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ORIGINAL ARTICLE

Montelukast Was Inefficient in Maintaining Steroid-Induced Remission in Adult Eosinophilic Esophagitis

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Abstract
Background and Aims Leukotriene D4 is produced by and functions as a chemotactic factor for eosinophils. Eosinophilic esophagitis (EoE) is characterized by esophageal eosinophilic infiltration, determining structural changes and dismotility symptoms. Montelukast, a selective leukotriene D4 receptor antagonist, has gained increasing consideration as a therapeutic agent for EoE. However, limited available information has shown that montelukast is not effective in reducing eosinophilic infiltration. Our paper aims at evaluating whether montelukast could be consider as a steroid-sparing therapy by assessing its efficacy in maintaining both clinical and histopathological remission achieved after topical corticosteroids in adult EoE patients.
Methods Eleven consecutively diagnosed adult EoE patients were prospectively studied. Esophageal biopsies were obtained before and after a 6-month treatment with fluticasone propionate 400 μg/twice a day. Immediately after that, montelukast 10 mg/day was instituted. A new endoscopy was foreseen after a new 3-month period, or as soon as the patients presented esophageal symptoms. Symptoms were assessed by using a questionnaire before and after fluticasone propionate treatment and after montelukast therapy.
Results Eosinophils density into the esophageal epithelium and lamina propria was significantly reduced after a 6-month treatment with topical steroids ($P = 0.003$) and increased to levels similar to baseline level into the first 3 months after treatment with montelukast. Baseline symptom scores significantly decreased after treatment with topical steroids ($P = 0.003$) and increased again after montelukast therapy, but baseline levels improved.
Conclusions Montelukast was not efficient in maintaining the histopathological or clinical response achieved by topical steroids in adult EoE patients.

Keywords Eosinophilic esophagitis · Allergic esophagitis · Montelukast · Anti-leukotriene · Leukotriene D4 · Dysphagia

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Introduction

Eosinophilic esophagitis (EoE) is a chronic inflammatory immune/antigen-mediated esophageal disease characterized by the presence of large numbers of intraepithelial eosinophils in esophageal biopsies, determining chronic fluctuant esophageal dysfunction symptoms [1].

Since first described nearly three decades ago, the number of both pediatric and adult patients diagnosed with EoE has exponentially increased. In fact, it is recognized today as the most common eosinophilic gastrointestinal disease [2]. Eosinophilic esophagitis is considered to be an

atopy-associated inflammatory disorder, whose epidemiology has risen in recent years parallel to other immunoallergic diseases [3–5]. As a result, several therapies with demonstrated efficacy in allergic diseases have also been used in the EoE patient, together with different forms of diet modification and endoscopic dilations [6].

As far as drug therapy, corticosteroids have been the most commonly used drugs in both pediatric and adults EoE patients. Prednisone has been one of the most widely used drugs since the first cases of the disease came to light [7–9], but topical steroids, especially fluticasone propionate and budesonide, have demonstrated equal effectiveness, inducing a rapid clinical and histological response, although the adverse effects were lower than in patients treated with systemic corticosteroids [10–13]. However, the standard is that the symptoms and the esophageal eosinophilic infiltrate reappear several weeks after treatment is discontinued, which forces patients to receive repeated cycles of therapy, or even continuous steroid therapy, weaned to the lowest possible dose [1]. Consequently, other drugs with a better long-term safety profile have been proposed for treating EoE as corticosteroid-sparing agents. While no benefit has been demonstrated with cromoglicate [14], little research has been carried out on montelukast.

Leukotriene D4 is a proinflammatory molecule both produced by and serving as a chemotactic factor for eosinophils. Montelukast is a selective antagonist drug which specifically blocks the receptor for leukotriene D4 expressed on eosinophils [15]. Montelukast has a well-established role in the management of patients with chronic asthma [16] and it is also useful in acute asthma exacerbations [17]. After demonstrating its efficiency in treating mild persistent bronchial asthma in adolescent and adult patients in monotherapy at dosages of 10 mg/day [18], it was first used in a small group of eight adult patients with EoE who were administered high dosages (up to 100 mg/day) [19]. After several weeks of treatment, seven patients showed remission of symptoms but none had significant histological improvement. In a more recent study, only three out of eight pediatric EoE patients showed at least partial clinical response to this treatment, while histological efficacy was not evaluated in every patient [20]. Available data seems to indicate that montelukast does not achieve clinical nor histological remission as initial therapy in many EoE patients. However, no studies have been developed until now to determine whether or not montelukast could offer benefits in replacing steroids after the eosinophilic inflammation and its derived symptoms have been resolved with these drugs. In this sense, our work aims at evaluating the possible efficiency of montelukast in maintaining both clinical and histopathological remission achieved by using topical corticosteroids in adult EoE patients for the first time.

Materials and Methods

Patients

Eleven adult patients naïve to medical and endoscopic therapy for EoE and consecutively diagnosed to be sufferers from this disease by presenting symptoms of esophageal dysfunction were studied. Diagnostic criteria for EoE included [1]: (a) infiltration of esophageal epithelium by $\geq$15 eosinophilic leukocytes per high power field (HPF) at 400× light microscopy; (b) absence of eosinophilic infiltration in biopsies obtained in gastric and duodenal mucosa; (c) elimination of gastroesophageal reflux as a cause of eosinophilia through either ambulatory 24-h pH-metry or persistence of eosinophilic infiltration after an 8-week treatment with omeprazole (20 mg/twice a day) plus negative endoscopy for signs of reflux diseases; and (d) exclusion by clinical history of drug intake, parasites, causticizations, hematological neoplasm, or other illnesses that could give rise to esophageal eosinophilia.

The study was conducted in accordance with the principles of the Declaration of Helsinki and approved by the Institutional Review Board of our hospital. Informed consent was obtained from all patients.

Endoscopy and Biopsy Procedure

All endoscopic exams were carried out by the same endoscopist (AJL) and were performed under conscious sedation with a flexible 9-mm-caliber Pentax EG-2770 K gastroscope with a 2.8-mm work channel. Biopsies were taken with the aid of standard needle biopsy forceps (Radial Jaw 4, Boston Scientific, Natick, MA, United States), in the upper and lower esophageal thirds, obtaining a minimum of five specimens in each location. These were then fixed in 4% formalin and routinely processed for histopathological analysis.

Treatment and Follow-up Period

All patients received topical treatment of a liquid suspension of 400 μg fluticasone propionate (FP) (Flixonase® 0.4, nasal drops, Glaxo-SmithKline, Durham, UK) during a 6-month period. Patients were told to swallow the liquid twice a day after breakfast and dinner and to avoid eating or drinking in the subsequent 2 or 3 h. No PPI treatment was administered during this period. No changes in diet, environment or medication between the baseline and follow-up biopsies were mandated.

After 6 months, the endoscopic procedure and sampling of esophageal biopsies were repeated as described above. At that time, and after checking the normal endoscopic appearance of esophageal mucosal surface and absence of

symptoms, the fluticasone propionate treatment was stopped in every patient, and Montelukast 10 mg/day (Singulair; Merck Sharp and Dohme Ltd, UK) was initiated, with the intention of repeating the endoscopy 3 months later, or as soon as esophageal symptoms recurred. Patients were asked to report any adverse event they noted during the study period.

Histological Study

All formalin-fixed digestive mucosa samples were routinely processed. Sections (5-μm thick) were cut from formalin-fixed, paraffin-embedded blocks and then placed on microscope slides and stained with haematoxylin and eosin. The histological stains were analyzed by a researcher who was blinded to the identity of the patient whose biopsy was taken. The peak number of eosinophils was counted with the aid of Nikon Eclipse 50i (Nikon Corporation, Tokyo, Japan) light microscopy in three HPF at 400× (the HPF area measured 0.212 mm^2). The mean eosinophil count per HPF was calculated in both epithelial and lamina propria (LP) strata (if present in the sample) by averaging the eosinophil counts in three HPF at the two esophageal levels. Results were expressed as cells/HPF.

All biopsies were analyzed by a blinded expert pathologist (JLY-C) accustomed to studying EoE biopsy samples.

Clinical Evaluation

Symptoms were assessed by means of a previously published score validated for achalasia and focusing on esophageal symptoms in adult patients [21], since no specific validated score is available for EoE. The duration and intensity of the dysphagia events, the frequency and intensity of pyrosis and regurgitation were recorded (Table 1).

The questionnaire was performed in all patients by one single, board certified gastroenterologist (AJL), at three different times along the period of study: (a) previously to initiate FP treatment; (b) just before the endoscopy after the FP treatment period; and (c) just before carrying out the last endoscopy after montelukast treatment. The interviewer was blinded to the previous marks offered by each patient in order to prevent bias over such marks.

Statistical Analysis

Data were shown as mean ± standard deviation for eosinophils and as median with interquartile rank (IQR) for score of clinical symptoms. The paired *t* test or Wilcoxon signed test were used to compare values before and after treatments. A 0.05 level of significance was used throughout.

Results

We examined a total of 11 EoE patients (9 male and 2 female) between 20 and 61 years of age (average 34.91 years) who had exhibited esophageal symptoms for a mean period of 42.55 months (range 12–72) (Table 2). Four out of 11 patients did not complete the scheduled 3-month period of treatment with montelukast for referring serious deterioration in their symptoms at month 2. No patients abandoned the study or were lost during the follow-up. No adverse events were described for fluticasone propionate and montelukast during the treatment period.

Table 1 Clinical symptom score according to severity and frequency (extracted from Zaninotto et al. [21])

For each symptom, a frequency score was added: 0 = never; 1 = occasionally; 2 = once a month; 3 = every week; 4 = twice a week; 5 = daily		
Dysphagia		
0	None	
1	Mild	Occasionally with coarse food (meat, sandwich, hard roll) lasting a few seconds
2	Moderate	Requires liquids to clear
3	Severe	History of meat impaction requiring medical attention
Regurgitation		
0	None	
1	Mild	Occasionally after straining, after a large meal, or lying down after a meal
2	Moderate	Predictable with a position change, straining, or lying down
3	Severe	History of aspiration
Heartburn		
0	None	
1	Mild	Recognizable symptom, occasional episodes, no history of medical treatment
2	Moderate	Primary reason for medical visit or "medical problem"
3	Severe	Constant, marked disability in activities of daily living

No endoscopic dilation was needed during the study period.

Histopathological Efficacy

Biopsy samples from eight out of the 11 included patients who exhibited a significant amount of LP allowed us to continue eosinophils in both epithelial and LP.

Baseline eosinophil mean densities into the esophageal epithelium and LP were 54.38 (standard deviation [SD] 23.82) and 17.02 (SD 13.17) cells/HPF, respectively. After topical steroid treatment, both intraepithelial and LP eosinophils significantly decreased to 1.8 (SD 2.75) cells/HPF (P= 0.003) and 3.27 (SD 3.09) cells/HPF (P = 0.043), respectively.

After the montelukast treatment period, density of epithelial eosinophils significantly increased (P = 0.003) reaching similar levels to baseline (mean 50.96; SD 36.13 cells/HPF), while the LP eosinophil density was also increased (mean 6.02; SD 6.01 cells/HPF), but not significantly (P = 0.225) (Figs. 1, 2).

Clinical Efficacy

The symptom score was obtained for each patient by adding the individual scores of dysphagia, regurgitation and heartburn, as previously described [21]. Baseline marks were significantly reduced after treatment with topical steroids (P = 0.003), and increased again after the montelukast therapy period.

Interestingly, marks of symptoms after montelukast were still significantly lower than in baseline conditions (P = 0.005). However, differences between the clinical improvement resulting from topical steroid treatment and that resulting from montelukast were observed (P = 0.003) (Table 3, Fig. 3).

Discussion

This work analyses for the first time the efficacy of standard doses of montelukast (10 mg/day) in maintaining the histological and clinical remission achieved after topical steroid treatment in adult patient sufferers of EoE. We have observed that inflammatory eosinophilic infiltrate and related symptoms recurred a few weeks after interruption of steroids despite receiving montelukast in every patient.

Montelukast has been shown to be highly efficient in treating symptoms of mild persistent bronchial asthma [16, 18], by inhibiting the action of cysteinyl leukotriene D4 through blocking its receptor. Cysteinyl leukotrienes are lipid mediators generated from arachidonic acid, a common

Table 2 Clinical characteristics of eosinophilic esophagitis (EoE) adult patients included in our study

Patient	Age	Sex	Time of evolution (months)	Symptoms	Endoscopy		Familiar background of atopy	Personal background of atopy
					Calibre	Mucosal appearance		
1	20	M	48	Dysphagia and food impaction	N	R, LF	Father: AR	AR
2	61	M	72	Dysphagia chronic and food impaction	R	LF	Sister: AR	AR
3	45	M	12	Dysphagia and food impaction	N	R	Sister: Dermatitis Son: FA	No
4	54	M	60	Dysphagia, regurgitation, pyrosis and self-limited food impaction	N	LF	Brother: FA, AR	Ba, FA
5	41	M	60	Dysphagia, pyrosis, chest pain and regurgitation	N	LF, WP	Mother: FA, Dermatitis	BA, AR
6	25	M	24	Dysphagia and food impaction	R	R, LF, WP	Mother: AR	DS, BA, FA
7	28	M	36	Dysphagia and self-limited food impaction	N Schatzky ring	R, LF	Brother: AR	Dermatitis
8	27	F	36	Dysphagia, food impaction, regurgitation, pyrosis and vomiting	N	LF, WP	Father: Dermatitis	No
9	33	F	24	Dysphagia and pyrosis	N	LF	Mother: AR	BA, AR
10	23	M	60	Dysphagia and frequent food impaction	N	LF, WP	Sister: AR	No
11	27	M	36	Dysphagia, food impaction, pyrosis and vomiting	N Schatzky ring	R, LF	Mother and Grandmother: BA	BA, AR, FA

M male, *F* female

Endoscopy: *N* normal, *R* rings, *LF* longitudinal furrows, *C* crêpe-paper appearance, *WP* white plaques, *S* stricture.

Atopy: *BA* bronchial asthma, *AR* allergic rhinitis, *FA* food allergy, *ND* not determined, *DS* drug sensitivity

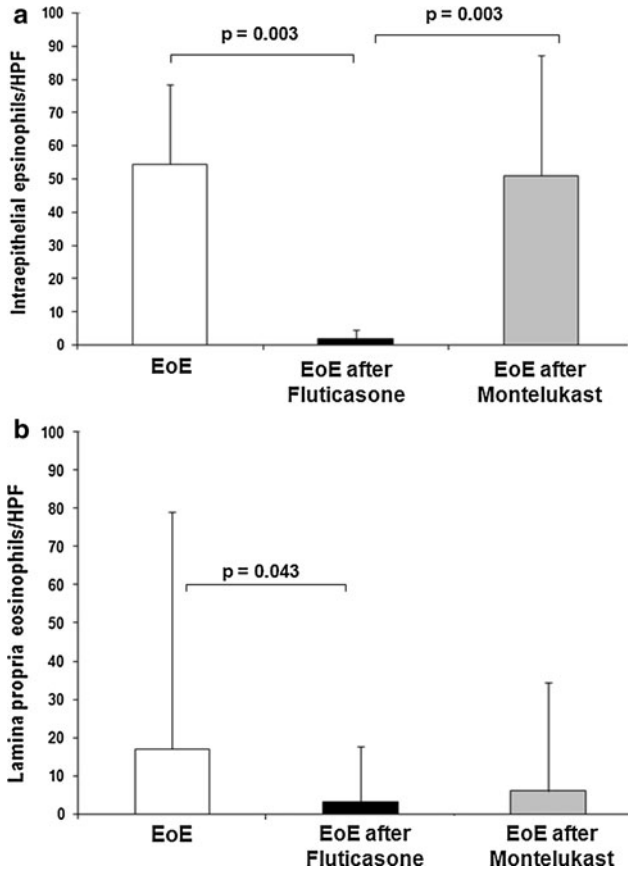

Fig. 1 Eosinophils density at epithelial (**a**) and lamina propria (**b**) strata on esophageal biopsies taken from 11 adult patients sufferers from eosinophilic esophagitis. Eosinophils densities were determined by averaging proximal and distal thirds. Changes in eosinophilic density at basal conditions, after a 6-month period on fluticasone propionate and after montelukast therapy are shown. *Error bars* refer to standard error

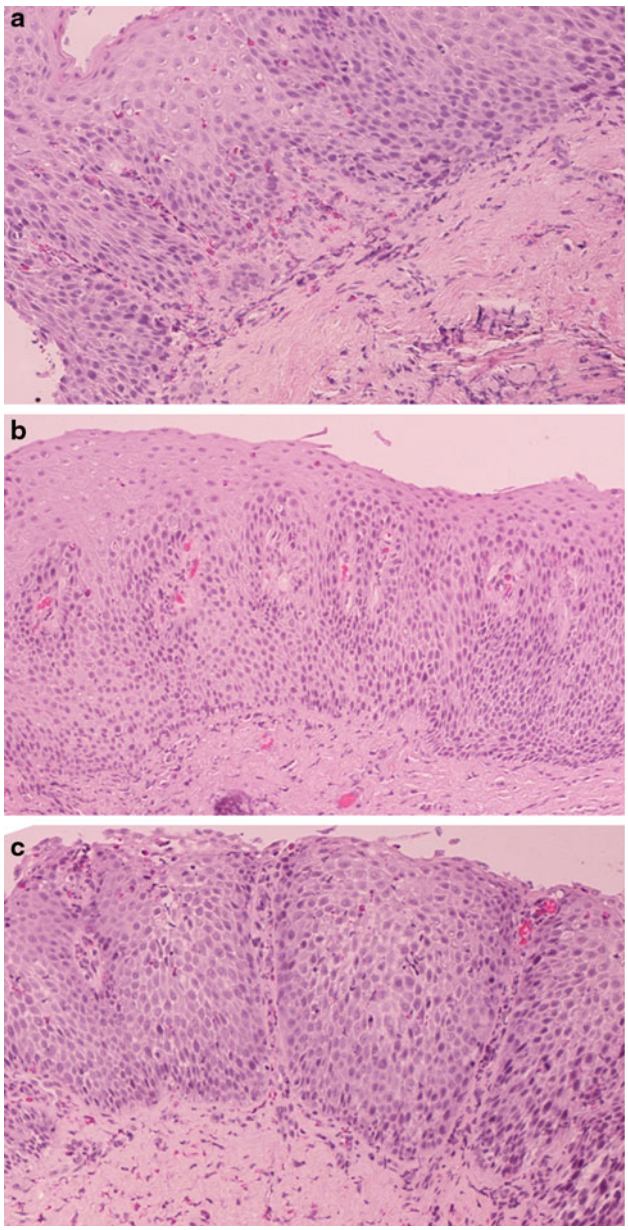

Fig. 2 Histopathological findings characteristic of eosinophilic esophagitis (EoE) corresponding to the same patient before (**a**) and after (**b**) therapy with topical steroids. In (**a**), a highly cellular esophageal epithelium with basal stratum proliferation and many eosinophils within the full-thickness mucosa can be seen. After 6 months under treatment with fluticasone propionate (**b**), the esophageal epithelium exhibits fewer cells and recovered stratification with no eosinophilic infiltration. After 3 months under montelukast therapy (**c**), biopsies showed reappearance of eosinophilic infiltration into the epithelial strata and lamina propria, and eosinophilic granular deposits, together with proliferative changes (hematoxylin and eosin, ×200)

component in the phospholipids bilayer of cell membranes, which are synthesized after several inflammatory cells, such as eosinophils, mast cells and macrophages, are activated [22]. The effects of leukotrienes include eosinophils attraction and migration, strong contraction of the smooth muscle, airways edema, mucous hypersecretion and reduction in cilia motility [19].

EoE and bronchial asthma share some commonalities [23]. Both are chronic diseases with an underlying inflammatory response mediated by Th2 cytokines [24] triggered after exposure to allergens to which patients are sensitized [25]; in both disorders eosinophils develop an outstanding effector role which leads to structural changes and the appearance of several spastic motor disturbances over smooth muscle, respectively responsible for dyspnea and dysphagia [26, 27]. A direct effect for leukotrienes in stimulating the esophageal smooth muscle has been proposed as a mechanism leading to dysphagia in EoE patients [28, 29]. This effect could act together with the major basic protein, derived from cytoplasmatic granules of eosinophils, which is capable of inducing M2 muscarinic receptor dysfunction leading to altered smooth muscle contractility [30]. In this sense, esophageal dysmotility has been reported in

Table 3 Clinical symptoms score (dysphagia, regurgitation and heartburn) in adult patients with eosinophilic esophagitis (EoE), after treatment with fluticasone and after treatment with montelukast

Patients	Score EoE	Score after fluticasone	Score after montelukast
1	5	0	4
2	5	0	3
3	6	0	4
4	10	0	6
5	12	2	5
6	7	2	4
7	4	0	3
8	15	2	9
9	12	4	8
10	4	0	4
11	10	4	9

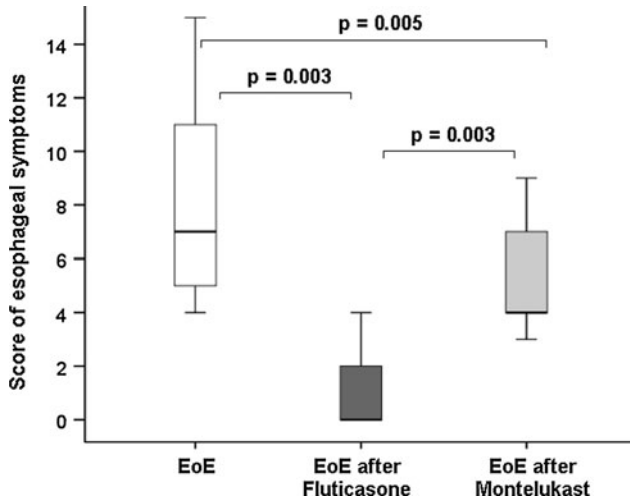

Fig. 3 Score of esophageal symptoms in adult eosinophilic esophagitis (EoE) patients at basal conditions, after fluticasone propionate treatment and after montelukast, determined by the method proposed by Zaninotto et al. for achalasia [21]. Median and interquartile range (IQR) are represented in the boxes, and whiskers (*vertical lines*) extend to a limit of ± 1.5 IQRs

EoE patients, and despite that its specific role in the pathophysiology of the disease has not been clearly established, it could justify esophageal symptoms. In contrast to the putative role of anti-leukotriene therapy in treating EoE patients, until now, very few works have evaluated the potential clinical utility of these drugs in such disease.

Attwood et al. treated for first time a small group of eight adult patients with EoE. All patients started on 10 mg/day, and doses were gradually increased to a maximum of 100 mg/day in order to achieve symptomatic relief, during a mean period of 14 months [19]. Six patients showed initial remission of symptoms, and five remained asymptomatic for a follow-up period of 4–28 months. However, no patients showed significant histological improvement in endoscopic exams carried out after 4 months of therapy. These data are consistent with those from a previous report of montelukast therapy in eosinophilic gastroenteritis (EG), in which it was shown that montelukast did not affect tissue eosinophilia or symptoms in a patient with severe EG with complications due to esophageal stricture [31]. It should be noted that high doses of montelukast (maintaining a dose two- to four-fold over standard dose) used in the research of Attwood et al. were needed to maintain symptomatic control. After the medication was discontinued or reduced, the symptoms reappeared. As far as side effects, nausea was observed in four patients and myalgia was observed in one more patient receiving montelukast, resulting more commonly with doses over 40 mg/day [19]. While anti-leukotriene drugs are generally safe in adults and children respectively used in standard 10 or 5 mg/daily doses, there has been some concern regarding a possible association between the use of antileukotrienes and Churg-Strauss syndrome (CSS) in asthma. As a result, monitoring patients for the development of CSS in all patients with EoE undergoing treatment with montelukast is recommended [32].

A study evaluating the use of montelukast in pediatric EoE has been recently published [20]. Montelukast was prescribed in eight children at standard doses (4–10 mg daily), but had to be withdrawn in five of them because it was clinically ineffective. Two children showed partial response and one more complete clinical response. Unfortunately, only four out of the eight children included in this work had follow-up biopsies while on montelukast therapy and an overall histological benefit could not be observed. Because of that, it can be supposed that remission of tissue eosinophilia could not be observed in the case of esophageal biopsies in every patient. This assumption is supported by the findings of other studies developed over mucosal esophageal samples on pediatric EoE patients, in which no differences were detected between children with EoE and normal controls in gene expression levels of cysteinyl leukotrienes [33]. Furthermore, cysteinyl leukotriene levels were independent of the severity of inflammation.

Regardless of the inefficacy of montelukast in EoE patients in terms of histological recovery, our small study showed that symptoms recurred in all patients during the montelukast treatment period, and in four cases the medication had to be terminated early because of poorly tolerated esophageal symptoms. From the limited data reported in literature, we know that montelukast did not achieve clinical efficacy in all treated cases. In fact, clinical efficacy showed by montelukast in reported cases could be attributed to the natural history of EoE, which is widely recognized as a chronic disease with intermittent symptoms

[34]. It has been clearly established that some EoE patients remain asymptomatic for long periods without treatment and symptoms may fluctuate spontaneously or depending on exogenous allergens [5, 35, 36].

Paradoxically, in our study, we observed that clinical scores after montelukast therapy were significantly lower than in baseline conditions, despite the recurrence in esophageal inflammation and derived symptoms. This data can be explained as follows. First of all, a primary endpoint of our study was to evaluate the reappearance of esophageal manifestations after montelukast, regardless of the baseline intensity of symptoms. In fact, the four patients who did not complete the terms of the study protocols required assistance because of poorly tolerated esophageal symptoms. Finally, from our observations, we can infer that the intensity of symptoms could reach baseline levels in every patient if the montelukast treatment period would have been long enough.

In our study, we used the standard dose of montelukast that is usually prescribed in bronchial asthma [18]. Regarding the differences between the standard 10 mg/day doses used in our study compared to the extremely high doses used in previously treated patients [19], several aspects should be considered. Since 10 mg/day could be insufficient to achieve a significant effect, all of our patients received montelukast when no pathologic inflammatory infiltration was demonstrated in esophageal biopsies; even in these circumstances, the drug was unable to avoid a fast relapse in eosinophilic inflammation. Our study prevents us to definitively establish if higher doses of montelukast would have been efficient in maintaining steroid-induced remission of EoE, but previously presented data induce us to think that montelukast could hardy reach the study goal. Moreover, using off-label high doses of montelukast increases both the economic cost and side effects of the therapy, and should be carefully monitored in long-term use.

Our results were obtained from the prospective study of only 11 adult EoE patients, and despite the previously discussed data, they should be analyzed in the strictest confidence since no control group was included. A different design could have strengthened our results, but our method for patient selection (under which all patients were consecutively diagnosed with EoE at our department) and the uniform clinical and histological evolution of all patients, contribute to making our results seem very plausible.

In addition, from the present study and available published information, we can conclude that the role of cysteinyl leukotrienes in EoE pathophysiology is not supported by strong evidence, and available proof hardly indicates montelukast as a treatment option in EoE patients, which should be treated with other drugs or dietary approaches that have been shown to be efficient in managing the disease [6].

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Conflict of interest None of the authors have any conflict of interest or affiliation with any of the institutions, organizations or companies mentioned in this manuscript.

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