

Efficacy of Combined Treatment on Eosinophilic Esophagitis in Adults: Case Study

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ABSTRACT

AIM: Eosinophilic esophagitis (EoE) is an increasing recognized disease involving eosinophil infiltration of the esophageal mucosa. Treatment with an anti-inflammatory agent or a proton pump inhibitor has been studied with clinical success, yet many patients relapse after completion of the treatment. We evaluated a combination regimen for symptomatic relief of patients with EoE.

METHODS: Eight patients from a single, adult gastroenterology unit with EoE were identified. Diagnosis was made by histological findings in addition to clinical symptoms. All the patients received 12-week treatment with combined oral pantoprazole 40 mg, montelukast 10 mg and swallowed fluticasone 880 micrograms daily. No maintenance medication was routinely used after the treatment.

RESULTS: Seven men and one woman with mean age at 35 years were evaluated. Seven patients presented with food impaction. Five patients had typical ringed-appearing esophagus. All patients had eosinophilic infiltration more than 15 per high power field histologically. Five patients (62.5%) had resolved or improved symptoms after the treatment. Two patients (25%) had recurrent but less severe symptoms 2 and 12 months after the treatment, respectively.

CONCLUSIONS: EoE affects predominantly middle-aged men and commonly presents with food impactions. The regimen of combined pantoprazole, montelukast and fluticasone might be effective in treating EoE and reducing recurrent symptoms. Additional studies, however, are warranted to further investigate the efficacy.

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Key words: Eosinophilic esophagitis; Pantoprazole; Montelukast;

Fluticasone

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INTRODUCTION

Eosinophilic esophagitis (EoE) is a primary clinicopathologic disorder of the esophagus. Although there are different diagnostic criteria in the literature, American Gastroenterology Association (AGA) institute made a consensus definition of EoE in 2007^[1], in which absence of pathologic gastroesophageal reflux disease (GERD) and a minimal of 15 intraepithelial eosinophil/high power field (HPF) in one or more biopsy specimens are required for the diagnosis of EoE.

Treatment of EoE remains difficult due to a poor understanding of etiologies and pathogenesis of the disease. Different regimens have been studied with variable success^[2-5]. Current attempted therapies consist of dietary restriction^[4], systemic or topical corticosteroids^[2,3], montelukast^[5], proton pump inhibitors (PPIs)^[6], and mechanical dilation^[7]. The most common clinical issue after a course of treatment, commonly 6-8 weeks, is frequent symptomatic recurrence^[5,8]. Repeated treatment is often required in patients with EoE. Given the possible multifactorial components in the pathogenesis of EoE, we postulated that a combined therapy by targeting different potential mechanism pathways of the disease might optimize the outcome of the treatment in EoE patients. In the present study, we evaluated the efficacy of a novel treatment for EoE using combined swallowed corticosteroid (fluticasone), oral montelukast and a PPI (pantoprazole).

METHODS

The study was approved by our Institutional Review Board. We have identified eight patients who were diagnosed with EoE since November 2006. The diagnosis was made by a combination of clinical symptoms and a peak count of eosinophils ≥ 15 /HPF in the esophageal mucosa. Patients with concomitant eosinophilic infiltration in the gastric mucosa were excluded because a different

entity, eosinophilic gastroenteritis, might be involved.

Symptomatic patients underwent endoscopy and random biopsies by a single gastroenterologist. The biopsies were reviewed by the pathologists at our institute. A peak count of esophageal eosinophils of ≥ 15 under a HPF was defined as mild, ≥ 20 as moderate and ≥ 30 as prominent infiltration.

Once the diagnosis was established, the patients were instructed to take a total 12-week course of medications of 2 puffs of fluticasone (220 mg/puff) swallowed twice daily, 10 mg montelukast once daily, and 40 mg pantoprazole once daily. Patients were instructed to swallow fluticasone without a spacer and to avoid drinking or eating 30 min after taking the medication. The patients were also instructed to rinse their mouths with water 30 min after fluticasone to minimize the side effect of oral thrush. The doses of medications and course of treatment in the present study were based on the literature^[1].

Telephone interview with a questionnaire was used to assess patients' symptoms, severity of the disease and response to medications prior to and after the treatment of combined medications (Table 1). The collected information included presenting symptoms, severity and frequency of the symptoms, use of PPIs prior to the treatment, response to medications, and recurrence of symptoms. The efficacy of the therapy was evaluated clinically. Repeated endoscopy and biopsies were not routinely performed.

Among eight patients, seven (87.5%) presented with food impaction, three (37.5%) with dysphagia, and two (25%) with both symptoms. Five of eight patients were on PPIs for a few months to five years prior to the diagnosis of EoE. The other three patients did not receive any medical treatment. Five patients reported history of endoscopy. Two patients were found to have Schatzki ring, one with a co-existent duodenal ulcer. The other three patients did not reveal endoscopic abnormality of the upper gastrointestinal tract.

All eight patients rated their symptoms as moderate or severe. Four of them reported affected quality of life due to the frequent symptoms. Three patients also had ER visits in the past. One type of food (e.g. meat, bread, rice) appeared to be more problematic than other types of food in these studied patients. No specific maneuver helped to relieve the symptoms except some patients reported slight improvement with slow swallowing and/or drinking water with food. Endoscopy was performed in all eight patients by a single gastroenterologist. Among the eight patients, three (37.5%) had Schatzki ring, four (50%) had hiatal hernias, and five (62.5%) had non-erosive gastropathy. Random biopsies of the esophagus showed eosinophil infiltration in the epithelium being mild in two patients, moderate in two patients, and prominent in four patients. The extent of eosinophil infiltration was not co-related to the frequency or severity of the symptoms.

Table 1 Questionnaire.

Before being diagnosed with EoE	
What are your symptoms?	[difficulty of swallowing; pain during swallowing; heartburn; food impaction]
How do you grade your symptoms?	[absent; mild; moderate; severe]
How often do you have symptoms?	[yearly; monthly; weekly; daily; constant]
What type of food is more problematic?	[water; banana; vegetables; bread; meats; nothing specific]
How long have you been on a Proton Pump Inhibitor?	
Has the symptoms improved after a Proton Pump Inhibitor?	[no; slightly; significantly; symptom free; improved but symptoms recurred]
Do you feel certain food restriction helping with the symptoms?	[no; slightly; significantly; improved but symptoms recurred]
Do the symptoms affect your quality of life?	[yes; no]
Are there any maneuvers that help you with the symptoms?	[swallow slowly; drink water; nothing helps]
How many endoscopies did you have in the past?	
How many Emergency Room visits did you have?	
After being diagnosed with EoE	
Are you on any medications for EoE now?	[no; yes] If yes, what are they and what dose you are on? For how long?
How often do you have symptoms now?	[absent; yearly; monthly; yearly; daily; constant]
How do you grade your symptoms now?	[absent; mild; moderate; severe]
Have your symptoms recurred after the treatment?	[no; yes] If yes, how long after the treatment?
Have you ever had esophageal dilation?	[no; yes]
Have you noticed any side effects of the medications?	[no; yes] If yes, what are they?

RESULTS

Seven men and one woman with EoE were included with mean age of 35, ranging from 25 to 45 years of old. Demographic and clinical data for the eight patients are shown in Table 2. None of the patients had a history of smoking and four of eight reported drinking alcohol occasionally. Use of coffee or tea was identified in five patients. Two patients had a history of asthma and two had seasonal allergy.

Table 2 Demographic and clinical features of the studied patients.

Patient	Age (yr)	Sex	Allergy	Atopy	History of	PPIs
#1	30	M	Food	None	None	Yes
#2	25	M	Food	Seasonal allergy	None	No
#3	30	M	Penicillin	Asthma	None	Yes
#4	45	M	None	None	Schatzki ring	Yes
#5	36	M	Food	Asthma	Schatzki ring	Yes
#6	42	M	None	None	None	No
#7	31	M	None	Seasonal allergy	None	No
#8	41	F	Food	None	GERD	Yes

M: male, F: female, GERD: gastroesophageal reflux disease; PPIs: proton pump inhibitors.

All eight patients completed a 12-week course of treatment with fluticasone, montelukast and pantoprazole after being diagnosed with EoE. No drug related side effects including oral thrush were reported by the patients. The comparison of clinical responses to medications before and after the treatment is shown in Table 3. Seven (87.5%) patients reported either complete resolution or improvement of the symptoms after the combination therapy. One patient (#6) found only minimal improvement after completion of the treatment and was reluctant to continue the medications. Three patients (37.5%) reported complete resolution of the symptoms and remained asymptomatic during follow-up periods between 13 to 25 months. Two of these three patients were not on any maintenance medications and one used a daily PPI. Two patients reported significantly reduced symptoms in severity and frequency after the treatment, yet still suffered from mild symptoms occasionally during the 13 to 15 months of follow-up. One patient had complete resolution of the symptoms but recurred twelve months after the treatment. The recurrent symptoms were reported as mild and only occurred once or twice during a six months period.

The patient did not have repeated treatment. One patient complained of recurrent symptoms two months after the treatment and was retreated with the same 12-week regimen. However, relapsed symptoms again were noticed eight months after the second trial of medications. The patient remained asymptomatic three months after the second trial.

as early as 2 months after completion of the treatment.

The end-points and efficacy assessment of therapy for patient with EoE are still controversial. Criteria such as improvement in histologic features of esophageal eosinophils, or in endoscopic appearances, or in clinical symptoms have been applied in different studies^[2,8,10]. No data, however, indicate whether endoscopic and/

Table 3 Comparison of clinical features before and after the 12-week course of treatment with combined fluticasone, montelukast, pantoprazole.

Patient	Before the treatment						After the treatment						
	Presenting symptoms	Severity	Frequency	Food	Relieving symptoms	EGD number	ER visits	Current medications	Recurrence sym	Reurrence time	Repeated treatment	Symptoms	
												Frequency	Severity
#1	FI	severe	mon-yr	bread	none	1	1	none	no	-	-	absent	-
#2	FI, Dys	moderate	daily	meat	drink water	1	0	none	yes	2 mo,	yes	absent	-
#3	FI	severe	mon	none	swallow slowly	0	1	PPI	8 mo	yes	yes	absent	-
#4	FI	severe	mon-yr	meat	none	0	0	none	no	-	-	absent	-
#5	FI	moderate	mon	meat	swallow slowly	1	1	none	no	-	-	yr	mild
#6	FI	moderate	daily	none	swallow slowly	1	0	none	yes	12 mo	no	daily	moderate
#7	FI, Dys	severe	daily	none	none	1	0	PPI	no	-	-	mon	mild
#8	Dys	moderate	daily	rice	drink water, restrict rice	0	0	none	no	-	-	yr	mild

FI: food impaction; Dys: dysphagia; mo: monthly; yr: yearly; EGD: esophagogastroduodenoscopy; ER: emergency room; PPI: proton pump inhibitor; mo: month.

DISCUSSION

EoE is an esophageal disease involving dense eosinophil infiltration in the squamous epithelium. Although the natural history of EoE is benign^[9], the related symptoms can notoriously affect patient's quality of life. The pathophysiology of the disease, however, remains unclear and probably multifactorial. Medications used in the treatment of EoE such as corticosteroids^[2,10], leukotriene receptor inhibitors^[5], PPIs^[6], anti-IL-5 mepolizumab^[11], and cromolyn sodium^[12] have all been studied targeting at different site of potential pathways. The present study applied the first three above-mentioned medications as the combined therapy.

Clinical improvement to fluticasone was demonstrated in about 90% of EoE patients with 21% histological resolution^[8,10]. Study also showed 87% of complete resolution of dysphagia after montelukast^[5]. The relationship between EoE and GERD is not clear. EoE was initially described in patients with GERD who showed poor response to anti-acid therapy^[13]. Histologically, eosinophilic infiltration in the esophageal mucosa was observed both in GERD and EoE but with a higher density in the latter^[14]. Some studies supported that GERD might contribute to the pathogenesis of EoE and might also coexist with EoE^[6,15,16]. A small study showed that PPI appeared to be effective on relieving dysphagia in patients with EoE^[17]. Due to the potential multi-factorial pathogenesis of EoE, the present study used a combined treatment of a corticosteroid, a leukotriene receptor inhibitor and a PPI targeting different pathways in attempt to optimize clinical outcomes.

Another rationale of using a combined therapy was to investigate its potential benefits on reducing symptom relapse^[5,8]. Studies have shown that six of eight (75%) patients who received montelukast experienced recurrence within 3 weeks of cessation or reduction in medication^[5]. Similarly, among patients who were treated with fluticasone, about 73% developed relapse symptoms at the 3-month^[8], and 60% at a 3-year follow-up^[18]. Patients with EoE often require prolonged treatment or repeated therapy after initial success^[5,18]. The mechanisms of high recurrence rate in the management of EoE remain unknown. Premature termination of a treatment, alternative pathogenic pathways of the disease, or re-activation of the previously subsided process are some of the possible mechanisms. In the present study, three of eight (37.5%) patients had complete resolution and two of eight (25%) patients had improved symptoms without recurrence or worsening of the symptoms. Two of eight (25%) patients reported recurrent symptoms

or histologic improvement is required to achieve for optimal outcome in patients with EoE. The present study applied clinical improvement as our main tool for efficacy evaluation. Each patient is used as own control. Only one patient underwent a post-treatment endoscopy, which revealed unchanged endoscopic findings but resolution of intra-epithelial eosinophil infiltration. However, given the patchy distribution of eosinophil infiltration, it is difficult to interpret the significance of the histological change in one case. Clinically, this patient remained symptomatic after the treatment.

There are a few limitations with current study. This is a case study without randomization or placebo control. We only have a small sample with eight adult patients and all patients are followed-up by a single gastroenterologist. In addition, longer period of follow-up after the treatment would be preferable.

In summary, EoE predominantly affects middle-aged men and commonly presents as food impaction and/or dysphagia. The combined treatment with swallowed fluticasone, oral montelukast and pantoprazole might be effective on relieving symptoms and reducing relapse. However, additional studies are warranted to further investigate the efficacy of the combined treatment on patients with EoE.

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