Treatment of Eosinophilic Esophagitis: Is Oral Viscous Budesonide Superior to Swallowed Fluticasone Spray?

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Eosinophilic esophagitis (EoE) is an immunologic reaction to ingested or inhaled allergens characterized by esophageal eosinophilia and gastrointestinal symptoms. In adults, this disease is more common in men than women, with a mean age of onset of 38 years. Recent data show that EoE is increasing in prevalence, with an incidence of 6–30 cases per 100,000 individuals.[1]

Case Report

A 28-year-old man presented with a long history of dysphagia and at least 2 episodes of food impaction. He was a nonsmoker, maintained a very healthy lifestyle, had a history of allergic rhinitis, and had a brother with EoE. An esophagogastroduodenoscopy (EGD) performed in 2007 revealed considerable esophageal trachealization and stenosis, which prevented complete passage of a standard gastroscope. Esophageal biopsies confirmed EoE (applying diagnostic guidelines). The patient was started on fluticasone propionate (FP) 220 mcg (2 puffs swallowed twice daily) and was instructed not to rinse his mouth, eat, or drink for 30–60 minutes after taking the medication. A repeat EGD with attempted dilatation was performed in early 2008 due to the lack of symptomatic improvement after 4 months of therapy. Concentric rings were seen (starting at the midesophagus), and luminal narrowing was noted. Controlled radial expansion (CRE) balloon dilatation to 8–10 mm failed to disrupt the mucosa; satisfactory mucosal disruption was obtained after CRE dilatation to 10–12 mm. Due to postprocedural chest pain, the patient underwent a chest radiograph, which demonstrated subcutaneous emphysema in the neck and superior mediastinum, resulting in a diagnosis of esophageal perforation. After hospital observation, the patient was discharged without requiring surgical intervention. Adjunctive management of EoE consisted of thorough allergy testing, including an allergy skin prick test and a specific immunoglobulin (Ig)E antibody assay to various food allergens (ImmunoCAP, Quest Diagnostics).[2] Total IgE was markedly elevated, with a reported value of approximately 500 IU/mL (normal range, 4–60 IU/mL). The patient was placed on a modified diet but did not experience significant symptom improvement.

In the middle of 2008, the patient presented with persistent dysphagia refractory to diet restriction and treatment with swallowed FP and a proton pump inhibitor. Initial management included the addition of montelukast (10 mg daily). Due to the lack of symptomatic relief, we discontinued swallowed FP and started treatment with oral viscous budesonide (BUD). As presented in recent pediatric studies, viscous BUD was prepared by dissolving 1 BUD 0.5-mg respule (Pulmicort, AstraZeneca) in five 1-g packets of sucralose (Splenda, McNeil Nutritionals), for a total volume of 10–15 mL, dosed at 0.5 mg twice daily.[3] Data were collected using the Modified Mayo Dysphagia Questionnaire to assess treatment response.[1,4] Following initiation of viscous BUD therapy, the patient reported significant improvement in dysphagia and greater tolerance of dietary variety (Tables 1 and 2). He was placed on an improved or extended diet. The dosage of viscous BUD was decreased to 0.5 mg every other day during the winter (December–February), with sustained control of symptoms. The patient noted a worsening of symptoms in the spring/pollen season (March–April); consequently, BUD dosage was increased to 0.5 mg twice daily

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Table 1. Improvement in Diet After Treatment with BUD

Restricted diet on FP	Diet improvement on BUD
Whey protein shakes	Rice
Blended yogurt, pudding	All cooked vegetables* (peas, onions)
Soft cheeses	Bread*, cake, doughnuts, muffins
Nonchunky dips (cheese, ranch, bean dip)	Thin deli meat*, chicken nuggets, meat†
Oatmeal, grits	Toasted waffles, pastries
Eggs	Thin crust pizza
Turkey bacon	Onion rings, French fries
Tomato soup	Chips
Instant potatoes, baked beans	Biscuits (flaky type)

*Most notable differences (as per patient).

†The only meats that the patient is able to eat are chicken, pork, or red meat (when tender, ground, or processed). The patient is allergic to apple, banana, celery, and soy-based products.

BUD=budesonide (0.5-mg respule dissolved in five 1-g packets of sucralose, volume of 10–15 mL); FP=fluticasone propionate (metered-dose inhaler).

Table 2. Results of the Patient's Modified Mayo Dysphagia Questionnaire* While on a Restricted Diet†

Month and year	April 2009	May 2009	June 2009
Weeks of therapy	0	4	8
Drug and dosage	FP 220 mcg BID	BUD 0.5 mg BID	BUD 0.5 mg BID
Difficulty swallowing			
Severity	3	0	0
Frequency	3	0	0
Heartburn			
Severity	1	1	1
Frequency	3	3	1
Nausea			
Severity	1	1	0
Frequency	1	1	0
Abdominal pain			
Severity	1	1	0
Frequency	1	1	0

*The severity and frequency of belching, chest pain, regurgitation, and waking at night were reported as "0."

†The patient was placed on a restricted diet when treated with FP (Table 1). The severity and frequency of each symptom was graded on a scale from 0 to 3, in which 0 signified the absence of the symptom.

BUD=budesonide (0.5-mg respule dissolved in five 1-g packets of sucralose, volume of 10–15 mL; FP=fluticasone propionate (metered-dose inhaler).

(Table 3). Given the patient's history of esophageal perforation, he repeatedly declined to undergo a follow-up EGD. Post-treatment morning cortisol levels were unchanged at 24 and 52 weeks of therapy.

Discussion

Our patient experienced a sustained response to viscous BUD treatment during a follow-up period of 12 months. Previous treatment with swallowed FP over more than 1 year had failed to provide therapeutic relief. Universally accepted treatment guidelines for EoE have not been developed. Available treatment options include hypoallergenic diets (dietary restriction, elimination diet, elemental formulas), topical corticosteroids, mast-cell inhibitors (sodium chromoglycate), leukotriene inhibitors (montelukast), and esophageal dilatation.

In 2 recent, double-blind, placebo-controlled, randomized controlled trials (RCTs), treatment with viscous BUD in children and nebulized BUD in adults achieved significant improvement in symptoms and endoscopic and histologic scores; the histologic endpoint (HEP) of no more than 6 eosinophils/high power field (HPF) was observed in 87% of 15 children over 3 months and in 72.2% of 15 adults and adolescents over 15 days.[5,6] These results are better when compared to another double-blind, placebo-controlled RCT in children using swallowed FP, with 50% of 20 patients responding to therapy (significant at HEP ≤1 eosinophil/HPF; no statistical difference at HEP ≤6 eosinophils/HPF).[7] The only other RCT involving steroids compared oral prednisone with swallowed FP.[8]

Two abstracts were also recently presented. One reported the results of a non-RCT in which BUD was combined with rincinol containing polyvinylpyrrolidone (Butler) at a dose of 3 mg/10 cc twice daily; 75% of 16 patients reported improvement in dysphagia (56% with complete resolution), and 33% of 8 patients thought that viscous BUD was more effective than swallowed FP.[9] In the other trial, a double-blind RCT involving 36 patients, viscous BUD suspension (at 1 mg/4 mL twice daily) was administered for active EoE. Approximately 61% of patients (11/18) in the viscous BUD group achieved

Table 3. Results of the Patient's Modified Mayo Dysphagia Questionnaire* While on an Improved Diet† After Starting BUD Therapy

Month and year	June 2009	October 2009	December 2009	February 2010	March 2010	April 2010	May 2010
Weeks of therapy	8	24	32	40	44	48	52
Dosage of BUD	0.5 mg BID	0.5 mg BID	0.5 mg QOD	0.5 mg QOD	0.5 mg QD	0.5 mg QD	0.5 mg BID
Difficulty swallowing							
Severity	1	1	1	1	2	3	1
Frequency	2	2	1	1	3	3	2
Heartburn							
Severity	1	1	1	1	1	1	1
Frequency	1	1	1	1	1	1	1
Nausea							
Severity	0	0	0	0	1	1	0
Frequency	0	0	0	0	1	2	0
Abdominal pain							
Severity	0	0	0	0	0	1	0
Frequency	0	0	0	0	0	1	0

*The severity and frequency of belching, chest pain, regurgitation, and waking at night were reported as "0."

†The patient was placed on an improved diet when treated with BUD (Table 1). The severity and frequency of each symptom was graded on a scale from 0 to 3, in which 0 signified the absence of the symptom.

BUD=budesonide (0.5-mg respule dissolved in five 1-g packets of sucralose, volume of 10–15 mL).

remission (HEP <5 eosinophils/HPF) compared to 5.7% (1/28) in the placebo group.[10]

No RCTs have been conducted to evaluate esophageal dilatation, and no guidelines have been established regarding the duration of medical therapy before attempting dilatation. Mucosal tears and subsequent perforations usually result from esophageal remodeling and development of strictures. In this context, viscous BUD therapy has been associated with improvements in epithelial remodeling.[11] Further studies are needed to prove that medical therapy (viscous BUD vs swallowed FP) would improve epithelial remodeling, thus preventing the need for dilatation.

Some patients with EoE experience seasonal variations in symptoms that correlate with seasonal changes in esophageal eosinophil levels.[12] Over our patient's 1-year follow-up, the therapeutic dosage of viscous BUD was decreased during the winter and increased at the onset of spring.

Results from clinical and pharmacokinetic studies in bronchial asthma and inflammatory bowel disease (IBD) appear to favor the use of BUD over FP in EoE. Most studies conducted in the management of asthma have shown that inhaled BUD undergoes reversible conjugation with intracellular fatty acids, prolonging airway retention, whereas inhaled FP does not undergo intracellular esterification and, thus, may have less tracheobronchial retention.[13] Inhaled FP is highly lipophilic and poorly water-soluble; in contrast, inhaled BUD is water-soluble and readily dissolves in mucosal fluids.[14,15] Oral enteric-coated (EC) BUD (~9 mg/day) is equivalent to prednisolone (~40 mg/day) and superior to placebo for induction of remission in active Crohn's disease (CD).[16] Budesonide enema is effective and better than placebo for treatment of distal ulcerative colitis (UC) and proctitis.[17] In treatment of active CD, oral FP was associated with poor clinical efficacy compared to prednisolone; for treatment of UC, oral FP was not as effective as prednisolone and no more

effective than placebo.[18-20] These studies suggest that oral FP is inferior to EC BUD for treatment of IBD; however, no comparative studies have yet been conducted. Whether the observed difference is due to insufficient dosage, inadequate bioavailability, or the highly lipophilic nature of oral FP in the gastrointestinal tract has yet to be determined. We hypothesize that BUD is superior to FP for treatment of gastrointestinal inflammatory conditions and theorize that for oral administration, swallowed FP provides less surface area over which the drug is effective than viscous BUD.

Dosing equivalency in asthmatic patients is based upon a double-blind, placebo-controlled, crossover study comparing single doses of inhaled BUD and inhaled FP (at 400 ug, 1,000 ug, 1,600 ug, and 2,000 ug).[21] At least 2-fold greater adrenal suppression was noted due to inhaled FP compared to the microgram-equivalent dose of inhaled BUD. Similar to the treatment of asthma, the current EoE therapeutic dosage of viscous BUD is twice the microgram-equivalent dose of swallowed FP.[3,5]

A Cochrane meta-analysis compared markers of adrenal function (morning cortisol and 24-hr urinary cortisol) between inhaled FP and inhaled BUD at a dose ratio of 1:2 in patients with chronic asthma and found no significant difference between treatment groups.[22] An extensive review summarizing 25 years of inhaled BUD use with different doses among diverse populations documented infrequent adverse events (adrenal crisis, reduced height, risk of fractures, and pregnancy complications).[23] For IBD treatment, a recent Cochrane review summarized multiple studies comparing response to adrenocorticotropic hormone (ACTH) stimulation. Treatment with EC BUD (3–15 mg/day) was significantly less likely than conventional corticosteroids (prednisone 20–40 mg/day) but more likely than placebo to cause an abnormal response to ACTH stimulation.[16] Hypocortisolism due to BUD should be uncommon at an EoE treatment dose of 1–2 mg per day. Patients requiring long-term therapy should nonetheless be observed for hypothalamic-pituitary-adrenal axis suppression, oral candidiasis, and osteoporosis.

Sucralose, a substituted disaccharide, is stable at a low pH, is water-soluble, and is nonbioaccumulative. Following consumption, 85% of sucralose is excreted unchanged in feces and 15% of absorbed sucralose is excreted unchanged in urine. Sucralose does not serve as a substrate for intestinal microflora.[24] Rincinol containing polyvinylpyrrolidone was used in one study.[9] This compound is a muco-adherent that forms a thin, protective coating over oral mucosa. Between these 2 compounding agents, we recommend sucralose for preparing viscous BUD doses, given its wider availability, extensively studied safety profile, and effective application in multiple RCTs.

In conclusion, larger studies of adults are needed to recommend viscous BUD as first-line therapy for EoE. An exclusively formulated viscous BUD for EoE that provides effective drug delivery should be developed. The long-term safety profile of BUD in the treatment of EoE should also be established. The dosage of BUD may need to be adjusted seasonally according to symptom variation. For treatment-refractory patients, a trial of viscous BUD can be attempted before proceeding with esophageal dilatation. In the interim, viscous BUD is an excellent alternative to swallowed FP for treating patients with EoE, and it may be the first-choice treatment in some patients.

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Review

Therapeutic Options for Eosinophilic Esophagitis

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Eosinophilic esophagitis (EoE) is an allergy-based disease with a genetic predisposition in which esophageal exposure to food antigens, perhaps primed by respiratory or extraesophageal allergic disease, has been postulated to contribute to a chronic inflammatory state, eventually resulting in fibrosis and stricture formation. As with many allergies, one of the mainstays of treatment for EoE is the use of steroids. Indeed, steroids are the only pharmacologic treatment that has shown clear benefit in EoE across numerous studies. Several studies, including double-blind, placebo-controlled trials, have demonstrated the efficacy of either systemic or topical steroids in treating EoE.[1-5] With emerging data and growing enthusiasm for understanding and treating this disease, physicians are now asking questions about which steroid preparations are most effective, for how long, and at what dose. Through good anecdotal evidence, the interesting case report by Krishna and associates proposes that viscous budesonide should comprise first-line treatment for patients with EoE.[6] Before embarking on a discussion of which steroid is most effective, however, it is important to consider several caveats when analyzing this case report and EoE studies in general.

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First, several studies evaluating the efficacy of steroids in EoE patients use symptoms as the primary endpoint. Unfortunately, in both children and adults, it has been well demonstrated that symptomatic response may not correlate with histologic response.[7] This finding may have several explanations. The use of standardized dysphagia scoring systems, which are useful for other dysphagic diseases, may be inadequate for evaluating EoE. Symptoms may be infrequent, particularly in adults, making it difficult to demonstrate a significant difference over a short time period. The effect of short-term steroids on symptomatic fibrotic strictures may be suboptimally appreciated at endoscopy, particularly with diffuse esophageal narrowing.

Second, not all studies agree on how to define histologic remission in response to therapy. For example, some studies define less than 1 eosinophil/high power field (HPF) as a complete response, whereas other studies use 0–6 eosinophils/HPF. Some studies may use scoring systems combining eosinophil counts with other histologic parameters such as basal zone thickness. Moreover, although all studies use HPF as the gold standard field of measurement, the diameter of this field (and, therefore, the eosinophil count) may vary widely among studies. Thus, when analyzing efficacy among various steroid preparations, one should be aware that comparisons may not be of equivalent units.

Third, studies with steroids have used different preparations, dosages, and durations of therapy. For example, a standard dose of 4 puffs of 220 micrograms

of fluticasone twice daily is still 240 micrograms less than 2 mg of budesonide once daily. Another study in adults used only 500 micrograms of fluticasone twice daily in adults, which is half of the usual budesonide dose. Other studies vary in their drug trial periods, ranging from 1 to 3 months. Whether these differences are therapeutically significant is unclear.

Finally, much of the success of a steroid preparation for treating patients with EoE rests on the premise that patients in the trial have EoE. With no gold standard for differentiating EoE from gastroesophageal reflux, this presumption may be problematic when comparing studies in which the distribution of these diseases may differ among experimental groups.

On an optimistic note, the use of steroids in EoE is not merely a "me too" phenomenon within the spectrum of allergic diseases. There are clear data demonstrating that steroids effectively and specifically treat the underlying pathophysiology and even improve fibrosis in these patients.[8] For example, all studies show that steroids effectively reduce and often eliminate eosinophils from esophageal mucosa. Even more interesting is the reduction in other inflammatory and fibrogenic markers. For example, budesonide has been demonstrated to reduce levels of mast cells, tumor necrosis factor-α, and epithelial cell apoptosis, all of which accompany inflammation and lamina propria fibrosis. Moreover, steroids have been shown to decrease transforming growth factor (TGF)-B1 and tenascin C, which are markers of fibrosis and remodeling. Similarly, fluticasone has been shown to reduce tissue levels of monoclonal anti–Ki-67, mast cells, and CD8 T cells. It is also encouraging that topical steroids have been reported to reverse fibrosis (as evidenced by biopsy staining for TGF-B1) and to decrease esophageal wall thickness (as measured by endoscopic ultrasound).[4,8] This benefit is far from proven, however; longer-term studies are needed to determine the potential of these therapies for reversing clinically significant esophageal narrowing.

With these points in mind, physicians who treat patients with EoE have to choose their primary and secondary therapies. Can one therapy be deemed superior? If so, why? Certainly, systemic steroids can be held in reserve for patients who are refractory to topical steroids or who cannot tolerate them. As a result, as was nicely discussed in the case by Krishna and colleagues, the most common treatment choices are inhaled fluticasone, inhaled budesonide, and viscous budesonide.[6] All 3 treatments share several similarities. The pharmacokinetics of these preparations when swallowed have not been well evaluated. In particular, it is possible that swallowed budesonide may not undergo the first-pass metabolism of slow-release budesonide absorbed in the small intestine. All 3 preparations appear to have minimal effect (if any) on the adrenal axis, as documented in asthma patients and several reports of EoE patients. There is a chance (at most, 15%) of developing oropharyngeal or esophageal *Candida* infection, which is commonly asymptomatic. All 3 preparations have similar rates of clinical and histologic efficacy, though there have not been any direct comparison studies. Both inhaled fluticasone and budesonide are inconvenient to administer, as patients must rinse their mouths with and expectorate water after dosing, as well as avoid eating or drinking for 30 minutes afterwards. Patients may also find it challenging to swallow a medication that is diffusely sprayed over their pharynx. Nevertheless, steroid nebulizers have undergone the most study and use by physicians. They are efficacious and immediately ready for use. However, it is unclear whether a small amount of the sprayed liquid can optimally and completely coat and penetrate an organ with a relatively large surface area. As a result, recent studies have supported the use of viscous budesonide.[9] This medication is particularly useful in children because of its sweet taste. A recent study of viscous budesonide in children demonstrated complete histologic response in 13 of 15 patients.

The price of these formulations should be considered as well. All of the preparations currently available in the United States are extremely costly. In our area, a 6-week course of fluticasone at 880 mcg BID costs $670, and a 6-week supply of budesonide liquid 2 mg BID taken from respules (Pulmicort, AstraZeneca) costs over $1,200. Cost is a major issue in the treatment of EoE, as the medications currently available are expensive not only initially, but potentially long term, given the nearly universal recurrence of the disease and the likelihood that some patients will require sustained treatment.[10]

We are fortunate to have safe and effective medications so early in the life of this disease. Whether fluticasone or budesonide will ultimately prove to be more efficacious and/or convenient is unclear. Much of our speculation will ultimately be settled by a double-blind comparison of these 2 medications, though it is likely that several trials will be needed in patients of different ages, as children may have different preferences and responses than adults. It is also likely that we will soon have formulations of these steroids designed specifically for delivery to the esophagus. For now, it is best to take into account the preferences and cost restraints of individual patients when choosing a formulation. As in the case report by Krishna and coworkers, if one formulation fails, another can be attempted, whether a topical or systemic steroid.[6] Nevertheless, this case report is (hypoallergenic) food for thought and should stimulate more intensive investigation of some of these important questions.

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