Published in final edited form as:

J Pediatr Gastroenterol Nutr. 2017 February ; 64(2): 172–173. doi:10.1097/MPG.0000000000001326.

Sticky steroids-In search of an approved treatment for eosinophilic esophagitis

Nathalie Nguyen, Glenn T. Furuta, and Calies Menard-Katcher

Digestive Health Institute, Section of Pediatric Gastroenterology, Hepatology and Nutrition, Children's Hospital Colorado, Gastrointestinal Eosinophilic Diseases Program, Department of Pediatrics, Mucosal Inflammation Program, University of Colorado School of Medicine, Aurora, CO 80045, USA

Keywords

eosinophil; eosinophilic esophagitis; budesonide

Current therapies for eosinophilic esophagitis (EoE) include topical corticosteroids, dietary restrictions, and esophageal dilation, however no Food and Drug Administration (FDA) approved medical treatments exist¹. Although dietary therapy can be highly effective in EoE, it can negatively affect quality of life and have low adherence due to food restrictions.

Swallowed topical corticosteroids are the mainstays of pharmacologic treatment in EoE. Faubion et al reported the successful use of topical steroids administered via a metered dose inhaler in 1998²; their seminal finding have been validated by a series of studies. In 2005, Aceves et al, reported the use of a novel preparation, oral viscous budesonide, in the treatment of children with EoE³. This preparation was developed to address concerns related to administration technique and mucosal coverage. To date, commercially available pre-prepared suspensions of topical steroids are still unavailable.

In this issue of JPGN, Salvatore et al report their findings from a single center, non-blinded pilot study that evaluated the efficacy and safety of a pre-prepared oral viscous budesonide suspension in 36 pediatric patients with EoE⁴. The authors demonstrate that 88.9% of patients had complete histological response after 12 weeks of pre-prepared viscous budesonide (PVB). Twenty-four weeks after cessation of PVB, most patients relapsed, but almost half maintained remission raising a question of seasonal effects or sampling bias. They found an improvement in symptoms, endoscopy scores and histology scores after treatment, indicating that pre-prepared viscous budesonide may be effective in inducing clinic-pathologic remission without untoward side effects related to adrenal suppression or infection.

Correspondence to: Calies Menard-Katcher, calies.menard-katcher@childrenscolorado.org **Telephone:** 720-777-7457.

Conflicts of Interest: Authors report no conflicts of interest related to this manuscript.

Author's contributions: Drs. Nguyen, Menard-Katcher and Furuta all contributed to concept development, writing and review of this article and provided final approval of the version to be published.

In previous studies and in clinical practice, oral viscous budesonide is formulated by combining liquid budesonide, intended for nebulized administration, with a substrate, typically sucralose (Splenda)³. However, many families are hesitant to use artificial sweeteners on a daily basis. Other substrates such as Neocate Nutra⁵ and a host of other foods including applesauce, honey, hot cocoa mix, pear sauce, xanthem gum, and rice cereal⁶ have also been reported to reduce eosinophilia. However, these alternatives still require choosing the best tolerated vehicle and mixing the suspension, factors that could contribute to variability in therapeutic responses. Salvatore et al provide data that, similar to previous studies using budesonide, a pre-prepared solution is feasible to use and can reduce eosinophils in the esophageal mucosa in a safe fashion.

Consistent with previous EoE therapeutic studies, this report notes again that symptom scores poorly correlate with mucosal eosinophilia⁷. The use of co-primary endpoints has become the standard for EoE therapeutic trials in which both patient reported outcomes as well as mucosal eosinophilia are assessed⁸. Gupta et al reported their experience with a prepared oral viscous budesonide formulation and found a histological response in 52% of children with 1.4 mg/day and 94.1% response with 2.8 mg/day⁹. However, a large percentage of placebo treated subjects reported an improvement in symptoms again demonstrating a poor correlation of symptoms with mucosal eosinophilia⁹. Capturing symptoms experienced can be challenging since patients often develop compensatory behaviors due to chronic symptoms associated with EoE. In the last several years, new symptom measurement tools have been developed to measure both symptoms as well as compensatory behaviors¹⁰. For example, the Pediatric Eosinophilic Esophagitis Symptom Scores 2.0 (PEESS) correlates with histopathology¹¹. Although the symptom score used by Salvatore addressed the varied symptoms that can be seen in EoE, it did not account for many compensatory behaviors associated with EoE. Perhaps a more robust metric would have provided better correlation with histology and symptoms.

Technological advances are providing additional means to assess the patient's response to novel therapeutics. Confocal assessments¹², mucosal impedance¹³ and Endolumenal Functional Lumen Imaging Probe (EndoFLIP)¹⁴ all may provide structural and functional outcomes in the future. In particular EndoFLIP may provide not only a structural correlate by means of measuring stiffness, but also a method to assess function and risk assessment¹⁴. The coming years will provide answers to the important question of what is the least tolerable burden of disease for a patient and family? With respect to new therapeutics, what is the best way to measure disease activity or treatment endpoints in EoE?

The authors in this study achieved similar remission rates than previous studies evaluating effectiveness of oral viscous budesonide (OVB). In the landmark study by Dohil et al, children experienced an 86.7% remission rate with 3 months of Budesonide 1–2 mg daily¹⁵. Here, Salvatore et al used higher doses of 2–4 mg daily of pre-prepared oral viscous budesonide for 3 months without identified side effects. In adolescents and adults, Straumann et al demonstrated 72.2% remission with 15 days of Budesonide 2 mg daily¹⁶.

Several limitations exist with this study including lack of untreated controls, lack of blinding to endoscopic or histologic assessments and lack of clarity as to the chemical properties that

permit PVB to reduce eosinophilia. With respect to the latter concern, it is likely that proprietary issues may exist that limit disclosure, but more information as to how this vehicle differs from our currently available vehicle would be important to know. As a pilot study, we are provided with a snapshot of the impact of this, but how it differs from other topical steroids in its mechanistic properties and whether it will be more effective or safer will need to be determined in future randomized, double blinded, placebo-controlled studies.

In summary, this report provides hope for another potential topical steroid option that limits the concern about variability related to preparation technique. As our understanding of the pathogenesis of the EoE evolves and studies continue to place an emphasis on the importance of clinically relevant outcomes, we await the first FDA approved treatment for pediatric and adult EoE.

Acknowledgments

Supported by: NIH 2T32DK067009-11 (NN), 1K24DK100303 (Furuta GT) and Consortium for Gastrointestinal Eosinophilic Researchers (CEGIR). CEGIR (U54 AI117804) is part of the Rare Diseases Clinical Research Network (RDCRN), an initiative of the Office of Rare Diseases Research (ORDR), NCATS, and is funded through collaboration between NIAID, NIDDK, and NCATS.

References

1. Liacouras CA, Furuta GT, Hirano I, et al. Eosinophilic esophagitis: updated consensus recommendations for children and adults. *J Allergy Clin Immunol*. 2011; 128:3–20e6. quiz 1–2. [PubMed: 21477849]
2. Faubion WA Jr, Perrault J, Burgart LJ, et al. Treatment of eosinophilic esophagitis with inhaled corticosteroids. *J Pediatr Gastroenterol Nutr*. 1998; 27:90–3. [PubMed: 9669733]
3. Aceves SS, Dohil R, Newbury RO, et al. Topical viscous budesonide suspension for treatment of eosinophilic esophagitis. *J Allergy Clin Immunol*. 2005; 116:705–6. [PubMed: 16159647]
4. Salvatore O, Rossetti D, Papoff P, et al. A New Formulation of Oral Viscous Budesonide in Treating of Paediatric Eosinophilic Oesophagitis: A Pilot Study. *J Pediatr Gastroenterol Nutr*. 2016 this issue.
5. 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; 59:317–20. [PubMed: 24821535]
6. Lee J, Shuker M, Brown-Whitehorn T, et al. Oral viscous budesonide can be successfully delivered through a variety of vehicles to treat eosinophilic esophagitis in children. *J Allergy Clin Immunol Pract*. 2016 PAP.
7. Pentiuk S, Putnam PE, Collins MH, et al. Dissociation between symptoms and histological severity in pediatric eosinophilic esophagitis. *J Pediatr Gastroenterol Nutr*. 2009; 48:152–60. [PubMed: 19179876]
8. Fiorentino R, Liu G, Pariser AR, et al. Cross-sector sponsorship of research in eosinophilic esophagitis: a collaborative model for rational drug development in rare diseases. *J Allergy Clin Immunol*. 2012; 130:613–6. [PubMed: 22857796]
9. Gupta SK, Vitanza JM, Collins MH. Efficacy and safety of oral budesonide suspension in pediatric patients with eosinophilic esophagitis. *Clin Gastroenterol Hepatol*. 2015; 13:66–76e3. [PubMed: 24907502]
10. Schoepfer AM, Straumann A, Panczak R, et al. Development and validation of a symptom-based activity index for adults with eosinophilic esophagitis. *Gastroenterology*. 2014; 147:1255–66e21. [PubMed: 25160980]
11. Martin LJ, Franciosi JP, Collins MH, et al. Pediatric Eosinophilic Esophagitis Symptom Scores (PEESS v2.0) identify histologic and molecular correlates of the key clinical features of disease. *J Allergy Clin Immunol*. 2015; 135:1519–28e8. [PubMed: 26051952]

12. Yoo H, Kang D, Katz AJ, et al. Reflectance confocal microscopy for the diagnosis of eosinophilic esophagitis: a pilot study conducted on biopsy specimens. *Gastrointestinal endoscopy*. 2011; 74:992–1000. [PubMed: 21944314]
13. van Rhijn BD, Verheij J, van den Bergh Weerman MA, et al. Histological Response to Fluticasone Propionate in Patients With Eosinophilic Esophagitis Is Associated With Improved Functional Esophageal Mucosal Integrity. *Am J Gastroenterol*. 2015; 110:1289–97. [PubMed: 26303134]
14. Nicodeme F, Hirano I, Chen J, et al. Esophageal distensibility as a measure of disease severity in patients with eosinophilic esophagitis. *Clinical gastroenterology and hepatology: the official clinical practice journal of the American Gastroenterological Association*. 2013; 11:1101–7e1. [PubMed: 23591279]
15. 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. [PubMed: 20457157]
16. Straumann A, Conus S, Degen L, et al. Budesonide is effective in adolescent and adult patients with active eosinophilic esophagitis. *Gastroenterology*. 2010; 139:1526–37. 37e1. [PubMed: 20682320]