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# Swallowed Topical Tacrolimus Induces Clinical and Histological Remission in a Subset of Patients with Severe Lymphocytic Esophagitis

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**Keywords**
Lymphocytic esophagitis · Eosinophilic esophagitis variants · Topical treatment · Tacrolimus · Histological remission

**Abstract**

***Introduction:*** Lymphocytic esophagitis (LyE) represents a chronic inflammatory disease of the esophagus with low response rates to topical steroids. Thus, novel treatment options such as swallowed topical tacrolimus, particularly for refractory cases, are urgently needed. ***Methods:*** We retrospectively analyzed patients with LyE enrolled in the Swiss eosinophilic esophagitis database that received treatment with a swallowed tacrolimus syrup (1 mg bid). We compared clinical (visual analogue scale [VAS] 0–10), endoscopic (VAS, Endoscopic Reference Score [EREFS]), and histological (peak lymphocyte count) disease activity before versus after treatment. ***Results:*** Out of 17 LyE patients, we identified a total of 7 patients undergoing tacrolimus treatment (4 males, median age 71.3 years, IQR: 61.3–76.5, median diagnostic delay of 51.0 months, IQR: 24.5–62.0). Six patients had been previously treated with PPI, five with topical and/or systemic steroids. All patients were treated with topical tacrolimus corresponding to 1 mg bid (for a median of 13 weeks, IQR: 11–15). All patients had clinically, and histologically active disease at baseline. Topical tacrolimus treatment resulted in histological remission (<30 lymphocytes/hpf) in 3/7 patients (42.9%), while 4/7 patients achieved symptomatic remission (VAS for dysphagia ≤2, 57.1%). Overall, clinical (VAS 5 vs. 2, $p = 0.0625$) and endoscopic activity (VAS 5 vs. 2, $p = 0.0625$, and EREFS 3 vs. 2, $p = 0.125$) decreased. Measurement of tacrolimus trough levels in 4/7 patients (range 2.1–3.9 µg/L) revealed some degree of systemic absorption. Mild adverse events to the tacrolimus treatment were seen in 2 patients (esophageal candidiasis, hyposensitivity around lips). No impact on kidney function was observed during the treatment period. ***Conclusion:*** Topical tacrolimus appears to be a potential treatment option for severe LyE, particularly after failure of PPI and/or topical steroids. Further studies are needed, in particular regarding the optimal galenic formulation to avoid systemic absorption.



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## Introduction

Lymphocytic esophagitis (LyE) has been known for several years and usually has been reported as an entity distinct from eosinophilic esophagitis (EoE) [1]. The following diagnostic criteria have been proposed: presence of a lymphocyte-predominant inflammation with high numbers of intraepithelial lymphocytes (≥30 per hpf), gathered mainly in peripapillary fields, with peripapillary spongiosis (dilated intercellular spaces), without the presence of intraepithelial granulocytes [2]. LyE seems to be more frequent in older women in contrast to EoE, which is more frequently diagnosed in younger men [3]. The clinical presentation is similar to EoE as dysphagia tends to be the most common symptom [4, 5]. Although endoscopic alterations are more subtle (up to one-third of the cases present with a normal mucosa), EoE typical abnormalities such as esophageal rings, strictures, and furrows can be observed [4]. The suggested treatment modalities are similar to those used in EoE and include PPI, topical steroids, oral prednisone, and repetitive esophageal dilations [6]. However, these treatments are anecdotal, as they remain without proper evaluation of therapeutic responses. Topical steroids appear to be considerably less effective than in EoE [3]. So far, no prospective trial has been conducted in patients suffering from LyE.

Tacrolimus is a calcineurin inhibitor, which has been used for treatment-refractory ulcerative colitis [7, 8]. It is known to regulate interleukin-2, interleukin-4, and interferon-y expression as well as to modulate the activity of TNF-induced NFkB [9, 10]. All these signaling proteins have been recently shown to be upregulated in esophageal biopsies from patients with LyE compared to esophagus-healthy controls [1]. Thus, a potential effect of tacrolimus on histological and eventually clinical disease activity in LyE might be assumed. In addition, topical tacrolimus (rectally administered) has been shown to effectively treat treatment-refractory ulcerative proctitis [11]. Therefore, a similar strategy with a topical (swallowed) formulation – as it is usually done for EoE – appears appealing for the management of LyE. Based on these preliminary findings and the urgent need for efficacious therapeutic options for LyE, we aimed at investigating the impact of topical tacrolimus on clinical, endoscopic, and histological disease activity of LyE.

## Methods

*Study Design*

This was a retrospective analysis of patients with LyE enrolled in the Swiss EoE database (SEECS, approved by the Local Ethics Committee of the Canton of Vaud, Switzerland, on October 25, 2022, IRB number CER-VD 148-15), with available written informed consent from all patients) [12] that received treatment with a swallowed tacrolimus syrup (1 mg bid). The study was conducted in accordance with the World Medical Association Declaration of Helsinki. Diagnosis of LyE was based clinically on the presence of symptoms of esophageal dysfunction and histologically on the presence of ≥30 lymphocytes/hpf. The primary outcome of this study was the proportion of patients achieving histological remission, defined by a peak lymphocytic count of <30 lymphocytes per hpf. Secondary outcomes were the proportion of patients achieving clinical and endoscopic remission, and the degree of reduction in clinical, endoscopic, and histological disease activity posttreatment.

*Study Population and Data Collection*

The following inclusion criteria were applied: (1) age 18 years or older; (2) documented evidence/presence of LyE; (3) histological evidence of active LyE; (4) no other causes of esophagitis, particularly no EoE and no uncontrolled gastroesopaphageal reflux disease (GERD); and (5) treatment with topical tacrolimus for at least 10 weeks with a follow-up esophagogastroduodenoscopy (EGD) and available esophageal biopsies pre- versus posttreatment. Patients were excluded for the following criteria: uncontrolled GERD as previously defined [13], or presence of another esophageal disease, particularly EoE; patients without a follow-up endoscopy and esophageal biopsies after a 3-month treatment with tacrolimus were also excluded. Clinical activity (presence of dysphagia) was measured on a visual analog scale (VAS) from 0 (absent) to 10 (most severe). Endoscopic activity was measured on a VAS from 0 (no activity) to 10 (most severe activity) and based on the EoE Endoscopic Reference score (EREFS) [14]. Histological activity was measured by peak lymphocytic counts (lymphocytes per hpf) based on H&E histology (judged by two expert pathologists). At the Swiss EoE clinics, esophageal biopsy sampling is standardized, with at least 2 biopsies taken from the proximal and 2 biopsies taken from the distal esophagus.

*Definitions*

The following definitions were used in our study:

- LyE: presence of symptoms of esophageal dysfunction (mainly dysphagia) and presence of a lymphocyte-predominant inflammation with high numbers of intraepithelial lymphocytes (≥30 per hpf), gathered mainly in peripapillary fields, peripapillary spongiosis (dilated intercellular spaces), in the absence of intraepithelial granulocytes [2].

**Table 1.** Demographic and disease characteristics of all patients with lymphocytic esophagitis within the Swiss EoE database

| Patient demographics and disease characteristics | Frequency ($n$ = 17 patients) |
|---|---|
| Males | 8 (47.1%) |
| Age at diagnosis (median, IQR), years | 70.7, 57.3–77.3 |
| Diagnostic delay (median, IQR), months | 40.6, 8.5–69.6 |
| Ethnicity | |
| White | 17 (100%) |
| Concomitant GERD | 1 (5.9%) |
| Concomitant atopic diseases | 6 (35.3%) |
| Previous esophageal surgery | 1 (5.9%) |
| Previous treatment | |
| PPI | 12 (70.6%) |
| Response to PPI | 2 (16.7%) |
| Swallowed topical steroids | 12 (70.6%) |
| Response to swallowed topical steroids | 5 (41.7%) |
| Systemic steroids | 1 (5.9%) |
| Response to systemic steroids | 0 |
| Diet | 1 (5.9%) |
| Response to diet | 0 |
| Previous dilations | 6 (35.3%) |

- Clinical remission was defined as VAS (0–10) for dysphagia ≤2.
- Endoscopic remission was defined as VAS (0–10) ≤2 or EREFS ≤2 [15, 16].
- Histologic remission was defined as a peak lymphocyte count of <30 lymphocytes/hpf.
- Stricture was defined as resistance to the passage of a standard gastroscope or inability to pass the scope based on the treating gastroenterologist's interpretation.

*Treatment*

Induction treatment with swallowed topical tacrolimus twice daily for 12 weeks was performed according to a predefined protocol (2 × 1 mg). 100 mL of the syrup consisted of 0.02 g prograf, 0.2 g stevioside 90% powder, 3 mL flavor of choice, and 97 mL of methocel E4M 2% stock suspension (potassium sorbate) q.s. Patients were treated with 5 mL (corresponding to 1 mg of prograf) twice daily. LyE patients were reminded to take the syrup after breakfast and after dinner and not to drink or eat anything during the 60 min following syrup ingestion.

*Statistical Analyses*

For statistical analyses, GraphPad Prism software version 8.3.0 was used. Metric data are presented as medians with IQR. Categorical data are depicted as percentage of the group total. Wilcoxon signed-rank test was used for comparison between pre- versus posttreatment if data were ordinary or continuous with a nonnormal distribution. If data were continuous and normally distributed, paired $t$ test was used. A two-sided $p$ value of <0.05 was considered statistically significant.

## Results

*Patient Demographics and Baseline Disease Characteristics*

Among a total of 17 LyE patients (median age at diagnosis of 70.7 years, 8 males, Table 1), we identified 7 patients treated with topical tacrolimus (41.2%, all white, 4 males, Table 2) due to a treatment-refractory disease course (PPI and/or steroids). Median age at the time of treatment was 71.3 years (IQR: 61.3–76.5), while the median diagnostic delay until diagnosis of LyE was 51.0 months (IQR: 24.5–62.0). Six patients had been previously treated with PPI, five with topical and/or systemic steroids, without any clinical or histological benefit. Two of the patients had undergone esophageal dilations in the past (1 patient with one dilation, 1 patient with five dilations). One patient had concomitant GERD which was controlled under PPI treatment. For details, see Table 2.

**Table 2.** Baseline patient and disease characteristics

| Patient demographics and disease characteristics at study inclusion | Frequency ($n$ = 7 patients) |
|---|---|
| Males | 4 (57.1%) |
| Age at diagnosis (median, IQR), years | 70.7, 60.6–76.5 |
| Age at the time of tacrolimus treatment (median, IQR), years | 71.3, 61.3–76.5 |
| Diagnostic delay (median, IQR), months | 51.0, 24.5–62.0 |
| Ethnicity | |
| White | 7 (100%) |
| Concomitant GERD | 1 (14.3%) |
| Concomitant atopic diseases | 0 (0%) |
| Previous esophageal surgery | 1 (14.3%) |
| BMI (median, IQR), kg/m$^2$ | 31.2, 25.6–32.7 |
| Previous treatment | |
| PPI | 6 (85.7%) |
| Response to PPI | 0 (0%) |
| Swallowed topical steroids | 4 (57.1%) |
| Response to swallowed topical steroids | 0 (0%) |
| Systemic steroids | 1 (14.3%) |
| Response to systemic steroids | 0 (0%) |
| Previous dilations | 2 (28.6%) |
| Symptoms | |
| Clinically active disease at baseline | 7 (100%) |
| Dysphagia (median, IQR) (VAS 0–10) | 5, 5–6 |
| Tacrolimus treatment | |
| Duration of treatment (median, IQR), weeks | 13, 11–15 |
| Compliance | |
| 100% | 7 (100%) |
| Side-effects | |
| Esophageal candidiasis | 1 (14.3%) |
| Hyposensitivity around lips | 1 (14.3%) |
| Concomitant treatment | |
| PPI | 1 (14.3%) |
| Swallowed topical steroids | 0 (0%) |
| Systemic steroids | 0 (0%) |

Patients were symptomatic at baseline (dysphagia), with a median VAS of 5, IQR: 5–6 (1 patient suffered from severe food bolus obstruction). Other non-dysphagia symptoms were rarely reported and included thoracic pain (28.6%), heartburn (14.3%), and nausea-vomiting (14.3%). However, 1 patient only suffered from such non-dysphagia symptoms at baseline (Fig. 1 is referring to VAS for dysphagia). Patients had endoscopically active disease before tacrolimus treatment (endoscopic activity median VAS 5, IQR: 2–6, and median EREFS 3, IQR: 1–5). Strictures were present in 4 patients (57.1%). Still, in 2 patients, endoscopy was judged normal (VAS 0) or in remission (VAS 1) based on VAS. Per inclusion criteria, all patients had considerable histological disease activity before initiation of tacrolimus treatment with a median peak lymphocyte count of 59 lymphocytes/hpf (IQR: 52–75). Increased eosinophil counts were found in 4 patients, with none of them fulfilling the diagnostic criteria for EoE (maximum peak eosinophil count of 12 eosinophils per hpf).

*Treatment with Swallowed Topical Tacrolimus*

All patients were treated with topical tacrolimus corresponding to 1 mg bid. Median duration of treatment was 13 weeks (IQR: 11–15). Self-reported adherence was 100%. In none of the patients, treatment was

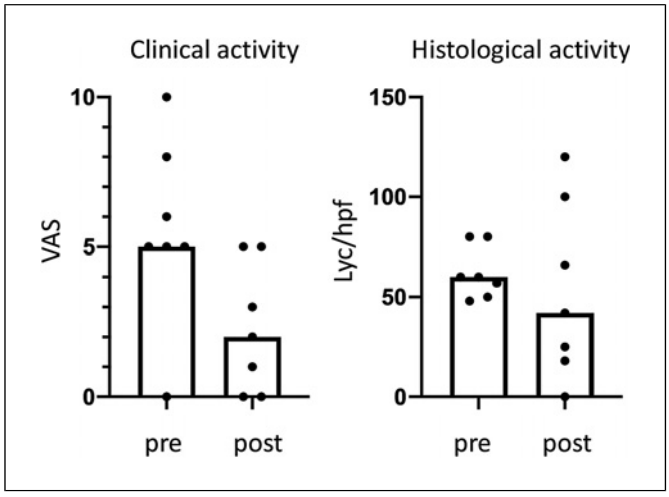


**Fig. 1.** Disease activity (clinical and histological) pre- versus post-tacrolimus treatment. Clinical activity measured on a visual analogue scale (VAS) from 0 (no activity) to 10 (most severe activity). Histological activity measured by peak lymphocyte count per hpf. Bar indicates median value.

discontinued early. One patient with concomitant GERD continued PPI (standard dose) during tacrolimus treatment. All patients had a follow-up upper endoscopy (including sampling of esophageal biopsies) at the end of the induction treatment (while still being under treatment at the time of endoscopy). Topical tacrolimus treatment resulted in histological remission in 3/7 patients (42.9%). In these 3 patients, median peak lymphocyte count decreased from 57 to 18 lymphocytes per hpf. In the remaining patients, histological activity improved in 1 patient. Lymphocyte counts did not decrease in the 1 patient with concomitant PPI treatment. Thus, when excluding the patient with concomitant GERD (under PPI), histological remission rate was 50% (3/6). Of note, elevated eosinophil counts decreased in all patients under tacrolimus treatment, in 1 patient a peak eosinophil count of 12 eos/hpf was reduced to 0. Four out of the 7 patients achieved symptomatic remission (57.1%). In the remaining 3 patients, clinical disease activity improved (decrease of at least VAS 2) in 2 patients. Thus, a total of 6 patients were considered to have a clinical response (85.7%). Overall, clinical activity (VAS 5 vs. 2, $p = 0.0625$) decreased considerably. 4 out of the 7 patients (57.1%) were in endoscopic remission (defined by VAS ≤2) at the end of the treatment period. Overall, endoscopic activity (VAS 5 vs. 2, $p = 0.0625$, and EREFS 3 vs. 2, $p = 0.125$) decreased under treatment. Of note, strictures disappeared in 2/4 patients with only one having undergone endoscopic dilation at baseline.

Of the 3 patients with histological remission, all patients were also in endoscopic remission, while 2 of them achieved clinical remission. However, in 1 patient, there was a mismatch between achievement of histological remission, but ongoing clinical activity. On the other side, 4/6 patients responded clinically (clinical response) with ongoing histological activity. One patient underwent dilation at baseline endoscopy before initiation of tacrolimus treatment. However, this patient did not show a mismatch between clinical and histological disease activity, as both clinical and histological remission were achieved with tacrolimus treatment. To further assess a possible concordance or discrepancy between clinical and biological disease activity in response to tacrolimus treatment, we used the following definitions: clinical improvement (clinical remission or clinical response of VAS ≥2), endoscopic improvement (endoscopic remission or endoscopic response of VAS ≥2), and histological improvement (histological remission or a decrease of the peak lymphocyte count of ≥15%). In 5/7 patients, clinical and endoscopic response correlated (5 patients with clinical and endoscopic improvement). In 2 patients, there was a discrepancy between symptoms and endoscopy. Concordance between histological and clinical response was lower and only present in 3 patients. However, 3 out of 4 patients with a histological response also improved clinically. Similarly, concordance between histological and endoscopic response was only present in 3 patients. Still, 3 out of 4 patients with a histological improvement also showed endoscopic response.

For disease activity before versus after treatment, see Table 3 and Figure 1 (and online suppl. Fig. 1; for all online suppl. material, see https://doi.org/10.1159/000542812). Figure 2 shows representative H&E histology pictures pre vs post treatment in a patient that achieved histological remission at week 12.

*Side-Effects*

Tacrolimus treatment was overall well tolerated and easy to handle. Mild adverse events to the tacrolimus treatment were seen in 2 patients (esophageal candidiasis, hyposensitivity around lips). No impact on kidney function was observed during the treatment period. In 4 patients, tacrolimus trough levels were measured after 4 weeks of treatment. These levels ranged from 2.1 to 3.9 μg/L, revealing some degree of systemic absorption. Although all patients received treatment instructions (no drinking or eating for at least 1 h after the drug administration, no mouth washing), none of the 4 patients had undetectable tacrolimus levels.

**Table 3.** Disease characteristics pre- versus post-tacrolimus treatment

| Disease activity pre- versus post-tacrolimus treatment | Pretreatment | Posttreatment |
|---|---|---|
| Clinical disease activity | | |
| Dysphagia VAS 0–10, median, IQR | 5, 5–6 | 2, 1–4 |
| Endoscopic disease activity | | |
| VAS 0–10, median, IQR | 5, 2–6 | 2, 2–4 |
| EREFS, median, IQR | 3, 1–5 | 2, 1–3 |
| Histological disease activity | | |
| Peak lymphocyte counts per hpf, median, IQR | 59, 52–75 | 42, 22–83 |

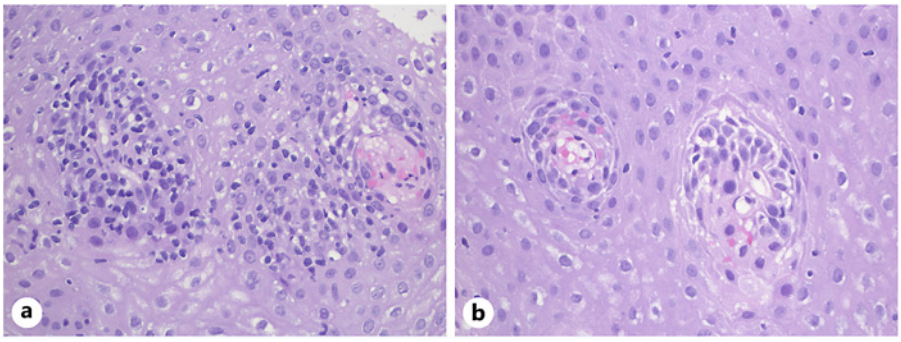


**Fig. 2.** Representative H&E histology slides from a patient with increased lymphocyte counts at baseline (**a**) and histological remission (**b**) after tacrolimus treatment.

## Discussion

In this retrospective observational study, we analyzed patients with lymphocytic esophagitis being treated with a novel swallowed topical tacrolimus formulation. Our main findings are: (1) topical swallowed tacrolimus induced histological remission in 43% and clinical remission in 57% of patients with severe lyE; and (2) topical tacrolimus was systemically absorbed to a considerable amount.

Topical tacrolimus was partially effective, both clinically and histologically in patients with severe LyE. This is particularly encouraging given the large proportion of patients with previous failure of PPI and steroids (both topical and systemic steroid formulation). In LyE, PPI might have a role for symptom control, as an escalating dosing strategy was associated with symptom relief in 59% of patients [5]. Similarly, topical steroids appear to be clinically effective in 50% of patients. However, firm data on PPI's and topical steroids' efficacy with regard to the control of histological activity in LyE is missing. In this study, we show PPI response in 2/12 (16.7%) and steroid response in 5/12 (41.7%, within the Swiss EoE database), so both clearly below 50%. Thus, LyE usually presents as an entity that is difficult to treat. Here, our combined clinical and histological data with regard to the treatment of tacrolimus – although preliminary in nature – starts to close an important gap in treatment evaluations in LyE. Several explanations speak in favor of tacrolimus being a potential therapeutic option: it is a calcineurin inhibitor that is used for atopic dermatitis or ulcerative proctitis. In atopic dermatitis, topical tacrolimus' relative efficacy and safety over steroids have been shown in several studies, including meta-analyses [17–19]. As atopic dermatitis is a Th2-mediated disease, similarly to EoE, and given some pathogenic overlaps between EoE and LyE [3], a potential efficacy of tacrolimus in LyE might be reasonable to suggest. In ulcerative proctitis, a topical form of tacrolimus (rectal administration) has been successfully used for treatment-refractory cases. Its efficacy has been shown in a randomized placebo-controlled trial including 20 patients with a clinical response rate of 73% and mucosal healing in 73% [11]. A larger trial confirmed its clinical efficacy, although no superiority to topical steroids was shown [20]. Still, these data – given the treatment-refractory disease course – are encouraging. Moreover, lymphocytes play an important pathogenic role in ulcerative proctitis, thus a histological effect in LyE appears

to be explainable. However, larger studies are needed, particularly prospective and in a randomized-controlled manner, to prove the efficacy of swallowed tacrolimus in LyE.

Topical tacrolimus was well tolerated and only minor side-effects have been reported. However, in all of the 4 patients with available drug trough levels, a systemic absorption was observed. This has to be considered, particularly given the rather old patient population. Long-term systemic exposure could potentially result in considerable side-effects as known from post-transplantation studies, among which are arterial hypertension, hyperlipidemia, diabetes, renal insufficiency, tremor, and alopecia [21, 22]. While cutaneous application of tacrolimus does not appear to have systemic effects, a recent real-world study evaluating the role of tacrolimus in ulcerative proctitis revealed considerably elevated drug levels [23]. These levels were higher (5.5 ng/mL) than the one seen in our analysis, although direct comparison is difficult due to wide interindividual variation and the dependence of drug measurement on drug intake and timepoint of blood draws. At least in our patients, all drug levels were below the target range in renal transplants of 4–8 ng/mL, and thus it might be questioned whether the low levels were immunologically relevant (particularly given the fact that they were not rigorously drawn 12 h after drug administration). Nevertheless, due to the systemic absorption, it cannot be completely ruled out that the observed effect of topical tacrolimus was due to systemic absorption rather than topical action. Nothing is known about systemic tacrolimus treatment in lymphocytic esophagitis, as the drug has never been used in this context. To disentangle the contribution of a topical vs systemic action of the drug, a direct comparison of a topical vs systemic regimen would be interesting, but the benign nature of the disease would probably not justify systemic treatment resulting in even higher trough levels than measured with the topical syrup. To overcome this limitation, measurement of tacrolimus in the esophageal mucosa would be an appealing option, ideally in a prospective manner for patients with newly initiated topical treatment. In any case, optimization of the current galenic formulation is clearly needed. Tacrolimus is a monohydrate, in the form of white crystals or crystalline powder, which makes it difficult to be dissolved in water. Nevertheless, the fact that our tacrolimus was still topically effective is encouraging and the therapeutic response rates might be even higher with a better topical formulation.

Our study has several limitations: the main drawbacks are the retrospective study design, the rather small number of patients and the lack of a control group. However, LyE still is a rare disease, and our analysis of 7 patients represents one of the largest therapeutic observational studies for this disorder. In addition, our study population corresponds to 41.2% of LyE patients within the Swiss EoE database, highlighting that the disease is frequently refractory to standard treatment. Nonetheless, a possible referral bias needs to be considered as LyE patients were mainly treated at tertiary centers. In contrast to previous reports on PPI and steroids – histological disease activity was used as our primary outcome, which makes our findings more robust. It is known from other chronic inflammatory diseases of the esophagus (EoE) that the placebo rate with regard to histological remission/response is 0% [24]. A limitation is the discrepancy between clinical and histological disease activity. One might speculate that other histological changes beyond pure peak lymphocyte counts are contributing to clinical and endoscopic improvement in patients showing ongoing lymphocytic infiltration. Such discrepancy is well known from EoE. Still, clinical and histological response was concordant in histological responders. The EREFS score was used – together with a VAS – to assess endoscopic activity. This score, however, is not validated for LyE. Finally, trough levels were only available in 4 of the 7 patients with a high interindividual variability. As it was a retrospective study, it was not possible to measure levels in the remaining 3 patients.

In conclusion, topical tacrolimus appears to be a potential treatment option for severe LyE, particularly after failure of PPI and/or topical steroids. However, further studies are needed, in particular regarding the optimal galenic formulation given the considerably increased trough levels in all of the 4 patients with available drug measurements. A systemic effect cannot be ruled out.


## Acknowledgments

We would like to thank all patients enrolled in the Swiss EoE cohort study for their participation and the involved physicians for their contribution.


## Statement of Ethics

The Swiss EoE cohort study has been approved by the Local Ethics Committee of the canton of Vaud, Switzerland ("Commission cantonal d'éthique de la recherche sur l'être humain") on October 25, 2022 (IRB number CER-VD 148-15), with available

written informed consent from all patients. The study was conducted in accordance with the World Medical Association Declaration of Helsinki.

## Conflict of Interest Statement

L.B. has received consulting fees and/or speaker fees from Falk Pharma GmbH, Esocap AG, Sanofi-Aventis AG and Calypso Biotech SA. A.M.S. is a consultant for Dr. Falk Pharma GmbH, Ellodi Pharmaceuticals Inc, Celgene-Receptos-BMS, GlaxoSmithKline, and Regeneron-Sanofi-Genzyme. A.S. has consulting contracts with Actelion, Celgene-Receptos, Dr. Falk Pharma GmbH, Roche-Genentech, GSK, Novartis, Nutricia and Sanofi-Regeneron. T.G. has consulting contracts with Sanofi-Regeneron, Janssen, BMS, Takeda, Abbvie and Dr. Falk Pharma GmbH, received travel grants from Dr. Falk Pharma GmbH and Vifor, speaker's fee from Norgine and an unrestricted research grant from Novartis. The other authors have nothing to declare. No company has been involved in the study design, execution, and analysis, or manuscript conception, planning, writing, or decision to publish.

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## Author Contributions

A.M.S.: conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, visualization, and writing – original draft. S.A.: conceptualization, data curation, formal analysis, investigation, methodology, software, validation, visualization, and writing – original draft. L.B. and A.K.: investigation, methodology, project administration, resources, validation, and writing – review and editing. A.G.: conceptualization, investigation, methodology, visualization, and writing – review and editing. C.D.S.: investigation, methodology, software, and writing – review and editing. A.S.: conceptualization, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, and writing – review and editing. T.G.: conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, visualization, and writing – original draft.

## Data Availability Statement

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

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