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Efficacy of Topical Corticosteroid Monotherapy in Inducing and Maintaining Clinical and Histologic Remission in Adolescent and Adult Patients with Eosinophilic Esophagitis: a Systematic Review and Meta-Analysis

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Background: Eosinophilic esophagitis (EoE) is the second most common cause of esophagitis. Topical steroids represent a promising group of drugs for inducing and maintaining clinical and histological remission in these patients.
Objective. To evaluate the effectiveness of topical steroids in inducing and maintaining clinical and histological remission in adolescent and adult patients with EoE.
Methods. A systematic literature search using defined keywords was performed up to March 20, 2021 in the MEDLINE / PubMed, EMBASE (Excerpta Medica), and Cochrane Central Register of Controlled Trials, ClinicalTrial.gov databases.
Results. 390 patients from 5 studies were included in this systematic review with meta-analysis. The meta-analysis showed that topical steroids, compared with placebo, was more effective in inducing (odds ratio (OR) 75.77; 95 % confidence interval (CI): (21.8; 263.41), $p < 0.001$) and maintaining complete histological remission (OR 103.65; 95 % CI: (36.05; 298.01), $p < 0.001$) in patients with EoE. Also, topical steroids significantly relieved disease symptoms compared with placebo in inducing and maintaining clinical remission (OR 4.86; 95 % CI: (1.4; 16.86), $p = 0.01$) and (OR 11.06; 95 % CI: (4.62; 26.45), $p < 0.001$) respectively.
Conclusions. Topical steroids represent an effective group of drugs for inducing and maintaining histologic and clinical remission in adolescent and adult patients with EoE.
Keywords: eosinophilic esophagitis, topical steroids, budesonide, fluticasone, maintenance therapy, dysphagia
Conflict of interest. All authors declare no potential conflict of interest requiring disclosure in this article.

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Эффективность монотерапии топическими глюкокортикостероидами в достижении и поддержании клинической и гистологической ремиссии у подростков и взрослых пациентов с эозинофильным эзофагитом: систематический обзор и метаанализ

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Актуальность проблемы: Эозинофильный эзофагит (ЭоЭ) — вторая по распространенности причина развития эзофагита. Топические глюкокортикостероиды (ГКС) представляют собой перспективную группу препаратов для достижения и поддержания клинической и гистологической ремиссии у данных пациентов.
Цель: оценить эффективность топических ГКС в достижении и при поддержании клинической и гистологической ремиссии у подростков и взрослых пациентов с ЭоЭ.
Методы. Систематический поиск литературы с использованием определенных ключевых слов проводился до 20 марта 2021 года включительно в базах данных MEDLINE/PubMed, EMBASE (Excerpta Medica) и Cochrane Central Register of Controlled Trials, ClinicalTrial.gov.

Результаты. 390 пациентов из 5 исследований были включены в данный систематический обзор с метаанализом. Метаанализ показал, что топические ГКС, по сравнению с плацебо, имели более высокую эффективность в достижении (отношение шансов (ОШ) 75.77; 95 % доверительный интервал (ДИ): 21,8–263,41, $p < 0,001$) и поддержании полной гистологической ремиссии (ОШ 103.65; 95 % ДИ: 36,05–298,01, $p < 0,001$) у пациентов с ЭоЭ. Также топические стероиды значимо облегчали симптомы заболевания по сравнению с плацебо при достижении и поддержании клинической ремиссии: ОШ 4,86; 95 % ДИ: 1,40–16,86, $p = 0,01$, и ОШ 11,06; 95 % ДИ: 4,62–26,45, $p < 0,001$ соответственно.
Выводы. Топические ГКС представляют эффективную группу препаратов для достижения и поддержания гистологической и клинической ремиссии у подростков и взрослых пациентов с ЭоЭ.
Ключевые слова: эозинофильный эзофагит, топические глюкокортикостероиды, будесонид, флутиказон, поддерживающая терапия, дисфагия.
Конфликт интересов. Все авторы заявляют об отсутствии потенциального конфликта интересов, требующего раскрытия в данной статье.

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Introduction

Eosinophilic esophagitis (EoE) is a chronic immune-mediated disease characterized by symptoms of esophageal dysfunction and dense eosinophilic infiltration of esophageal mucosa (>15/per high-power field (eos/hpf)) in the absence of secondary causes of eosinophilia [1–3]. The incidence and prevalence of EoE has increased dramatically in recent decades, according to a major meta-analysis performed in 2019 of 7.7 cases per 100,000 persons per year (95 % CI, 1.8–17.8, $I^2 = 99.9$ %) and 42.2 cases per 100,000 persons (95 % CI, 31.1–55.0; $I^2 = 99.9$ %) in adults in Europe and North America, respectively [4]. Following a retrospective analysis by a group of authors from the Netherlands, the incidence of EoE has increased several-fold over the past 25 years, from 0.01 cases per 100,000 people per year in 1995 (95 % CI, 0.00–0.04) to 3.16 cases per 100,000 people per year in 2019 (95 % CI, 2.90–3.44) [5]. The disease is caused by a combination of genetic predisposition, impaired immune response, and exposure of environmental allergens. The most common presentations of the disease are dysphagia, including episodes of food impaction, and chest pain not associated with swallowing [1, 3, 6]. EoE significantly reduces quality of life, affecting not only the physical but also the psychoemotional state of patients [7].

Topical steroids are first-line drugs proven to be effective in achieving clinical and histological remission [3, 8]. There have been many studies demonstrating safety, high efficacy and adherence to topical steroids therapy [1, 9–11], but the variability of inclusion criteria and definition of histological and clinical remission, daily dosages, duration of therapy and form of drugs makes comparative analysis of studies difficult. Since EoE has a chronic relapsing course, most patients experience a relapse of symptoms after discontinuing the medications [12, 13]. In addition, long-term maintenance therapy at therapeutic doses is associated with a reduced risk of submucosal fibrosis and episodes of food impaction [13, 14]. Thus, inducing remission and following maintenance therapy represent an essential part of treatment of patients with EoE. However, studies on the selection of optimal regimen, drug formulation, and criteria for achieving remission are still ongoing, and data on long-term therapy with topical steroids are limited and unstructured. The purpose of the current systematic review with meta-analysis is to evaluate the efficacy of topical steroids in inducing and maintaining clinical and histologic remission in adolescent and adult patients with EoE.

Materials and methods

Literature search

Literature searches were performed on MEDLINE / PubMed (www.ncbi.nlm.nih.gov/pubmed), EMBASE (Excerpta Medica), Cochrane Central Register of Controlled Trials, and ClinicalTrial.gov databases with the following terms: ("Fluticasone" OR "Budesonide" OR "Topical corticosteroids" OR "Topical steroids") AND ("Eosinophilic Esophagitis" OR "EoE" OR "Eosinophilic Oesophagitis"). The date of the last request was March 20, 2021. We limited our search to English-language studies and human studies. Three reviewers screened excerpts from the database results according to the inclusion and exclusion criteria. Selected studies were analyzed and relevant data were extracted.

Systematic reviews and meta-analyses published on the same topic were examined for further reference. The review was written according to the PRISMA protocol [15].

Inclusion and exclusion criteria

Inclusion Criteria: The drugs included in the search request were topical steroids (fluticasone, budesonide) in any form (aerosol, suspension) were approved for clinical use in EoE. Randomized clinical trials (RCTs), including phase III studies comparing topical steroids monotherapy and placebo therapy for EoE, were included in the meta-analysis. Other inclusion criteria: age over 14 years, reporting the efficacy of therapy, such as achievement and maintenance of histological remission (<15 eos/hpf) and clinical remission (positive dynamics of dysphagia, episodes of food impaction and chest pain unassociated with swallowing). With maintenance therapy, the duration of remission should be at least 6 months.

Exclusion criteria: studies without baseline data, such as systematic reviews and meta-analyses, single case descriptions, case-control studies, preclinical studies, phase I–II clinical trials, reviews and expert opinions, and studies whose results were published only in the form of abstracts were excluded from this meta-analysis. Studies of combination therapy with other treatment options were also excluded. A manual reference search of the identified articles was performed to identify additional studies that might be of interest.

Statistical analysis

Results were reported as standardized mean differences for quantitative variables and odds ratios (ORs) for categorical variables with 95 % confidence intervals (CIs). Descriptive statistics were calculated for summary analysis for each indicator of interest based on data presented in individual studies. Outcome frequencies were weighted according to the number of patients in each case series. The heterogeneity of the included studies was assessed by the Cochran Q test and the heterogeneity index (I^2). I^2 >40 % was considered an indicator of high heterogeneity and a random-effects model was used in such cases. High I^2 values were associated with a high Q statistic, which is manifested by the statistical significance of heterogeneity ($p < 0.05$). I^2 < 40 % was considered insignificant heterogeneity, in such cases a fixed effect model was used. All statistical analyses in this study were performed using RevMan 5.4 statistical software (Cochrane Collaboration, Oxford, UK). The risk of systematic research errors was assessed using the Cochrane Collaboration questionnaire for assessing the risk of systematic errors in randomized controlled trials [16]. The following formula was used to translate the median into the arithmetic mean in the absence of providing data in the study [17]:

$$\overline{x} \approx \frac{a + 2m + b}{4},$$

Where x is the mean, m is the median, a is the minimum, b is the maximum.

Results

The initial search found 830 articles. Of these, 597 were excluded, including 250 duplicates, 100 reviews, 45 systematic reviews and meta-analyses, 165 clinical cases, 37 phase I–II clinical trials, and 223 articles did not fit the review topic. Of the 10 articles selected for detailed review, the following were excluded: two articles were retrospective studies, and three studies included comparisons and descriptions of several treatment options. As a result, 5 RCTs evaluating the efficacy of topical steroids monotherapy in achieving and maintaining clinical and histologic remission in adolescent and adult patients with eosinophilic esophagitis were included in the meta-analysis (Fig. 1). Since one study included 2 dosing regimens, the meta-analysis evaluated the results separately for each intervention group using one control group [18].

Characteristics of studies

The main characteristics of each study are summarized in Table 1. Our meta-analysis included five RCTs with a total of 390 patients. Fluticasone was used in one study involving 34 patients [19]; budesonide was used in four studies with a total of 356 patients [18, 20–22]. All studies were designed to compare therapy with topical steroids and placebo in inducing or maintaining remission in EoE. Three studies focused on induction of clinical and histologic remission [19–21] and two studies on maintenance of remission [18, 22]. Fluticasone was administered as an aerosol for swallowing, budesonide was either used as a suspension [20, 22], or in orodispersible tablet [18, 21]. All patients underwent esophagogastroduodenoscopy (EGDS) with biopsy before and at the end of treatment to quantify changes in the number of eosinophils in esophageal biopsy, and specialized questionnaires were provided to determine the dynamics of clinical

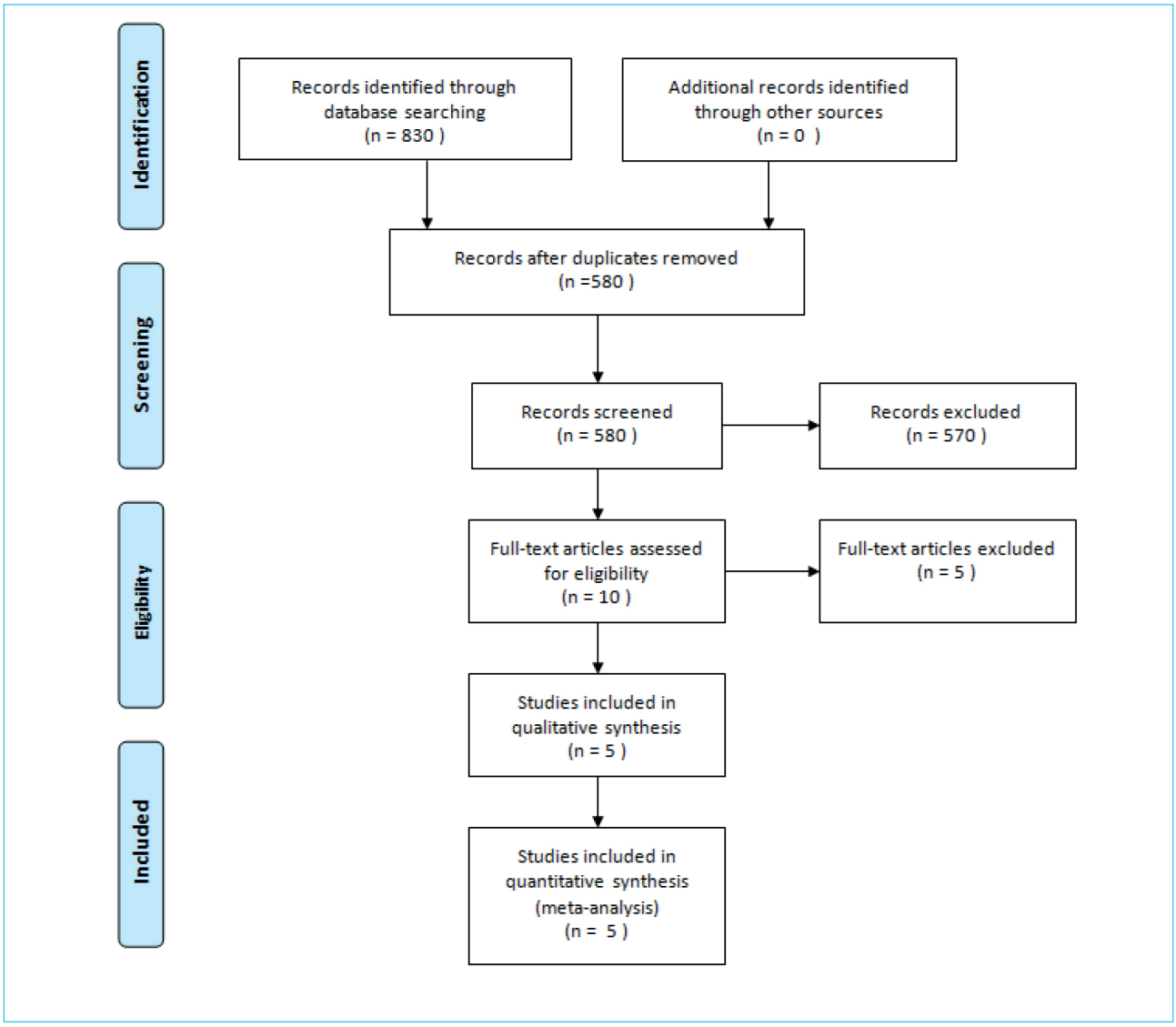

Fig. 1. Block diagram. Publications inclusion algorithm

response. All five studies reported histologic and clinical response data and were included in the meta-analysis. In assessing the risk of systematic error, most of the included studies demonstrated satisfactory quality. The main results of all RCTs are shown in Table 2.

Histological remission

In all studies, histologic response was defined as the change in the number of eosinophils persisting in the esophageal biopsy per high-power field microscope based on morphologic examination of biopsy specimens before and after therapy. Most studies provided data on the change in the peak number of eosinophils, and one study provided data on the change in the mean number (Table 1). However, it has been proved that these indices correlate with each other [23].

All studies demonstrated advantage of both induction and maintenance therapy with topical steroids compared to placebo (Table 2). A meta-analysis of 3 studies of achieving histologic remission in adolescent and adult patients with EoE showed high efficacy of this group of drugs (Fig. 2) OR 75.77 (95 % CI: 21.8; 263.41), $p < 0.001$. Since the heterogeneity index (I^2) was 53 %, a random-effects model was used. A quantitative analysis of clinical studies on the maintenance of histological remission in this patient group showed even more significant results (Fig. 3) OR 103.65 (95 % CI: 36.05; 298.01), $p < 0.001$. The heterogeneity index (I^2) was 0 %; accordingly, a fixed-effect model was used.

Table 1

Study, year	Straumann et al., 2010 [20]	Lucendo et al., 2019 [21]	Alexander et al., 2012 [19]	Straumann et al., 2020 [18]	Straumann et al. 2011 [20]
Study design	RCT	RCT	RCT	RCT	RCT
Duration of therapy	Induction therapy 15 days	Induction therapy 6 weeks	Induction therapy 6 weeks	Maintenance therapy 48 weeks	Maintenance therapy 50 weeks
Number of patients (drug/ placebo)	36 (18/18)	88 (59/29)	34 (19/15)	204 (68/68/68)*	28 (14/14)
Evaluation of therapy effectiveness	Histological response: Complete remission — mean eosinophil count <5 eos/hpf Clinical response: Complete remission — ≥3 reduction in dysphagia score from baseline*	Complete remission was defined as a combination of histological and clinical response. Histologic response: Complete remission — peak eosinophil count <5 eos/hpf Clinical response: Complete remission — reduction in dysphagia and odynophagia scores of at least 2 points for each score (NRS — numerical rating scale**)	Histological response: Complete remission — decrease in peak eosinophil count by 90 % or more of baseline count* Clinical response: Complete remission — absence of dysphagia**	Complete remission was defined as a combination of histological and clinical response. Histologic response: Complete remission — peak eosinophil count <5 eos/hpf Clinical response: Complete remission — reduction in dysphagia and odynophagia scores of at least 2 points for each score (NRS — numerical rating scale**)	Histological response: Complete remission — mean eosinophil count <5 eos/hpf Clinical response: Complete remission — dysphagia scores ≤2 points*
Drug, formulation and dosage	Budesonide suspension 1 mg × 2 per day	Budesonide orodispersible tablet 1 mg × 2 per day	Fluticasone in aerosol (swallow) 800 ug × 2 per day	Budesonide orodispersible tablet Mode 1: 500 ug × 2 per day Mode 2: 1 mg × 2 per day	Budesonide suspension 250 ug × 2 per day
	* Non-validated dysphagia rating scale (0 to 9)	* Numerical rating scale for the severity of odynophagia and dysphagia (0 to 10)	*the baseline peak eosinophil count was ≥20 eos/hpf **assessed using the 2-week version of the Mayo Dysphagia Questionnaire	*Two dosing regimens were used ** Numeric rating scale for odynophagia and dysphagia (0 to 10)	*Non-validated dysphagia rating scale (0 to 9)

Table 2.

No	Authors, year	Study design	Sample size (treatment/control)	Intervention/treatment	EOS count/HPF (M ± SD)			
					Topical steroids		Placebo	
					Baseline	Post-treatment	Baseline	Post-treatment
1	Strauman et al. (2010)	Randomised controlled trial	36 (18/18)	OVB vs placebo	Mean eosinophils 68.2 ± 37.7 Peak eosinophils 147.8 ± 61.3	Mean eosinophils 5.5 ± 9.4 Peak eosinophils 17.7 ± 26.7	Mean eosinophils 62.3 ± 37.1 Peak eosinophils 134.8 ± 86.7	Mean eosinophils 56.5 ± 39.9 Peak eosinophils 125.6 ± 67.6
2	Lucendo et al. (2019)	Randomised controlled trial	88 (59/29)	BOT vs placebo	Peak eosinophils 242 ± 141	Peak eosinophils 16 ± 69	Peak eosinophils 239 ± 125	Peak eosinophils 224 ± 95
3	Alexander et al. (2012)	Randomised controlled trial	34 (19/15)	FP vs placebo	Mean eosinophils 40.95 ± 19.25** Peak eosinophils 50 ± 20	Mean eosinophils 8 ± 8 Пик эозинофилов 13.5 ± 12.5	Mean eosinophils 30.25 ± 13.5 Peak eosinophils 44 ± 15	Mean eosinophils 45.7 ± 34 Peak eosinophils 56 ± 33
4	Straumann et al. (2020)*	Randomised controlled trial	136 (68/68)	BOT (0,5 mg) vs placebo	Peak eosinophils 0 ± 1.4	Peak eosinophils 38 ± 112.6	Peak eosinophils 1 ± 3.6	Peak eosinophils 262 ± 216.3
5	Straumann et al. (2020)*	Randomised controlled trial	136 (68/68)	BOT (1 mg) vs placebo	Peak eosinophils 0 ± 1.7	Peak eosinophils 21 ± 64.0	Peak eosinophils 1 ± 3.6	Peak eosinophils 262 ± 216.3
6	Straumann et al. (2011)	Randomised controlled trial	28 (14/14)	OVB vs placebo	Mean eosinophils 0.4 ± 0.9	Mean eosinophils 31.8 ± 41.2	Mean eosinophils 0.7 ± 2.2	Mean eosinophils 65.0 ± 43.0
No	**Authors, year**	**Study design**	**Sample size (treatment/control)**	**Intervention/treatment**	**Symptoms (M ± SD/ %)**			
					Topical steroids		**Placebo**	
					Baseline	**Post-treatment**	**Baseline**	**Post-treatment**
1	Strauman et al. (2010)	Randomised controlled trial	36 (18/18)	OVB vs placebo	Dysphagia Scale 5.61 ± 1.33	Dysphagia Scale 2.22 ± 2.07	Dysphagia Scale 5.33 ± 0.97	Dysphagia Scale 4.72 ± 1.96

2	Lucendo et al. (2019)	Randomised controlled trial	88 (59/29)	BOT vs placebo	Dysphagia Scale 34.6 ± 16.1	Dysphagia Scale 14.5 ± 16.4	Dysphagia Scale 36.4 ± 12.4	Dysphagia Scale 24.9 ± 11.0
3	Alexander et al. (2012)	Randomised controlled trial	34 (19/15)	FP vs placebo	–	–	–	–
4	Straumann et al. (2020)*	Randomised controlled trial	136 (68/68)	BOT (0,5 mg) vs placebo	Dysphagia Scale 1 ± 0.9	Dysphagia Scale 0 ± 2.0	Dysphagia Scale 1 ± 0.8	Dysphagia Scale 3 ± 2.9
5	Straumann et al. (2020)*	Randomised controlled trial	136 (68/68)	BOT (1 mg) vs placebo	Dysphagia Scale 1 ± 0.9	Dysphagia Scale 0 ± 1.8	Dysphagia Scale 1 ± 0.8	Dysphagia Scale 3 ± 2.9
6	Straumann et al. (2011)	Randomised controlled trial	28 (14/14)	OVB vs placebo	Dysphagia Scale 0.79 ± 1.37	Dysphagia Scale 2.29 ± 2.43	Dysphagia Scale 0.71 ± 1.20	Dysphagia Scale 4.0 ± 2.18

Clinical remission

In most studies, the primary criterion for assessing clinical response was the dynamics of dysphagia (Fig. 1), and in two studies, additionally, odynophagia [18, 21]. Alexander et al. [19] used a 2-week version of the Mayo Dysphagia Questionnaire as an assessment scale [24]. Lucendo et al. [21] and Straumann et al. [18] evaluated clinical remission using a numerical dysphagia and odynophagia rating scale of 0 to 10 points, according to the severity of the symptoms. The Straumann et al. studies [20, 22] used a non-validated rating scale. Data of rating scales before and after treatment are shown in Table 2.

According to the results of our meta-analysis, topical steroids showed greater efficacy than placebo in inducing and maintaining clinical remission — OR 4.86 (95 % CI: 1.4; 16.86), $p = 0.01$ and OR 11.06 (95 % CI: 4.62; 26.45), $p < 0.001$, respectively. The heterogeneity index (I^2) was 61 % and 44 %, and a random-effects model was used.

Discussion

The aim of our systematic review with meta-analysis was to evaluate the efficacy of topical steroids compared with placebo in the therapy of EoE in adolescent and adult patients. Five RCTs were included in the quantitative analysis. In all studies, the primary efficacy criterion was the achievement of clinical and histological remission, which corresponds to the latest Russian and European clinical guidelines [1, 3]. In this meta-analysis, we obtained data clearly demonstrating the advantage of topical steroids therapy over placebo in both achieving and maintaining histological and clinical remission. In several major meta-analyses, the efficacy of topical steroids in the induction and maintenance of histological remission completely correlates with our results, but the effectiveness of drugs in achieving and maintaining clinical response was lower, or did not reach statistical significance compared to placebo [9, 25]. Most likely, this discrepancy is associated with the study of the therapeutic effect in both adult patients and in the pediatric population, which is characterized by more diverse clinical manifestations.

In all studies investigating induction therapy, rapid histologic remission was observed with both budesonide and fluticasone, whereas clinical response required longer therapeutic exposure. In the study by Lucendo et al. [21] the duration of induction therapy was 6 weeks;

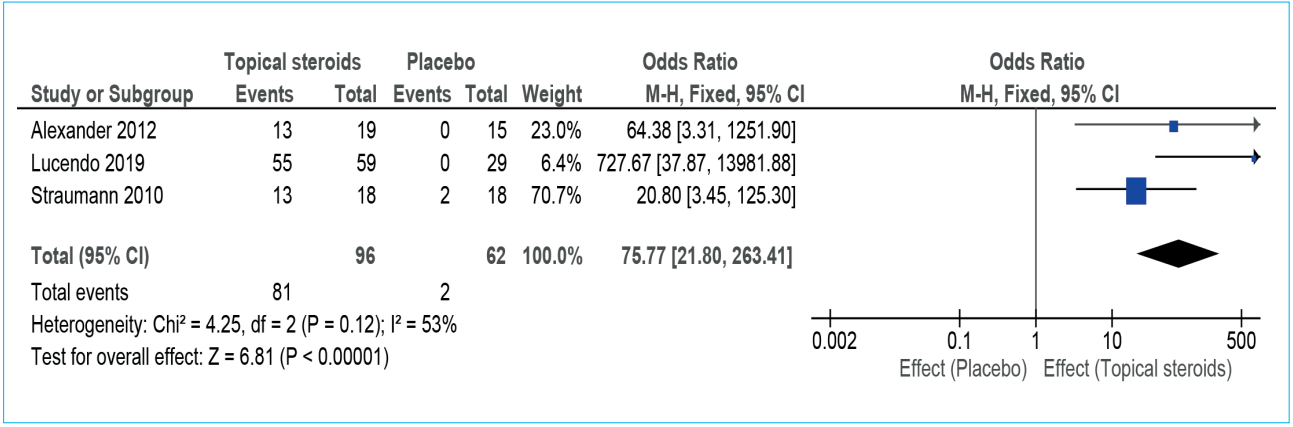

Fig. 2. Comparison of efficacy of topical steroids and placebo in inducing histological remission

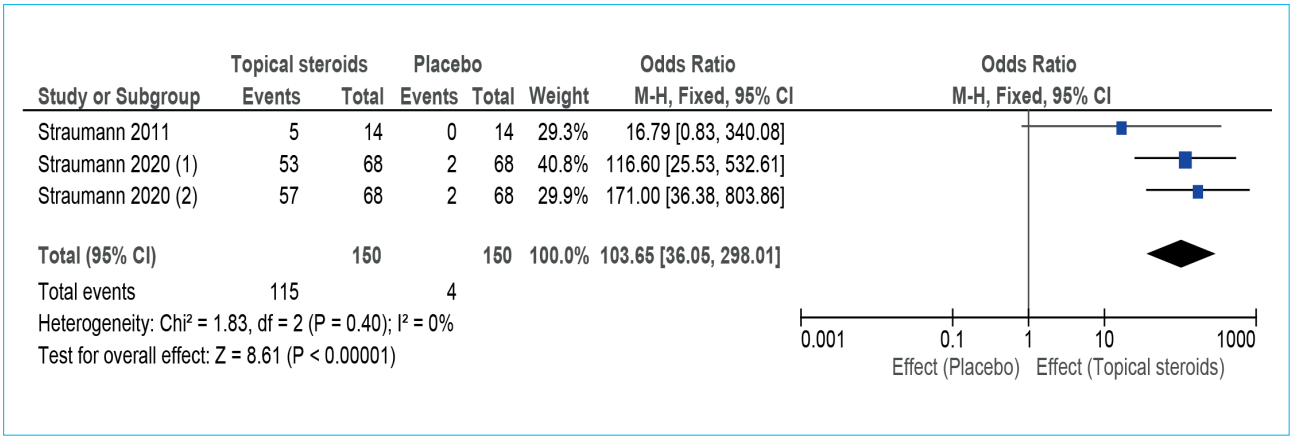

Fig. 3. Comparison of efficacy of topical steroids and placebo in maintaining histological remission

by the end of treatment, 93.2 % of patients in the main group reached histologic remission, whereas only 59.3 % of patients achieved clinical remission. After the primary part of the study, there was an additional phase of 6 weeks open-label budesonide treatment, in which patients from the control group and patients from the main group who did not respond to the initial therapy were included. The dose and method of drug administration was equal to the first phase of the study. As a result, by 12 weeks of budesonide therapy, 84.7 % (50 of 59) of patients had achieved complete clinical and histological remission. The slower clinical response is most likely associated with the process of remodeling as a pathophysiological manifestation of the disease expressed by the development of submucosal fibrosis and formation of strictures, especially in the long-term absence of therapy. It has been shown that the expression of genes associated with tissue remodeling, in particular TGF-B1 and tenascin C, significantly decreases during treatment with topical steroids, which does not exclude the possibility of preventing remodeling, as well as the reversibility of this process with prolonged therapy [20, 22, 26, 27].

A comparative analysis of different modes of drug administration and dosing regimens revealed the advantage of the liquid form (suspension, orodispersible tablet) over aerosol due to a longer contact with the mucous membranes and a prolonged therapeutic effect. The optimal dose of budesonide in inducing remission is 1 mg twice daily, while fluticasone is 800 ug twice daily. In a study by Straumann et al. [18] investigated different dosing regimens of budesonide for long-term maintenance remission of EoE, no statistically significant difference was found between the use of 1 mg twice daily and 2 mg twice daily, both regimens demonstrated high efficacy and safety. In a previously published study by Straumann et al., it was noted that budesonide maintenance therapy at a dose of 250 ug twice daily is slightly superior to placebo in effectiveness and is not adequate for long-term maintenance of histological and clinical remission of the disease [22]. Thus, budesonide at a dose of 1 mg twice daily is the optimal choice for maintenance therapy of EoE.

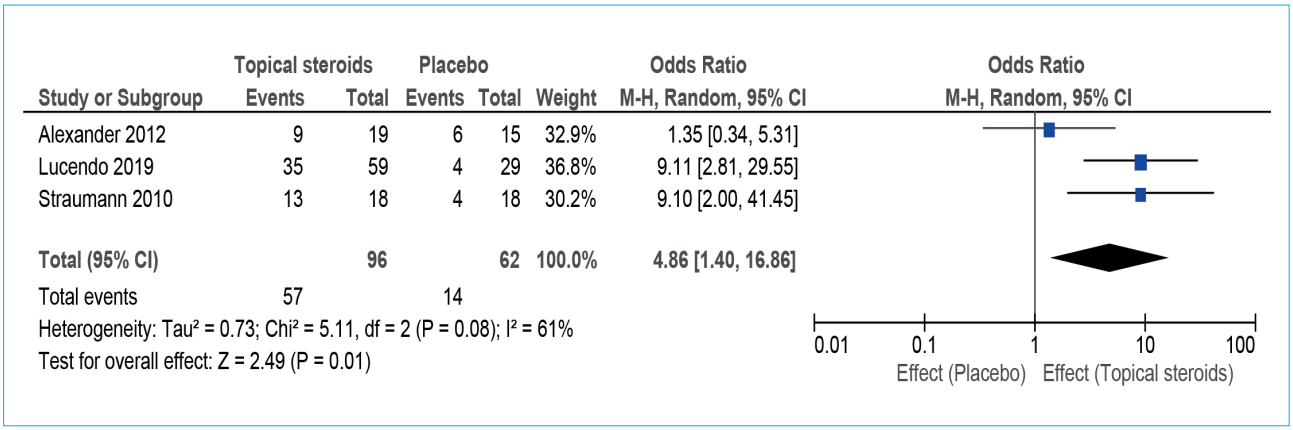

Fig. 4. Comparison of efficacy of topical steroids and placebo in inducing clinical remission

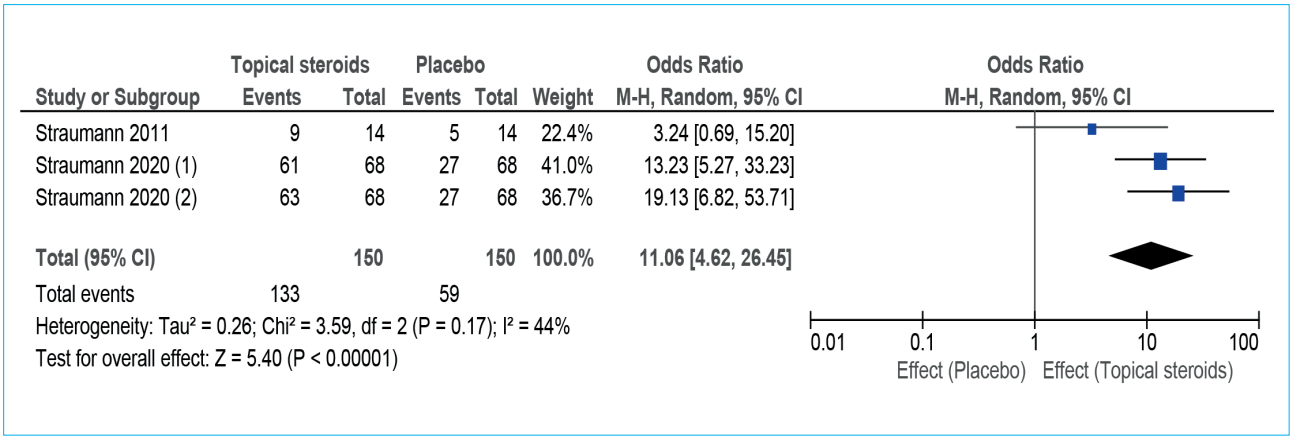

Fig. 5. Comparison of efficacy of topical steroids and placebo in maintaining clinical remission

In all studies, topical steroids demonstrated high safety and no significant adverse effects. Esophageal candidiasis in the main group occurred in an average of a quarter of patients, and in most cases it was asymptomatic and had a mild form. Thus, this is the first systematic review and meta-analysis evaluating complex effect of topical steroids therapy both for induction and maintenance of clinical and histological remission in adolescent and adult patients with EoE. The main limitation of our work is the small amount of published studies dedicated to the induction and maintenance of remission in adolescent and adult patients. Also, the lack of a standardized validated clinical symptom assessment scale complicated the assessment of the dynamics of clinical response.

Conclusion

Topical corticosteroids represent an effective group of drugs for inducing and maintaining histologic and clinical remission in adolescent and adult patients with EoE compared with placebo. More prospective clinical studies on the induction and maintenance of remission and the development and use of a single validated clinical symptom assessment scale are needed to further investigate the effects of topical steroids in EoE therapy.

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