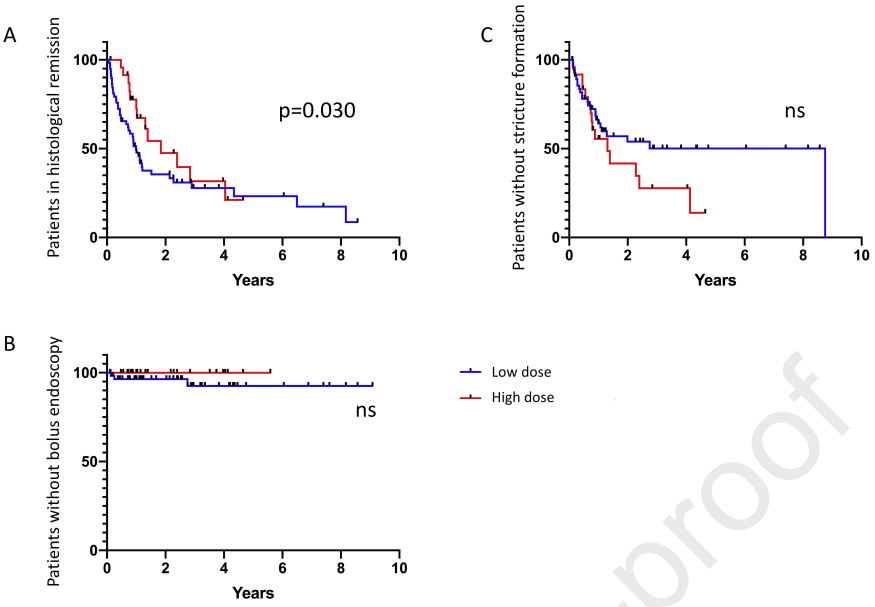
Patient demographics and disease characteristics	Low dose (n=58)	High dose (n=24)	p-value
Males	41 (70.7%)	17 (70.8%)	p=0.990
Age at EoE diagnosis (mean, SD) (years)	36.8, 14.1	38, 15.3	p=0.723
Diagnostic delay (median, IQR, range) (years)	5.6, 2.0-14.7, 0-39	11.0, 7-20.5, 1.7-47.6	**p=0.003**
Positive family history for EoE	6 (10.3%)	8 (33.3%)	**p=0.012**
Concomitant atopic diseases	36 (62%)	16 (66.6%)	p=0.694
Concomitant gastroesophageal reflux disease	13 (22.4%)	10 (41.6%)	p=0.077
Baseline visit (histological remission)			
Age at baseline visit (mean, SD) (years)	38.0, 14.3	38.7, 15.2	p=0.853
EREFS (median, IQR, range)	1, 0.25-2, 0-5	1, 0.5-2, 0-7	p=0.934
Peak eos count (median, IQR, range) (eos/hpf)	0, 0-2.75, 0-12	1.5, 0-2.25, 0-10	p=0.140
Deep histological remission	42 (72.4%)	12 (50%)	p=0.051
PPI co-treatment	22 (37.9%)	11 (45.8%)	p=0.507
Follow-up			
Follow-up (median, IQR, range) (years)	2.3, 1.1-4.1, 0.1-10.0	1.4, 0.9-3.6, 0.1-5.6	p=0.220
Number of follow-up visits (median, IQR, range)	2.0, 1.0-3.8, 1.0-10.0	2.0, 1.0-3.0, 1.0-9.0	p=0.326
Time to first follow-up	6.0, 2.3-13.0, 1.0-24.0	8.0 (4.8-12.0, 1.0-28.0	p=0.683
Average time between follow-up visits (median, IQR, range) (months)	12.1, 7.7-14.0, 1.0-51.0	8.2, 6.2-13.0, 1.0-28.0	p=0.311
STC treatment (median, IQR, range) (ug per day)	500, 227.5-500, 220-500	1000, 1000-1500, 750-2250	**p<0.001**
Histological relapse	42 (72.4%)	13 (54.2%)	p=0.110
Stricture formation	25 (43.1)	15 (62.5%)	p=0.110
Endoscopic bolus removal	3 (5.2%)	0 (0%)	p=0.256
Esophageal candida infection	3 (5.2%)	2 (8.3%)	p=0.586

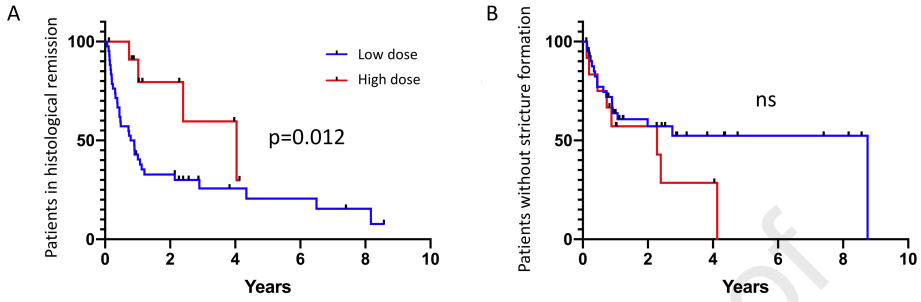
Table 2: Low dose vs. high dose steroid group comparison

Multivariable Cox Regression, all patients, n=82 (event: histological relapse)	**Hazard ratio (95% CI, p-value)**
High dose steroids	0.35 (0.12-0.99, p=0.048)
Time between follow-up visits (in months)	0.86 (0.81-0.91, p<0.001)
Peak eosinophil count at baseline remission visit (in eos/hpf)	0.95 (0.86-1.05, p=0.356)
Dilation prior to maintenance treatment phase	0.73 (0.37-1.44, p=0.368)
Female sex	0.45 (0.23-0.87, p=0.018)
Diagnostic delay (in years)	1.00 (0.97-1.03, p=0.965)
Steroid type (Fluticasone)	0.60 (0.23-1.57, p=0.300)
MultivariableCox Regression, patients in deep histological remission at baseline, n=54 (event: histological relapse)	**Hazard ratio (95% CI, p-value)**
High dose steroids	**0.20 (0.05-0.82, p=0.026)**
Time between follow-up visits (in months)	0.88 (0.81-0.94, p<0.001)
Dilation prior to maintenance treatment phase	0.79 (0.34-1.84, p=0.587)
Female sex	0.51 (0.24-1.09, p=0.084)
Diagnostic delay (in years)	1.01 (0.97-1.05, p=0.646)
Steroid type (Fluticasone)	0.90 (0.31-2.64, p=0.855)

Table 3: Multivariable Cox regression model for prediction of histological relapse

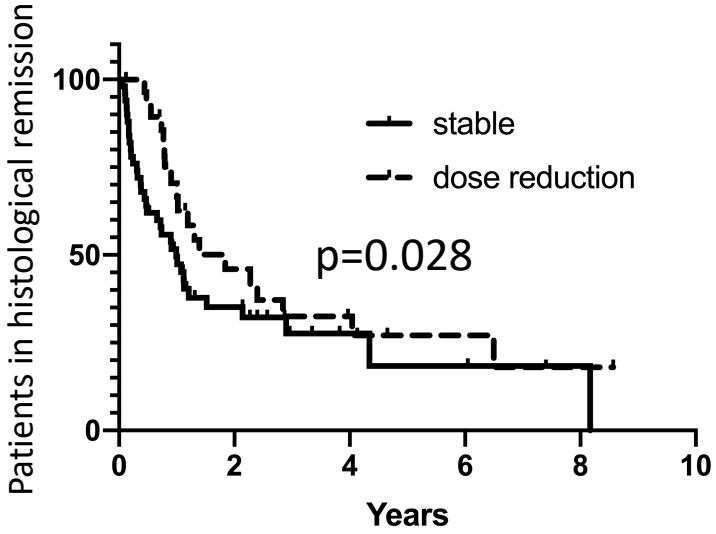






Supplementary Figures

A



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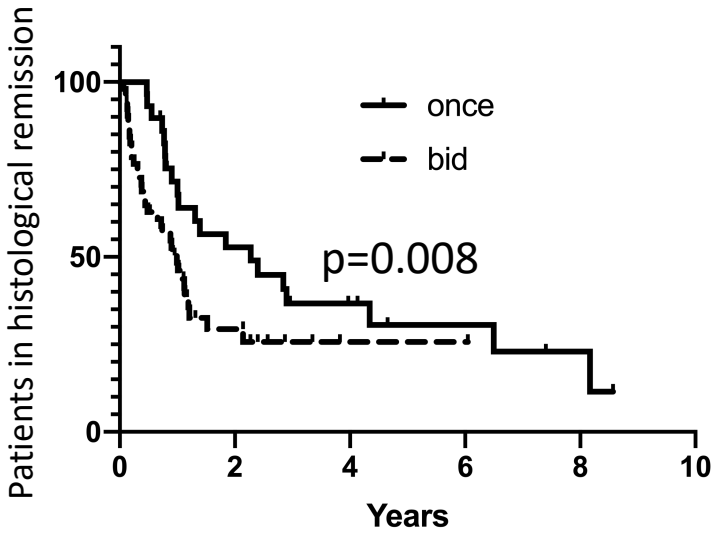

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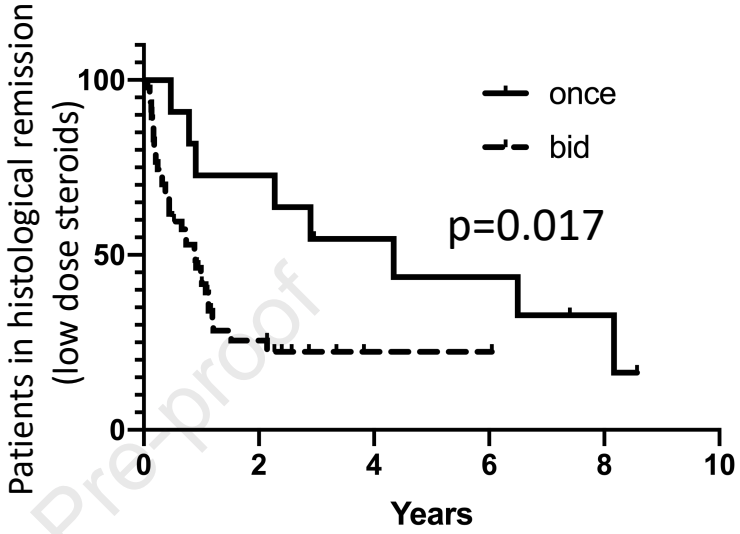

SUPPLEMENTARY METHODS

Subjects and data collection

Patients were recruited at five EoE referral centers in the US (Mayo Clinic, Rochester, MN; University of North Carolina, Chapel Hill, NC; Northwestern University, Chicago, IL; Icahn School of Medicine at Mount Sinai, New York, NY) and Switzerland (Swiss EoE Clinic, Zurich, Switzerland). The following data were collected: demographic characteristics of patients, disease characteristics at diagnosis, timepoint of initial histological remission (baseline remission visit) including clinical, endoscopic and histological characteristics at that time, type and dose of STC maintenance treatment, disease characteristics including clinical, endoscopic and histological disease activity at each follow-up endoscopy visits, and details about complications in the follow-up (dilations, bolus impactions, strictures). All data were anonymized.

Mucosal atrophy

Mucosal atrophy has been previously described as steroid-induced reduction of the thickness of the epithelial layer (which was assessed semi-quantitatively by the pathologist).[1]

Statistical analyses

For statistical analyses, statistical package program STATA (version 16, College Station, Texas, USA) and GraphPad Prism software (version 8.3.0, La Jolla, CA) were used. Metric data are presented as medians with interquartile range (IQR) or means +/- standard deviation (SD). Categorical data are depicted as percentage of the group total. For comparisons between continuous variables, two-sample t-test and Wilcoxon rank-sum test were used depending on whether data was normally distributed or not. Comparison between categorical data was performed by using Chi-square test. For time to histological relapse and to development of disease complications, Kaplan Meier curves were computed. For prediction of disease relapse based on steroid doses in the follow-up, multivariable Cox regression models were computed, adjusted for average time between follow-up visits, peak eosinophil count at baseline (remission), dilation before maintenance phase, sex, diagnostic delay and steroid type. For the purposes of this study, a p-value of < 0.05 was considered statistically significant.

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Supplementary Table 1

Steroid regimens in the follow-up	
Low dose (n=58)	Fluticasone - 110ug, bid (10) - 125ug, bid (1) - 220ug, qd (5) - 250ug, bid (36) - 440ug, qd (2) - 500ug, qd (1) Budesonide - 500ug, qd (3)
High dose (n=24)	Fluticasone - 375ug, bid (1) - 440ug, bid (3) - 500ug, bid (1) Budesonide - 750ug, qd (1) - 100ug, qd (11) - 1500ug, qd (5)* - 2000ug, qd (1) - 2250ug, qd (1)

Supplementary Table 1: Steroid regimens in the follow-up stratified by low vs. high dose. *one patient with 3000ug qad.

What is known:

- Swallowed topical corticosteroids (STC) are very efficacious in inducing clinical, endoscopic and histological remission in patients with active eosinophilic esophagitis (EoE)
- In contrast to the plethora of available studies on short-term induction STC treatment, data on STCs' efficacy in the long-term are limited
- There is no study fully published evaluating efficacy of different STC doses in the long-term management of EoE

What is new:

- Histological relapses are frequently observed regardless of the specific STC dose with recurrent disease activity in 67%
- Histological relapse occurs significantly earlier in patients under low dose STC (≤0.5mg per day) compared to high dose STC (>0.5mg per day), even in those with well-controlled disease activity at baseline (deep histological remission)
- Both low dose and high dose STC regimens are safe and well-tolerated with an esophageal candidiasis incidence of 5.2 and 8.3%, respectively
- Despite recurrent disease activity, ongoing STC treatment is able to maintain disease remission in 28 (low dose) and 46% (high dose), and to effectively prevent severe bolus impactions