

A randomized, double-blinded, placebo-controlled study of the use of viscous oral cromolyn sodium for the treatment of eosinophilic esophagitis



Jay Adam Lieberman, MD ^{*}; Jie Zhang, MD [†]; John Whitworth, MD ^{*}; Cary Cavender, MD ^{*}

^{*} Department of Pediatrics, The University of Tennessee Health Science Center, Memphis, Tennessee

[†] Department of Pathology, The University of Tennessee Health Science Center, Memphis, Tennessee

ARTICLE INFO

Article history:

Received for publication January 4, 2018.

Received in revised form February 12, 2018.

Accepted for publication March 6, 2018.

ABSTRACT

Background: There is a need for effective, nonsteroid pharmacologic therapies for eosinophilic esophagitis (EoE). Cromolyn sodium offers an option because mast cells have been implicated in the symptomatology of EoE and cromolyn has been shown to have some anti-eosinophilic properties.

Objective: To evaluate the efficacy of cromolyn in decreasing esophageal eosinophilia in patients with EoE. Secondary outcomes included symptom improvement and adverse effects.

Methods: We conducted a randomized, double-blinded, placebo-controlled trial of viscous oral cromolyn for EoE in pediatric patients. Subjects were randomized to 100 mg (2–11 years of age) or 200 mg (12–17 years of age) of cromolyn or placebo 4 times daily. The medications were mixed with powdered sugar at home to make them viscous.

Results: Sixteen subjects (50% boys, median age 11.4 years) were enrolled. Nine were randomized to cromolyn and 7 were randomized to placebo. Cromolyn decreased the peak eosinophil count from 62.1 to 57.3 eosinophils per high-powered field ($P = .78$) and placebo decreased the peak eosinophil count from 87.0 to 71.3 eosinophils per high-powered field ($P = .62$). One subject randomized to cromolyn and none in the placebo arm had complete resolution of eosinophilia. Cromolyn decreased symptom scores from a mean baseline score of 37.8 to a mean post-therapy score of 17.5, which was a 54% decrease ($P = .04$). Placebo decreased the symptom scores from a baseline score of 32.2 to a post-therapy score of 23.3, which was a 28% decrease ($P = .05$).

Conclusion: Cromolyn, when mixed into a viscous preparation, did not significantly decrease esophageal eosinophilia. However, it did decrease symptom scores (although not significantly more than placebo) and led to complete resolution in 1 subject.

© 2018 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.

Introduction

Eosinophilic esophagitis (EoE) is a clinicopathologic disease that appears to be increasing in prevalence in the United States.^{1,2} In the pediatric population, the disease typically manifests as abdominal pain, dysphagia, reflux, nausea, and vomiting, a symptom pattern that can lead to failure to thrive.³ Although few natural history

studies exist, available data suggest that if left untreated, EoE is likely to lead to a fibro-stenotic phenotype that can lead to food impactions, possibly requiring emergency removal of food boluses, and risk for esophageal wall rupture with dilations.^{4,5}

The exact etiology of EoE has not yet been elucidated; however, most data suggest that the disease is immune mediated and antigen driven. This has been proved clinically by demonstrating that most patients will have resolution of symptoms and histologic findings after treatment with an amino acid-based formula that is devoid of protein antigens.^{6,7}

Currently, treatment options for patients with EoE include dietary therapy and/or pharmacotherapy.¹ Dietary therapy can be accomplished with elemental or elimination (empiric or allergy-test driven) diets.⁷ Although the elemental diet is typically more effective, it can be very difficult to adhere to. The disadvantage of elimination diets is that there are no reliable tests to predict which foods will be the trigger in any given patient. Pharmacotherapy for EoE entails swallowing respiratory preparations of corticosteroids so that they can

Reprints: Jay Adam Lieberman, MD, Department of Pediatrics, The University of Tennessee Health Science Center, 51 North Dunlap, Suite 400, Memphis, TN 38105; E-mail: jlieber1@uthsc.edu.

Disclosures: Dr Lieberman is an associate editor for *Annals of Allergy, Asthma, & Immunology*. He has served on the advisory board for Aimmune Therapeutics. He is a principal investigator for clinical trials sponsored by Aimmune Therapeutics and Biotest Pharma. Drs Zhang, Whitworth, and Cavender have no conflicts of interest to report.

Funding Sources: This study was funded in part through the American College of Allergy, Asthma, and Immunology Young Investigator Award (to Dr Lieberman). Trial Registration: [ClinicalTrials.gov](https://clinicaltrials.gov) Identifier NCT02371941.

<https://doi.org/10.1016/j.anaai.2018.03.006>

1081-1206/© 2018 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.

act topically on the esophagus. Double-blinded, randomized, placebo-controlled trials have shown efficacy of swallowed fluticasone and budesonide (and case reports providing data on other corticosteroids).⁸ Unfortunately, there is no consensus on the duration of therapy, and studies to date have shown recurrence of eosinophilia and symptoms within months of stopping therapy, even with addition of steroid-sparing agents, such as montelukast.^{9–11}

Given that none of the current treatment options are ideal, there is clearly a need for novel and effective therapies for EoE. One candidate therapy that is yet to be formally studied is oral cromolyn sodium, which has been reported on retrospectively in only a very small number of patients.¹² Cromolyn is an attractive alternative to swallowed steroids for a number of reasons. First, oral cromolyn has minimal to any systemic absorption. In fact, in studies of adults and children, less than 1% of orally administered cromolyn gets absorbed.¹³ Hence, cromolyn is a first-line agent in the treatment of the gastrointestinal manifestation of systemic mastocytosis, but not for the systemic manifestations of the disease. Second, because of its poor absorption, the side effect profile of cromolyn sodium is almost nonexistent, and it is approved by the Food and Drug Administration for use in patients 2 years of age.¹⁴ Third, data exist to show increased numbers of mast cells in the esophageal epithelium and smooth muscle (muscularis mucosa) of patients with EoE vs controls.¹⁵ This same report showed that mast cells expressed transforming growth factor- β 1 and that transforming growth factor- β 1 could induce human esophageal smooth muscle contraction *in vitro*, thus perhaps contributing to the symptoms of EoE. Fourth, cromolyn, when inhaled and used by patients with asthma, causes a decrease in sputum eosinophils; and the clinical benefit in asthma has been directly linked to a decrease in eosinophils in bronchial alveolar lavage specimens.¹⁶ In fact, after 16 weeks of treatment with inhaled cromolyn, researchers found a significant decrease in activated eosinophils in bronchial submucosa, an effect that was similar to treatment with fluticasone propionate, but not seen with placebo or salmeterol.¹⁷

Based on these properties of cromolyn, we designed a randomized, double-blinded, placebo-controlled trial of viscous oral cromolyn for the treatment of EoE.

Methods

Subjects

We enrolled pediatric subjects 2 to 17 years of age from 2014 to 2016 with a diagnosis of EoE (≥ 15 eosinophils per high power field [eos/hpf]) despite at least 8 weeks of therapy with a high-dose proton pump inhibitor or a normal esophageal pH probe. Exclusion criteria included concomitant treatment with swallowed corticosteroids (any prior use of swallowed corticosteroids required an 8-week washout period), pregnancy, evidence of pathologic eosinophilia in other locations in the gastrointestinal tract, active participation in another research protocol, and/or renal or hepatic insufficiency.

Treatment

Subjects were randomized (in a block fashion) to receive cromolyn sodium or placebo. The cromolyn was kindly provided free of charge by Meda Pharmaceuticals (Somerset, New Jersey) and later by Mylan (Canonsburg, Pennsylvania). The 2 treatments were in plastic tubes containing 5 mL of the assigned treatment. Subjects were told to mix 1 vial with 1 tablespoon of powdered sugar to make a viscous preparation and take orally 4 times daily after meals and before bedtime. They were instructed not to eat or drink for 30 minutes after dosing. Subjects 2 to 12 years of age were to take 1 vial (100 mg if assigned to cromolyn) 4 times daily and sub-

jects 12 to 18 years of age were instructed to take 2 vials (200 mg if assigned to cromolyn) 4 times daily.

Outcomes

The primary outcome of this study was the change in peak esophageal eosinophilia after 8 weeks of therapy. Secondary objectives included the change in symptom score at 4 and 8 weeks of therapy and adverse events of therapy. Symptom scores were assessed using the Pediatric Eosinophilic Esophagitis Symptom Score (PEESS).¹⁸ Post hoc staining of biopsy specimens using tryptase as a marker of mast cell burden and counting tryptase plus cells per high-powered field was performed.

Statistics

To establish a power calculation, an a priori power of the primary end-point analysis was estimated using Fisher exact test with .05 and 2-tailed significance level. Assuming a histologic response rate of 80% in the oral viscous cromolyn group and 10% in the placebo group, there was 85% power to detect a significant between-group difference with sample sizes of 10 subjects in each group. Within-group differences were calculated using the Mann-Whitney *U* test and change from baseline between placebo and cromolyn for changes in peak eosinophilia and symptoms scores were calculated using an analysis of covariance. All statistics were analyzed using SPSS software (IBM Corporation, Armonk, New York).

Results

We enrolled 16 patients; 9 were randomized to cromolyn and 7 were randomized to placebo. One subject in the placebo group dropped out because of uncontrolled gastrointestinal symptoms before any post-therapy data collection. The study flow is presented in Figure 1. The average age of subjects was 11.5 years, 50% were boys, and 100% were Caucasian. Seven subjects (43.8%) had atopy (as defined by a positive skin test reaction to any allergen and corresponding atopic condition). There was no difference between treatment groups. Of note, this population is slightly skewed with a larger female proportion compared with other cohorts of patients with EoE. Table 1 presents the background information for subjects in the 2 treatment groups.

Histologic Changes

Neither cromolyn nor placebo significantly decreased the peak eosinophil count. Cromolyn decreased the peak eosinophil count

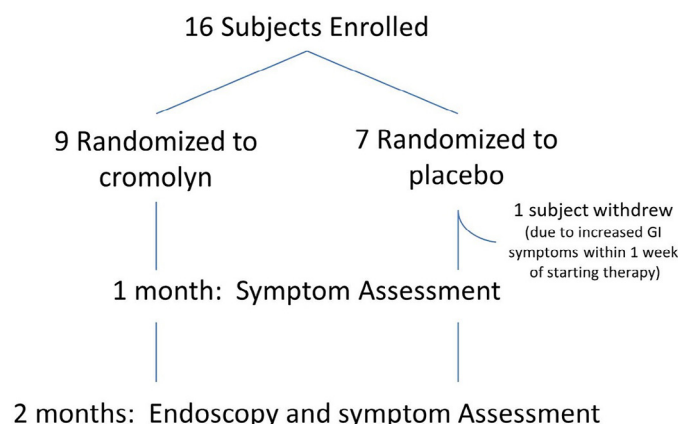


Figure 1. Study flow diagram.

Table 1
Baseline Status of Subjects

	All subjects (N = 16)	Cromolyn (n = 9)	Placebo (n = 7)	P value
Age (y), mean $\pm$ SD	11.5 $\pm$ 4.0	10.4 $\pm$ 4.1	12.8 $\pm$ 3.7	.24
Boys, n (%)	8 (50)	4 (44.4)	4 (57.1)	1.00
Atopy, n (%)	7 (43.8)	5 (55.6)	2 (28.6)	.36
Duration of symptoms (y), mean $\pm$ SD	3.4 $\pm$ 2.7	4.0 $\pm$ 3.5	2.8 $\pm$ 1.7	.42
History of food impaction, n (%)	7 (43.8)	4 (44.4)	3 (42.9)	1.00
Peak eosinophil count/hpf, mean $\pm$ SD	73.8 $\pm$ 37.6	62.1 $\pm$ 24.9	87.0 $\pm$ 51.5	.16

Abbreviation: hpf, high-powered field.

from 62.1 to 57.3 eos/hpf ($P = .78$) and placebo decreased the peak eosinophil count from 87.0 to 71.3 eos/hpf ($P = .62$). Peak eosinophil count changes for the 2 groups are shown in Figure 2. The change from baseline was not different between the placebo and cromolyn groups ($P = .64$). There was 1 complete responder (defined by a post-therapy eosinophil count of 0 eos/hpf at all levels) in the cromolyn group and none in the placebo group. There were 3 subjects in the cromolyn group and 1 in the placebo group who had a decrease greater than 50% in peak eosinophil count.

Symptom Changes

Cromolyn decreased symptoms scores from a mean baseline score of 37.8 to a mean post-therapy score of 17.5, which was a 54% decrease ($P = .04$). Placebo decreased the symptom scores from a mean baseline score of 32.2 to a mean post-therapy score of 23.3, which was a 28% decrease ($P = .05$). Symptom scores for the 2 groups are shown in Figure 3. The greater change in improvement in the cromolyn group was not statistically significant ($P = .37$).

Mast Cells

In a post hoc analysis, we stained available slides with tryptase and counted tryptase plus cells as a marker for mast cell burden. There was no correlation between mast cell burden and symptom score in our patient population (Spearman $r = -0.07$, $P = .75$). In addition, there was no correlation of symptom resolution and change in mast cell burden (data not shown).

Adverse Events

There were no serious adverse events in either group. The most common adverse events reported throughout the study were nausea (56% in the cromolyn group and 17% in the placebo group) and abdominal pain (44% in the cromolyn group and 33% in the placebo group) and these were not related to doses. One subject in the placebo arm withdrew from the study within 1 week of study entry because of uncontrolled gastrointestinal symptoms, believed to be a flare in her EoE. The full list of adverse events is presented in Table 2.

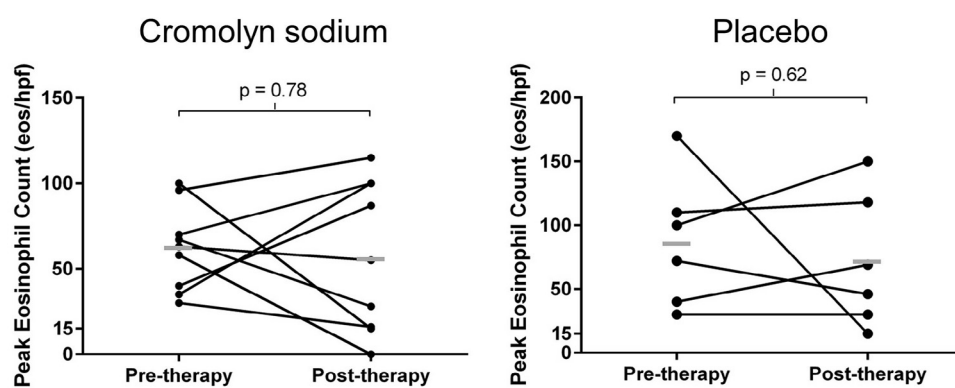
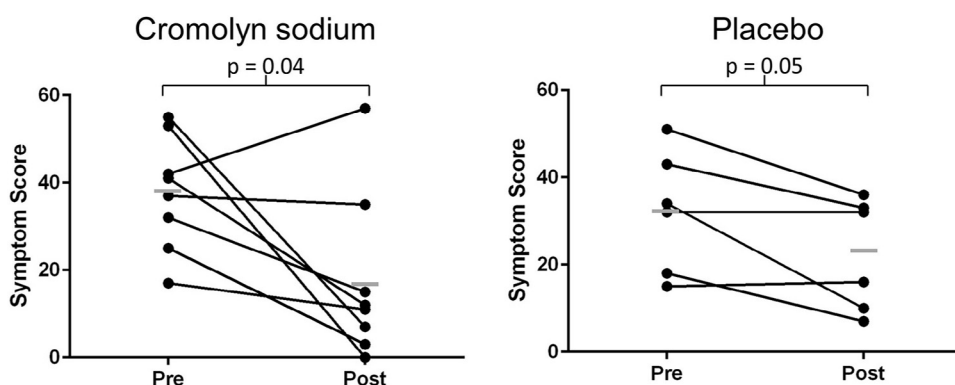
**Figure 2.** Peak eosinophil counts per high-powered field (eos/hpf) before and after therapy in the cromolyn and placebo groups. Gray bars represent means.**Figure 3.** Symptom scores before and after therapy in the cromolyn and placebo groups. Gray bars represent means.

Table 2
Adverse Events Reported (Number of Subjects Reporting in Each Group)

Adverse event	Cromolyn group	Placebo group
Nausea	5	1
Abdominal pain	4	2
Headache	4	1
Vomiting	2	1
Upper respiratory tract infection	2	1
Fatigue	2	0
Sore throat	2	0
Lip swelling	1	0
Sinus infection	1	1
Dysphagia	1	0
Diarrhea	1	0
Eye pain	1	0
Mood change	1	0
Hypernatremia	1	0

Discussion

We report on the results of a randomized, double-blinded, placebo-controlled study of viscous cromolyn sodium in the treatment of pediatric and adolescent patients with EoE. Our results suggest that viscous cromolyn is not effective in decreasing esophageal eosinophilia beyond that of placebo. However, there are several interesting findings from this study.

First, cromolyn completely resolved the eosinophilia in 1 of the 9 subjects treated and alleviated eosinophilia in another 2 subjects (85% and 50% decreases in peak eosinophil counts). No subjects in the placebo group had resolution and 1 subject in the cromolyn group had improvement. Thus, there could be certain responders to this therapy. Although it might make sense that the responders might have more evidence of an atopic diathesis, post hoc review did not show that these subjects had any more atopic diseases or more positive skin test reactions to inhalant or food allergens than those who did not respond to therapy. However, given the limited number of subjects in this study, any statistical analysis of this could not be done.

Treatment adherence could be another explanation. However, adherence rates were surprisingly high in this study, although the active and placebo treatments required dosing 4 times a day. Rates of adherence ranged from 69% to 94% based on the number of doses returned and did not differ between placebo and cromolyn. There was no evidence that increased adherence led to an increased response.

Second, cromolyn did lead to an overall 54% decrease in symptoms. Unfortunately, this was not statistically significantly better than placebo (which improved overall symptoms by 32%), but our study was not powered to detect this. We do believe that a 54% decrease in symptoms is quite fascinating, because mast cells are clearly seen in the epithelium of patients with EoE,^{19,20} and mast cells in the lamina propria or near the smooth muscle have been implicated in the disease process.¹⁵ In addition, to date, the role that eosinophils play in the symptomatology of EoE is unclear, with studies showing that tissue eosinophilia does not always correlate with symptoms and resolution of eosinophilia does not always correlate with resolution of symptoms (a findings mirrored in our study).^{18,21} However, in our small study, mast cell burden in the biopsy specimens did not show any correlation with symptom scores or any association with treatment response, unfortunately. However, simple staining of tryptase might not accurately describe mast cell activity and we could not assess mast cell burden in the lamina propria, where they might play a stronger role in symptoms.

Another explanation for response could be simply how much contact time the medication was able to have in the esophagus. Examination into swallowed topical steroids has suggested that contact

time on the esophagus appears to be of importance to treatment response.²² Other studies have shown that the thickening agent used to make the medication viscous might not be important, because various agents have been used.^{23,24} In our study, we did not specifically measure the viscosity of the preparation; however, we did, informally, visually compare our slurry with the budesonide-sucralose slurry and we designed the ratio of cromolyn to powdered sugar to be visually comparable.

Our study has several limitations. First, we enrolled slightly lower than the initial planned enrollment goal, thus decreasing our power. However, because we did not find any differences in the primary outcome, we do not believe this would have changed any outcomes.

Second, because of the small numbers of subjects, we could not make any conclusions regarding treatment responders and whether there were markers that would allow prediction of responders (symptomatically and/or histologically). Third, we did not power the study to examine symptoms, and the symptom scoring tool that we used is not a validated tool.

In conclusion, we report data from a randomized, double-blinded, placebo-controlled trial of viscous oral cromolyn for EoE. In this study, cromolyn did not alleviate esophageal eosinophilia to a greater degree than placebo. Interestingly, cromolyn did decrease symptoms by 54% (although this was not a statistically significant improvement over placebo) and 1 patient in the active arm had complete resolution of eosinophilia and symptoms. Given this finding and the excellent side effect profile of this medication, it is reasonable to investigate this product further as a steroid-sparing agent.

References

- Liacouras CA, Furuta GT, Hirano I, et al. Eosinophilic esophagitis: updated consensus recommendations for children and adults. *J Allergy Clin Immunol*. 2011; 128:3.e26–20.e26, quiz 21–22.
- Prasad GA, Alexander JA, Schleck CD, et al. Epidemiology of eosinophilic esophagitis over three decades in Olmsted County, Minnesota. *Clin Gastroenterol Hepatol*. 2009;7:1055–1061.
- Spergel JM, Brown-Whitehorn TF, Beausoleil JL, et al. 14 years of eosinophilic esophagitis: clinical features and prognosis. *J Pediatr Gastroenterol Nutr*. 2009; 48:30–36.
- Straumann A, Bussmann C, Zuber M, et al. Eosinophilic esophagitis: analysis of food impaction and perforation in 251 adolescent and adult patients. *Clin Gastroenterol Hepatol*. 2008;6:598–600.
- DeBrosse CW, Franciosi JP, King EC, et al. Long-term outcomes in pediatric-onset esophageal eosinophilia. *J Allergy Clin Immunol*. 2011;128:132–138.
- Kelly KJ, Lazenby AJ, Rowe PC, et al. Eosinophilic esophagitis attributed to gastroesophageal reflux: improvement with an amino acid-based formula. *Gastroenterology*. 1995;109:1503–1512.
- Arias A, Gonzalez-Cervera J, Tenias JM, et al. Efficacy of dietary interventions for inducing histologic remission in patients with eosinophilic esophagitis: a systematic review and meta-analysis. *Gastroenterology*. 2014;146:1639–1648.
- Lieberman JA. Pharmacotherapy for eosinophilic esophagitis. *Ann Allergy Asthma Immunol*. 2015;114:357–363.
- Helou EF, Simonson J, Arora AS. 3-yr-follow-up of topical corticosteroid treatment for eosinophilic esophagitis in adults. *Am J Gastroenterol*. 2008;103: 2194–2199.
- Lucendo AJ, De Rezende LC, Jimenez-Contreras S, et al. Montelukast was inefficient in maintaining steroid-induced remission in adult eosinophilic esophagitis. *Dig Dis Sci*. 2011;56:3551–3558.
- Alexander JA, Ravi K, Enders FT, et al. Montelukast does not maintain symptom remission after topical steroid therapy for eosinophilic esophagitis. *Clin Gastroenterol Hepatol*. 2017;15:214–221.e212.
- Liacouras CA, Spergel JM, Ruchelli E, et al. Eosinophilic esophagitis: a 10-year experience in 381 children. *Clin Gastroenterol Hepatol*. 2005;3:1198–1206.
- Edwards AM, Holgate ST. Chapter 90. The Chromones: Cromolyn Sodium and Nedocromil Sodium. In: Adkinson NF Jr, Bochner BS, Burks AW, et al. Middleton's Allergy: Principles and Practice. 7th ed. Philadelphia: Mosby Elsevier; 2009.
- Celltech Pharmaceuticals, Inc. Gastrocrom Package Insert. Rochester, NY: Celltech Pharmaceuticals; 2006.
- Aceves SS, Chen D, Newbury RO, et al. Mast cells infiltrate the esophageal smooth muscle in patients with eosinophilic esophagitis, express TGF-beta1, and increase esophageal smooth muscle contraction. *J Allergy Clin Immunol*. 2010; 126:1198–1204, e1194.
- Diaz P, Galleguillos FR, Gonzalez MC, et al. Bronchoalveolar lavage in asthma: the effect of disodium cromoglycate (cromolyn) on leukocyte counts, immunoglobulins, and complement. *J Allergy Clin Immunol*. 1984;74:41–48.

- [17] Lindqvist A, Karjalainen EM, Laitinen LA, et al. Salmeterol resolves airway obstruction but does not possess anti-eosinophil efficacy in newly diagnosed asthma: a randomized, double-blind, parallel group biopsy study comparing the effects of salmeterol, fluticasone propionate, and disodium cromoglycate. *J Allergy Clin Immunol*. 2003;112:23–28.
- [18] Penttinen S, Putnam PE, Collins MH, et al. Dissociation between symptoms and histological severity in pediatric eosinophilic esophagitis. *J Pediatr Gastroenterol Nutr*. 2009;48:152–160.
- [19] Kirsch R, Bokhary R, Marcon MA, et al. Activated mucosal mast cells differentiate eosinophilic (allergic) esophagitis from gastroesophageal reflux disease. *J Pediatr Gastroenterol Nutr*. 2007;44:20–26.
- [20] Mulder DJ, Mak N, Hurlbut DJ, et al. Atopic and non-atopic eosinophilic oesophagitis are distinguished by immunoglobulin E-bearing intraepithelial mast cells. *Histopathology*. 2012;61:810–822.
- [21] Spergel JM, Rothenberg ME, Collins MH, et al. Reslizumab in children and adolescents with eosinophilic esophagitis: results of a double-blind, randomized, placebo-controlled trial. *J Allergy Clin Immunol*. 2012;129:456–463, e451–453.
- [22] Dellon ES, Sheikh A, Speck O, et al. Viscous topical is more effective than nebulized steroid therapy for patients with eosinophilic esophagitis. *Gastroenterology*. 2012;143:321.e321–324.e321.
- [23] Rubinstein E, Lee JJ, Fried A, et al. Comparison of 2 delivery vehicles for viscous budesonide to treat eosinophilic esophagitis in children. *J Pediatr Gastroenterol Nutr*. 2014;59:317–320.
- [24] Hefner JN, Howard RS, Massey R, et al. A randomized controlled comparison of esophageal clearance times of oral budesonide preparations. *Dig Dis Sci*. 2016; 61:1582–1590.