Supplemental Materials

Supplemental Methods

Overview of the parent clinical trial

This study was the observation phase of a randomized clinical trial comparing OVB to MDI for initial treatment of EoE; the full details of the parent study (clinicaltrials.gov NCT02019758) have been previously reported,[1] and are summarized in the Supplemental Materials. The study was approved by the UNC IRB, and all authors had access to the study data and reviewed and approved the final manuscript. In brief, patients aged 16-80 with a new diagnosis of EoE per consensus guidelines at the time of study design were included.[2, 3] Patients had symptoms of esophageal dysfunction, at least 15 eosinophils per high-power field (eos/hpf) in esophageal biopsies after a high-dose PPI trial, and exclusion of competing causes of esophageal eosinophilia. While patients with severe esophageal strictures precluding the passage of a standard adult endoscope were excluded, patients with less severe strictures could be enrolled and dilation could be performed at the endoscopist discretion. There was no symptom threshold requirement for entry. After informed consent was obtained and baseline measures were collected, subjects were randomized 1:1 to either OVB 1mg/4mL BID + placebo inhaler or fluticasone MDI 880 mcg BID + placebo slurry. After 8 weeks of treatment, endoscopy was repeated and outcome measures were collected. During this phase, all subjects, investigators, and study staff (save the investigational drug pharmacist) were masked as to treatment allocation.

Statistical analysis and sample size considerations

For sample size considerations, based on estimates in the literature at the time of the parent clinical trial design, we expected at least 80% of subjects in the OVB arm,[4-7] and at least

50% of subjects in the fluticasone MDI arm,[8-12] to have a histologic response (<15 eos/hpf) after the initial treatment period. Therefore, we anticipated that approximately 42 subjects in the OVB arm and 27 subjects in the MDI arm would enter the follow-up period. Though there were no prospective comparative data on symptomatic or histologic recurrence rates for these two medications, based on these sample sizes and estimating a recurrence rate of 80% in the MDI group, we would be able to detect a hazard ratio for symptomatic recurrence of 0.43 or lower with a power of 0.8 for OVB compared with MDI. Similarly, for histologic recurrence, we would be able to detect a difference as low as 36% with a power of 0.8 for OVB compared with MDI.

Details on outcome measures

In order to quantify symptom severity at the time of recurrence or at the 1 year time point (if there were no recurrent symptoms), subjects completed the Dysphagia Symptom Questionnaire (DSQ)[13-15] and the EoE Symptom Activity Index (EEsAI).[16] The DSQ is a validated 3-question daily diary that measures dysphagia severity and frequency, with a score ranging from 0-84 (higher scores indicate more severe symptoms). The EEsAI is a validated PRO with a 7-day recall that incorporates measures of dysphagia frequency and severity, as well as dietary avoidance, modification, and slow eating. The score ranges from 0-100 (higher scores indicate more severe symptoms).

Histologic and endoscopic outcomes were also assessed. For histology, we determined the peak eosinophil count at the time of the endoscopy performed for symptom recurrence or at the 1 year follow-up. Esophageal biopsies were obtained (4 fragments from the distal esophagus and 4 fragments from the proximal esophagus) and were examined by the study pathologist

(JTW) using our previously validated and reliable protocol.[17, 18] In brief, 5 hpfs (hpf=0.24 mm^2) were examined for each of the 8 biopsy fragments in order to identify peak count. Histologic relapse was defined as a peak eosinophil count ≥15 eos/hpf. To determine endoscopic severity, the EoE Endoscopic Reference Score (EREFS) was used.[19] This is a validated and responsive measure of 5 endoscopic features of EoE: exudates (graded 0-2), rings (graded 0-3), edema (graded 0-1), furrows (graded 0-2), and stricture (graded 0-1, with estimated diameter also recorded). The score ranges from 0-9, with higher scores indicating more severe endoscopic involvement.

Supplemental references

1. Dellon ES, Woosley JT, Arrington A, et al. Efficacy of Budesonide vs Fluticasone for Initial Treatment of Eosinophilic Esophagitis in a Randomized Controlled Trial. Gastroenterology. 2019;157:65-73.e5. Epub 2019/03/16.
2. Liacouras CA, Furuta GT, Hirano I, et al. Eosinophilic esophagitis: Updated consensus recommendations for children and adults. J Allergy Clin Immunol. 2011;128:3-20.e6. Epub 2011/04/12.
3. Dellon ES, Gonsalves N, Hirano I, et al. ACG Clinical Guideline: Evidence based approach to the diagnosis and management of esophageal eosinophilia and eosinophilic esophagitis. Am J Gastroenterol. 2013;108(5):679-92.
4. Dellon ES, Sheikh A, Speck O, et al. Viscous Topical is More Effective than Nebulized Steroid Therapy for Patients with Eosinophilic Esophagitis. Gastroenterology. 2012;143:321-4.e1. Epub 2012/05/09.
5. Dohil R, Newbury R, Fox L, et al. Oral Viscous Budesonide Is Effective in Children With Eosinophilic Esophagitis in a Randomized, Placebo-controlled Trial. Gastroenterology. 2010;139:418-29. Epub 2010/05/12.
6. Gupta SK, Collins MH, Lewis JD, et al. Efficacy and Safety of Oral Budesonide Suspension (OBS) in Pediatric Subjects With Eosinophilic Esophagitis (EoE): Results From the Double-Blind, Placebo-Controlled PEER Study Gastroenterology. 2011;140 (Suppl 1):S179.
7. Straumann A, Conus S, Degen L, et al. Budesonide is effective in adolescent and adult patients with active eosinophilic esophagitis. Gastroenterology. 2010;139(5):1526-37, 37 e1. Epub 2010/08/05.
8. Alexander JA, Jung KW, Arora AS, et al. Swallowed Fluticasone Improves Histologic but Not Symptomatic Responses of Adults with Eosinophilic Esophagitis. Clin Gastroenterol Hepatol. 2012;10:742-9.e1. Epub 2012/04/06.
9. Konikoff MR, Noel RJ, Blanchard C, et al. A randomized, double-blind, placebo-controlled trial of fluticasone propionate for pediatric eosinophilic esophagitis. Gastroenterology. 2006;131(5):1381-91.
10. Moawad FJ, Veerappan GR, Dias JA, et al. Randomized controlled trial comparing aerosolized swallowed fluticasone to esomeprazole for esophageal eosinophilia. Am J Gastroenterol. 2013;108(3):366-72. Epub 2013/02/13.
11. Peterson KA, Thomas KL, Hilden K, et al. Comparison of esomeprazole to aerosolized, swallowed fluticasone for eosinophilic esophagitis. Dig Dis Sci. 2010;55:1313-9.
12. Schaefer ET, Fitzgerald JF, Molleston JP, et al. Comparison of oral prednisone and topical fluticasone in the treatment of eosinophilic esophagitis: a randomized trial in children. Clin Gastroenterol Hepatol. 2008;6(2):165-73.
13. Dellon ES, Irani AM, Hill MR, et al. Development and field testing of a novel patient-reported outcome measure of dysphagia in patients with eosinophilic esophagitis. Aliment Pharmacol Ther. 2013;38:634-42. Epub 2013/07/11.
14. Hudgens S, Evans C, Phillips E, et al. Psychometric validation of the Dysphagia Symptom Questionnaire in patients with eosinophilic esophagitis treated with budesonide oral suspension. J Patient Rep Outcomes. 2017;1(1):3. Epub 2017/01/01.
15. Dellon ES, Katzka DA, Collins MH, et al. Budesonide Oral Suspension Improves Symptomatic, Endoscopic, and Histologic Parameters Compared with Placebo in Patients with Eosinophilic Esophagitis. Gastroenterology. 2017;152:776-86.e5.

16. Schoepfer AM, Straumann A, Panczak R, et al. Development and validation of a symptom-based activity index for adults with eosinophilic esophagitis. Gastroenterology. 2014;147(6):1255-66 e21. Epub 2014/08/28.
17. Dellon ES, Fritchie KJ, Rubinas TC, et al. Inter- and intraobserver reliability and validation of a new method for determination of eosinophil counts in patients with esophageal eosinophilia. Dig Dis Sci. 2010;55(7):1940-9. Epub 2009/10/16.
18. Rusin S, Covey S, Perjar I, et al. Determination of esophageal eosinophil counts and other histologic features of eosinophilic esophagitis by pathology trainees is highly accurate. Hum Pathol. 2017;62:50-5.
19. Hirano I, Moy N, Heckman MG, et al. Endoscopic assessment of the oesophageal features of eosinophilic oesophagitis: validation of a novel classification and grading system. Gut. 2013;62:489-95. Epub 2012/05/24.