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Swallowed topical corticosteroids for eosinophilic esophagitis: Utilization and real-world efficacy from the EoE CONNECT registry

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Abstract

Background: Swallowed topical corticosteroids (tC) are common therapy for patients with eosinophilic esophagitis (EoE). Widely heterogeneous results have occurred due to their active ingredients, formulations and doses.

Objective: To assess the effectiveness of topical corticosteroid therapy for EoE in real-world practice.

Methods: Cross-sectional study analysis of the multicentre EoE CONNECT registry. Clinical remission was defined as a decrease of ≥50% in dysphagia symptom scores; histological remission was defined as a peak eosinophil count below 15 per high-

power field. The effectiveness in achieving clinico-histological remission (CHR) was compared for the main tC formulations.

Results: Overall, data on 1456 prescriptions of tC in monotherapy used in 866 individual patients were assessed. Of those, 904 prescriptions with data on formulation were employed for the induction of remission; 234 reduced a previously effective dose for maintenance. Fluticasone propionate formulations dominated the first-line treatment, while budesonide was more common in later therapies. A swallowed nasal drop suspension was the most common formulation of fluticasone propionate. Doses ≥0.8 mg/day provided a 65% CHR rate and were superior to lower doses. Oral viscous solution prepared by a pharmacist was the most common prescription of budesonide; 4 mg/day provided no benefit over 2 mg/day (CHR rated being 72% and 80%, respectively). A multivariate analysis revealed budesonide orodispersible tablets as the most effective therapy (OR 18.9, $p < 0.001$); use of higher doses (OR 4.3, $p = 0.03$) and lower symptom scores (OR 0.9, $p = 0.01$) were also determinants of effectiveness.

Conclusion: Reduced symptom severity, use of high doses, and use of budesonide orodispersible tablets particularly were all independent predictors of tC effectiveness.

KEYWORDS
budesonide, clinical remission, dysphagia, effectiveness, eosinophil count, eosinophilic esophagitis, fluticasone propionate, histological remission, orodispersible, swallowed topical corticosteroids

INTRODUCTION

Eosinophilic esophagitis (EoE) is a chronic inflammatory disease mediated by the immune system. Symptoms present as impaired function of the esophagus, histologically characterized by dense infiltration by eosinophils in this organ.[1] These symptoms have a significantly negative impact on patients' and their families' mental health-related quality of life,[2,3] and persistent inflammation may deteriorate the esophageal function, causing dysmotility and strictures due to fibrous remodeling,[4,5] thus indicating a need for treatment.

Drug-based anti-inflammatory EoE therapies consist of proton pump inhibitors (PPI),[6] tC,[7] or a recently approved monoclonal antibody targeting Th2 cytokines.[8] Although PPIs are the most commonly used initial treatment,[9] tC represents the most extensively studied option, with many observational studies,[10,11] randomized controlled trials and systematic reviews[7,12] demonstrating their superiority over placebo to achieve disease remission.

tC mostly based on flutiasone propionate (FP) and budesonide (BUD) formulations are extensively used to induce and maintain remission in real-world practice.[13] However, the use of different active ingredients and doses, administration methods,[11,14–16] formula composition,[17] and changing volumes[18] have provided widely heterogeneous results.[19]

Recently, a standardized formulation of tC based on BUD has become available on the market, providing predictable results in the majority of EoE patients.[15,20] However, this drug is not yet widely available or restricted to the most serious patients or those refractory to other therapies. Therefore, tC treatment remains one of the most variable aspects in EoE patient management in clinical practice,[21] and much of its efficacy and optimal treatment approaches are still unknown, largely because studies comparing the effectiveness of available alternatives are lacking.

Through an analysis of EoE CONNECT, the largest international and multicentre registry of EoE patients, this study aims to provide data on the efficacy of tC treatment in actual clinical practice and to identify determinants of effectiveness.

PATIENTS AND METHODS

Study design and database

This is a cross-sectional analysis of EoE CONNECT, a large, collaborative, prospectively maintained European database. All recruitees are diagnosed with EoE based on evidence-based guidelines criteria[1] and the AGREE conference.[22] After consenting, patient demographic and clinical characteristics, diagnostic work out and therapy outcomes are recorded at various sites across Europe. EoE CONNECT definitions, detailed study protocols and operational procedures have been published elsewhere.[23]

Data collection

Practitioners input information into the registry from face -to-face or virtual appointments. Extracted variables retrieved for this study

included patients' demography, disease characteristics at treatment onset (phenotype, Dysphagia Symptom Score and endoscopic findings), starting date of tC used (active principle, dose regimen, daily dose, length of therapy), treatment purpose (i.e. induction or maintenance of remission), effectiveness (including clinical and histological responses) and date of evaluation. Findings at baseline endoscopy were assessed by the EREFS scoring system.[24]

Data on any tC used in by patients in up to 5 consecutive lines of treatment in order to induce clinical and histological remission were extracted and evaluated. Corticosteroid-based treatments carried out under a clinical trial were not considered for effectiveness analyses. Clinical remission was defined by a decrease >50% in the Dysphagia Symptom Score.[23] Histological remission was defined as a peak of eosinophil count <15 eosinophils/high-power field (HPF) after treatment at all esophageal levels.[25] The primary effectiveness criterion was clinico-histological remission (CHR), which was present when both responses concurred.

Database monitoring and quality data assessment was performed manually at the individual treatment data level to evaluate information coherence and completeness according to EoE CONNECT protocol.[23] Data discordances were resolved by an investigator query.

Statistical analysis

A descriptive analysis was carried out, showing categorical variables as frequencies and continuous variables as mean and standard deviation or median and interquartile range according to the distribution. The Kolmogorov-Smirnov test was used to evaluate normality in continuous variables. Frequency tables were generated for treatment use details and effectiveness.

Categorical variables were compared to assess factors influencing treatment response rates using the chi-square test, with Fisher's exact or Fisher-Freeman-Halton's test used if frequencies were less than 5 and no null value. Similarly, quantitative variables were compared by Student's *t*-test or Mann-Whitney's *U*-test. A binary logistic regression model was used for the multivariate analysis. Odd ratios (OR) were reported for those significant variables. A *p*-value <0.05 was considered significant.

Role of the funding source

EUREOS played no role in study design, data collection, analysis or interpretation, or writing of the report.

Key summary

Established knowledge

- Topical corticosteroids (tC) are widely used to induce and maintain EoE remission in real practice. However, different products provide very heterogeneous results due to the variation in the active components, doses, forms of administration, compositions and volumes used.
- EoE CONNECT is a database that systematically collects data on the treatment of EoE patients from routine clinical practice in Europe, providing a robust picture of the use and efficacy of therapy and information to improve care strategies.

New or significant findings

- Fluticasone propionate (FP) formulations dominated first-line treatment (especially nasal drop suspension, swallowed), while budesonide was more common in later therapies (predominantly the viscous oral suspension prepared by a pharmacist).
- Higher doses of futicasone (0.8 mg/day and over) were effective in inducing clinico-histological remission (CHR) in 65% of patients; for budesonide, higher doses of viscous solution provided no additional benefit (CHR rates being 72% and 80% for 4 and 2 mg/daily doses, respectively).
- A multivariate model revealed budesonide orodispersible tablets as the most effective therapy (OR 18.9, $p < 0.001$); use of higher corticosteroid doses (OR 4.3, $p = 0.03$) and lower symptom scores (OR 0.9, $p = 0.01$) were also significant predictors or CHR.
- After reducing a previously effective dose, only 46% of patients treated with FP and 69% of patients treated with budesonide maintained EoE clinico-histologic remission.

RESULTS

Study population and swallowed topical corticosteroids treatments

At data extraction on 21 March 2023, 2314 patients were registered in EoE CONNECT; a total of 5843 treatments were prescribed up to the fifth line, and 866 patients had received 1456 prescriptions (24.9%) consisting of tC monotherapy. The main demographic and clinical characteristics of patients are summarized in Table 1; Supplementary Table S1 summarizes tC and treatment aim details. The use of tC increased as the line of treatment progressed, from 9% in the first-line up to 48% in the fifth-line therapy ($p < 0.001$); similarly, BUD prescriptions increased from 29% first-line to 54% fifth-line ($p < 0.001$). Only 6% of tC treatments registered corresponded to clinical trials, with a slight increase in further lines of treatment and predominance of BUD over FP (82 *vs.* 10 individual treatments).

A total of 904 treatments of 976 registered overall had data on tC formulation used, with FP therapies being more common than BUD (59% vs. 41%). Regarding maintenance, 234 treatments were prescribed at a lower dose to that effective for induction after successfully achieving CHR (53% being FP and 47% BUD).

TABLE 1 Demographic and clinical characteristics of patients treated with topical corticosteroids in monotherapy in any of the first five lines of treatment.

Number of patients		**866**
Male, (%) (n = 866)		663 (76.6)
Mean (SD) age at first tC treatment, years (n = 858)		32.4 (14.8)
Children at diagnosis, n (%)[a] (n = 798)		202 (25.3)
Country of origin (n = 866)	Spain, n (%)	703 (81.2)
	Italy, n (%)	128 (14.8)
	Denmark, n (%)	29 (3.3)
	France, n (%)	6 (0.7)
Phenotype at diagnosis (n = 794)	Inflammatory, n (%)	584 (73.5)
	Mixed, n (%)	91 (11.5)
	Stricturing, n (%)	119 (15.0)
Dysphagia symptom score at diagnosis (n = 559)	1–4 points, n (%)	162 (29.0)
	5–15 points, n (%)	397 (71.0)
Median EREFS at diagnosis (IQR), score (n = 637)		3 (2–4)
Endoscopic signs of fibrosis[b] (n = 637)	Yes, n (%)	400 (62.8)
	No, n (%)	237 (37.2)

Abbreviations: EREFS, endoscopic score scoring system, measuring edema, rings, exudates, furrows, and strictures; IQR: interquartile range; SD: standard deviation.

[a]Patients under 18 years-old were considered children.

[b]Presence of rings and/or strictures.

Fluticasone propionate to induce EoE remission

Data on formulations and dosages for FP inducing CHR remission are shown in Table 2. The most common FP presentation used in 74% of the treatments was a nasal drop suspension (FP-NDS) swallowed instead of applied inside the nose. The most frequent daily dose was 0.8 mg (69% of FP-NDS). Lower doses (0.4 mg/daily) were used in 12% of treatments and higher doses (1.2 or 1.6 mg/day) in 19%. Assessment of treatment effectiveness was performed after a median of 109 (IQR: 84–185) days/15.6 weeks after treatment initiation.

Metered-dose FP (FP-MD), either from inhalation or spray devices, applied in the mouth and then swallowed, was the second most used formulation (24%). The most common dosage was 1 mg/daily (46% of prescriptions), followed by 0.5 mg/day (30%), with other options being a minority. Treatment effectiveness was assessed after a median of 198 days (IQR 90–651) days/28.3 weeks.

Home-made oral viscous FP solutions (FP-OVS-HM) were exclusively used at one Italian site and represented 2% of FP prescriptions.

Among all FP-based induction treatments, it accounted for 94% of initial tCs, either after failure to PPI or dietary treatment or as first-line induction therapy. Changing from BUD to FP represented only 3% of induction FP-based treatments; the remaining 3% of treatments changed their FP formulation to FP-NDS. Figure 1a summarizes the flow of patients who started on FP-based therapy, with many changing to BUD before they achieved EoE remission.

Effectiveness of fluticasone propionate therapy to induce remission

Several variables were evaluated by univariate analysis to identify associations between CHR for FP-NDS and FD-MD formulations (Supplementary Table S2).

For FP-NDS (Supplementary Table S3), dosage was the variable that most determined effectiveness, with 0.8 mg/day or higher doses clearly superior to 0.4 mg/day in achieving CHR (65% vs. 30%, $p < 0.001$). However, a dosage of 1.2 mg/day or higher provided no additional advantage over 0.8 mg/day (CHR rates being 59% and 66%, respectively). Assessment of effectiveness after a treatment length up to 12 weeks provided better effectiveness compared to longer duration (74% vs. 60%, $p < 0.001$), probably due to lower adherence for longer treatments.

For FP-MD formulas (Supplementary Table S4), although CHR was higher for ≥1 mg/day dosage, among patients with fewer symptoms and for those with an inflammatory phenotype, none of these differences reached statistical significance ($p = 0.27$, $p = 0.16$ and $p = 0.21$, respectively).

Budesonide as treatment to induce remission

Data on formulations and dosages for BUD-induced remission are shown in Table 3. Oral viscous BUD solutions prepared by a pharmacist (BUD-OVS-P) were the most commonly used formulation (57%), followed by orodispersible tablets (BUD-ODT) (26%). Two mg/daily was the most frequently prescribed dose for both (69% and 56%, respectively). For BUD-OVS-P, treatment evaluation was undertaken after a median of 115 days (IQR: 90–194)/16.4 weeks, but for BUD-ODT, it was undertaken after a median of 53 days (IQR: 42–129)/7.6 weeks only.

The remaining BUD formulations represented only 17% of all BUD-based treatments: home-made viscous solution (BUD-OVS-HM) 9% and metered-dose (BUD-MD) swallowed from inhalation devices, 8%. The most common dosage for induction of CHR was 2 mg/day (44% and 68%, respectively).

BUD-based induction therapies were less commonly used than FP as the first tC choice (75% of all treatments), with 20% of treatments prescribed after the failure of FP-based alternatives. The remaining 5% were prescribed after the failure of another BUD formula (with 44% and 33% of them changing to BUD-ODT and BUD-OVS-P, respectively). Figure 1b documents the flow of patients who started on a BUD-based treatment. Almost no patient changed

TABLE 2 Fluticasone propionate prescriptions are distributed according to the type of formulation and dosage used to induce EoE remission.

FP formula	*n* (%) of treatments	Doses used	*n* (%) treatments/ formulation	Response rates: *n* of responders/evaluated patients (%)		
				Clinical remission	Histological remission	Clinico-histological remission
Home-made oral viscous solution	12 (2.3)	1 mg/day	1 (8.3)	-	-	-
		1.5 mg/day	11 (91.7)	10/11 (90.9)	5/9 (55.6)	5/9 (55.6)
Metered-dose in an inhalation or spray device applied in the mouth and then swallowed	126 (23.7)	<0.25 mg/day	6 (4.8)	-	-	-
		0.25 mg/day	9 (7.1)	-	-	-
		0.5 mg/day	38 (30.2)	18/26 (69.2)	10/16 (62.5)	7/17 (41.2)
		0.75–0.9 mg/day	8 (6.4)	-	-	-
		1 mg/day	58 (46.0)	38/43 (88.4)	23/34 (67.6)	21/35 (60)
		1.5–2.0 mg/day	6 (4.8)	-	-	-
		Unknown	1 (0.8)	-	-	-
Nasal drop suspension, swallowed instead of applied inside the nose	393 (74.0)	0.4 mg/day	47 (12.0)	24/34 (70.6)	10/28 (35.7)	8/27 (29.6)
		0.8 mg/day	270 (68.7)	195/ 237 (82.3)	147/208 (70.7)	145/219 (66.2)
		1.2 mg/day	10 (2.5)	6/7 (85.7)	5/7 (71.4)	5/7 (71.4)
		1.6 mg/day	65 (16.5)	44/59 (74.6)	37/59 (62.7)	34/59 (57.6)
		Unknown	1 (0.3)	-	-	-
Total	531			359/ 447 (80.3)	251/384 (65.4)	237/394 (60.2)

Note: Clinical, histological and clinico-histological responses are reported for those alternatives prescribed in at least 10 patients.

to FP before CHR was achieved. Supplementary Figure S1 shows the flow distribution of EoE patients for overall tC treatments.

Effectiveness of budesonide therapy to induce remission

Univariate analyses were performed on the same variables previously described to find associations between CHR and BUD-OVS-P (Supplementary Table S5). The only significant association observed was for symptom severity, as those patients with lower DSS at baseline presented higher CHR rates than those with elevated DSS (91% vs. 71%, respectively; $p = 0.02$). A 4 mg/daily dose was not superior to 2 mg/daily in achieving CHR (72% vs. 80%, respectively), while the 1 mg/day dose was less effective (64%), it was not statistically significant ($p = 0.25$), probably because of the reduced number of patients in this group (7% of BUD-OVS-P).

Regarding BUD-ODT, only 4 patients of the 64 evaluated for CHR showed no response to treatment, preventing univariate analyses for most variables being performed. However, all 4 patients were treated at a dose of 1 mg/daily, inferior to a 2 mg/daily dose in achieving CHR (86% vs. 100%, respectively, $p = 0.04$). This low patient number also inhibited statistical analyses for the other three BUD formulations. Taking this limitation into account, we observed high CHR rates for BUD-MD at 2 mg/day and for BUD-OVS-HM at both 1 and 2 mg/day (93%, 100% and 80%, respectively) (Table 3).

Finally, BUD-based therapies used after the failure of FP-based options were less effective than those prescribed as first-line tC therapy (CHR rates being 67% and 86%, respectively, $p < 0.01$).

Determinants for tC therapy effectiveness in inducing remission

To identify the factors that determine the effectiveness of tC in achieving CHR, we evaluated the four main treatment options (FP-NDS, FP-MD, BUD-OVS-P and BUD-ODT) together with demographical and clinical variables. A univariate analysis was carried out in the 615 CHR-assessed patients. Symptom severity, treatment length (i.e., days until evaluation) and treatment option were found as significant, while endoscopic findings were close to significance (Supplementary Table S6).

With these results and those obtained from single univariate analyses for each tC option, a multivariate model was created by including age at diagnosis, sex, EoE phenotype, DSS, dosage and treatment option (Table 4). Corticosteroid treatment proved to be the most important determining factor, with BUD-ODT presenting the highest effectiveness (OR 18.9, $p < 0.001$). High doses (OR 4.3, $p = 0.03$) and symptom severity measured by DSS (OR 0.9, $p = 0.01$;

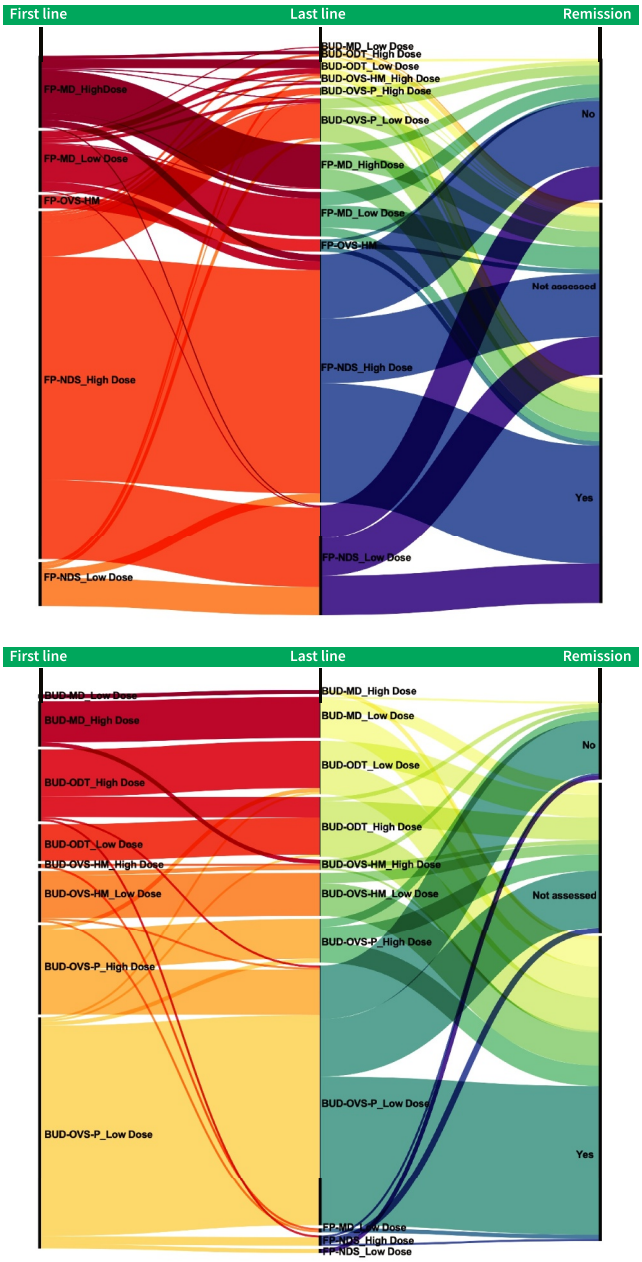

FIGURE 1 Alluvial flow diagram indicating the distribution of EoE patients who started a fluticasone propionate (a) or budesonide-based (b) treatment; the final treatment option received at the point of data analysis; and clinico-histological response to final topical corticosteroid treatment used, including remission, non-remission or non-assessment. BUD-MD, fluticasone propionate metered-dose from inhalation devices; BUD-ODT, budesonide orodispersible tablets; BUD-OVS-HM: budesonide oral viscous solution home-made preparation; BUD-OVS-P: budesonide oral viscous solution prepared by a pharmacist; FP-MD, fluticasone propionate metered-dose from inhalation devices; FP-NDS, fluticasone propionate nasal drop suspension, swallowed instead of inhaled; FP-OVS-HM, fluticasone propionate oral viscous solution home-made preparation. We considered high doses: FP-NDS of 0.8 mg/day and above, FP-MD of 1 mg/daily and above, BUD-MD, BUD-OVS-HM and BUD-OVS-P of 4 mg/day and above, and BUD-ODT of 2 mg/day. The remaining doses were considered low. Diagrams were developed with RAWGraphs, available at https://app.rawgraphs.io.

each point of DSS increase reduced the probability of achieving CHR) were also found as significant determining factors.

Finally, we evaluated whether the efficacy of tCs in inducing EoE remission varied according to their use as first-line treatment or after failure of other therapeutic options (Supplementary Table S7). Overall, 51% of patients used CT after the failure of PPI, 4% after the failure of dietary therapy, 21% after the failure of the two previous options, and 24% as the initial treatment for EoE. Efficacy was similar in all cases for each tC and statistical analyses found no differences for FP ($p = 0.54$) or BUD ($p = 0.60$).

Dose reduction of tC treatments to maintain EoE remission

After successful achievement of remission induction, some patients underwent further tC dose reduction. These included 124 FP-responder patients and 110 additional patients who responded to BUD (Table 5).

For FP, only 2 and 13 patients respectively treated with FP-OVS-HM and FP-MD had their dose decreased, providing insufficient data to truly estimate the effectiveness of dose reductions. Among FP-NDS-responders, 86 patients had initially effective doses reduced to 0.4 mg/day; CHR was maintained in 30 of the 66 patients with response evaluated (46%). Twenty-three patients had a dose reduction to 0.8 mg/daily; CHR persisted in 6 of the 10 patients who had the response assessed.

As for BUD-based treatments, dose reduction was performed in a minority of patients effectively treated with BUD-OVS-HM and BUD-MD. Effectiveness to maintain CHR at reduced doses was similar among the most commonly used BUD-based options. Reducing BUD-OVS-P doses from 4 to 2 mg/daily ($n = 18$; 16 patients having been evaluated for CHR) and from 2 to 1 mg/daily ($n = 52$; 44 patients with response evaluated) maintained 67% and 68% of patients in CHR, respectively. For responders to BUD-ODT, dose reduction from 2 to 1 mg/daily ($n = 19$) maintained 67% of patients assessed ($n = 12$) in remission.

Grouping the data only by the active ingredient drug used, BUD provided higher effectiveness than FP for remission maintenance overall after dose reduction (69% *vs.* 46%, respectively; $p < 0.01$).

DISCUSSION

This study provides the most extensive assessment of the effectiveness of tC treatment in EoE patients in real clinical practice in various European centers, offering essential information and complementing results from other clinical trials and systematic reviews.

We show that FP and BUD, used in a range of formulations, presentations and dosages, are the exclusively used active ingredients at EoE CONNECT participating centers. Results are widely variable in terms of clinical and histological remission and generally superior for BUD compared to FP, thus clarifying previous discrepancies from some small patient series comparing both drugs.[26,27]

TABLE 3 Budesonide prescriptions are distributed according to the type of formulation and dosage used to induce EoE remission.

BUD formula	*n* (%) of treatments	Doses used	*n* (%) treatments/ formulation	Response rates: *n* of responders/evaluated patients (%)		
				Clinical remission	Histological remission	Clinico-histological remission
Home-made oral viscous solution	34 (9.1)	0.5 mg/day	1 (2.9)	-	-	-
		1 mg/day	14 (41.2)	14/14 (100)	14/14 (100)	14/14 (100)
		1.5 mg/day	1 (2.9)	-	-	-
		2 mg/day	15 (44.1)	13/13 (100)	9/11 (81.8)	8/10 (80)
		>2 mg/day	3 (8.8)	-	-	-
Metered-dose in an inhalation or spray device applied in the mouth and then swallowed	28 (7.5)	0.5–1 mg/day	5 (17.9)	-	-	-
		2 mg/day	19 (67.9)	15/15 (100)	14/15 (93.3)	14/15 (93.3)
		>2 mg/day	4 (14.3)	-	-	-
Oral disintegrating tablet	97 (26.0)	1 mg/day	43 (44.3)	30/32 (93.8)	25/28 (89.3)	25/29 (86.2)
		2 mg/day	54 (55.7)	38/38 (100)	35/35 (100)	35/35 (100)
Oral viscous solution prepared by a pharmacist	214 (57.4)	<1 mg/day	6 (2.8)	-	-	-
		1 mg/day	14 (6.5)	10/12 (83.3)	7/11 (63.6)	7/11 (63.6)
		2 mg/day	147 (68.7)	108/120 (90.0)	94/111 (84.7)	89/111 (80.2)
		4 mg/day	44 (20.6)	31/37 (83.8)	27/37 (73.0)	26/36 (72.2)
		>4 mg/day	3 (1.4)	-	-	-
Total	373			287/312 (92.0)	244/291 (83.8)	237/290 (81.7)

Note: Clinical, histological and clinico-histological responses are reported for those alternatives prescribed in at least 10 patients.

TABLE 4 Multivariate analysis by binary logistic regression to evaluate the influence of demographical and clinical variables on the effectiveness of topical corticosteroid therapy to induce clinico-histological remission of EoE.

Variable	Categories	*p*-value	OR (95% Confidence interval)
Age at diagnosis	-	0.074	1.02 (0.99–1.04)
Sex	Male	0.566	Reference
	Female		0.85 (0.50–1.47)
EoE phenotype	Inflammatory	0.817	Reference
	Mixed or stricturing		0.94 (0.57–1.56)
Dysphagia symptom score	-	0.008	0.92 (0.86–0.98)
Dose	Low	0.030	Reference
	High		4.27 (1.15–15.78)
Treatment modality	FP-MD		Reference
	FP-NDS	0.591	0.78 (0.32–1.93)
	BUD-OVS-P	0.163	2.03 (0.75–5.49)
	BUB-ODT	<0.001	18.91 (3.67–97.36)

Note: Age at diagnosis and Dysphagia Symptom Score were used as quantitative variables, and doses and EoE phenotype as qualitative variables, according to the classification described in Supplementary Table S2.

Abbreviations: BUD-ODT, budesonide orodispersible tablets; BUD-OVS-P, budesonide oral viscous solution prepared by a pharmacist; FP-MD, fluticasone propionate from a metered dose inhalation device; FP-NDS, fluticasone propionate nasal drop suspension; OR, Odds ratio.

TABLE 5 Topical corticosteroids formulas are used to maintain EoE remission with dose reduction from that effective for inducing remission.

Active ingredient	Formulation	*n* (%) of prescriptions	Daily dose (mg)	*n* (%) prescriptions/ formulation
Fluticasone propionate (*n* = 124)	Home-made oral viscous solution	2 (1.6)	1	2 (100)
	Metered-dose from inhalation systems	13 (10.5)	≤0.25	5 (38.5)
			0.50–0.75	6 (46.2)
			1–1.5	2 (15.3)
	Nasal drop solution, swallowed instead of inhaled	109 (87.9)	0.4	86 (78.9)
			0.8	23 (21.1)
Budesonide (*n* = 110)	Home-made oral viscous solution	6 (5.4)	0.5	3 (50)
			1	3 (50)
	Metered-dose from inhalation systems	12 (10.9)	0.5	2 (16.7)
			1	10 (83.3)
	Orodispersible tablets	19 (17.3)	1	19 (100)
	Oral viscous solution prepared by a pharmacist	73 (66.4)	0.5	1 (1.4)
			1	52 (71.2)
			2	18 (24.7)
			>2	2 (2.7)

Effectiveness also depended on presentation –lower for FP-MD swallowed from inhalation systems, and on the daily dose –FP doses lower than 0.5 mg/day—but adequate for daily doses from 1 mg of BUD.

Our study analyzed the different tC used by EoE patients in up to 5 consecutive lines of treatment, thus capturing changes (in active ingredient, method of administration and dose) in pursuit of CHR. We also identified independent factors related to CHR by binary logistic regression, consisting of symptom severity (lower score, better remission rate) and use of high doses of active ingredient. However, the use of BUD-ODT was identified as the most significant independent factor determining EoE remission, thus confirming the results of two previous network meta-analysis.[28,29] Previous studies identified stricturing phenotype as a predictor of poor response to tC[30] and even PPI,[6] a finding not reproduced in this research.

Once remission was achieved, some patients had the effective dose reduced to try and maintain CHR. Generally speaking, half of the patients treated with low doses of FP and assessed for effectiveness presented disease recurrence; the same occurred in two thirds of patients who underwent a dose reduction of any previously effective formulation or dose of BUD. Despite being based on a limited number of patients, these data are novel in the literature and suggest that if well-tested formulations of tC with reproducible results are not available, keeping responsive patients on the initial same dose therapy might be an acceptable alternative.

The strengths of our study include the use of a large, multicenter series of EoE patients prospectively recruited from multiple sites in four European countries and managed according to the criteria of the treating physician. This provides representative data and reflects actual clinical practice. However, sites that contribute to EoE CONNECT are greatly interested in EoE and may have better knowledge of more advanced treatment strategies, which could result in bias toward more favorable clinical outcomes.[31] The response criteria were evaluated in a rigorous and standardized manner, and combined both histological remission and clinical improvement. The histological remission criterion of less than 15 eos/HPF has been proposed by expert consensus,[25] and the 50% reduction of the baseline DSS has already demonstrated responsiveness in previous registry analyses.[6,13,32]

Some important limitations should also be acknowledged. The fact that patients were recruited over a 7-year period in which treatment options may have varied; this was not taken into account in the analyses, since our main goal was to compare therapeutic alternatives. Also, so as not to complicate the analysis, the number of intakes in which the entire daily dose was distributed, was not evaluated. Neither was CHR evaluated in a proportion of patients. Assumptions should not be made that CHR in patients who were not assessed for response would have been the same as for those who were. Moreover, determinants of response to treatment were identified from a limited number of variables, and did not include body mass index, which has been recently linked independently to poor response to EoE treatment with tC.[33] All possible viscous formulations of BUD or FP were grouped into only two categories (prepared by a pharmacist or home-made); variability in solvents

and volumes potentially leading to variable effectiveness was not taken into account.[34] Finally, we did not evaluate adverse events associated with the different tC-based treatment options; this issue will be the specific subject of a future analysis of the EoE CONNECT registry.

In conclusion, this research documents the high variability in the use of tC and provides comparative evidence on the effectiveness of different corticosteroids-based therapies for EoE in real-world practice. Less symptom severity, high doses of active ingredients, and using BUD-ODT particularly, were all independent predictors of treatment effectiveness. Reduction of effective doses led to disease recurrence in at least one-third of patients.

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Guarantor of article: Alfredo J Lucendo; specific author contributions: Alfredo J Lucendo and Emilio J Laserna-Mendieta: study design and writers; Pilar Navarro and Emilio J Laserna-Mendieta: database monitoring and quality assessment; Emilio J Laserna-Mendieta and Ángel Arias: data extraction and analysis. All authors collected and registered the data, and approved the final version of the article, including the authorship list.

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CONFLICT OF INTEREST STATEMENT

The authors declare that there are no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The authors confirm that the journal's ethical policies, as noted on the author guidelines page, have been adhered to. The Ethic

Committees at all sites contributing to EoE CONNECT evaluated the protocol and approved participation.

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