Abstract

Eosinophilic Esophagitis (EoE) is a serious, chronic disorder that has been increasing in incidence and prevalence, and without adequate treatment, is associated with substantial morbidity. Given the lack of consensus on best practice for treating EoE, the invasiveness and potential side effects of current treatments, as well as the likelihood of recurrence of symptoms after discontinuing treatment, we propose a pilot study to explore a novel treatment approach for EoE in the pediatric population. No studies have been published on the efficacy of combining the 2 most common maintenance treatments, swallowed steroids and an elimination diet. In a cohort study with 38 newly diagnosed patients, this treatment protocol combines and simplifies steroid and diet therapy. Patients will be treated on dedicated clinic days by the pediatric gastroenterologist and dietitian in Wake Forest Baptist's pediatric GI program designed to provide continuity of care and ongoing education and support to our patients and families of patients living with allergic digestive disorders. The therapy initially combines swallowed steroids and a 2-food elimination diet (dairy and soy) for 3 months to relieve symptoms, then alternates treatment with only 2-food elimination for 3 months, then only steroids for 3 months. Patients will undergo endoscopies 3 times throughout treatment after diagnosis to monitor resolution of symptoms over 9 months. We hypothesize that a study on this approach will demonstrate resolution of clinical symptoms, histological improvement, strong adherence to treatment, and increased quality of life while decreasing the potential for harmful side effects of treatments and the burden of an extensive elimination diet.

Specific aim

1) To determine the degree of efficacy of combining and alternating swallowed steroids and elimination of milk and soy from the diet in treatment of pediatric EoE for comparison to single use therapies (dietary therapy OR pharmacologic therapy) in a larger multicenter study in the future.

Background/significance

Eosinophilic Esophagitis (EoE) is a chronic, immune/antigen-mediated clinicopathic disorder that is associated with substantial morbidity when left untreated[1,2]. Multiple treatment options are in place and demonstrate effectiveness in achieving clinical and histological remission, but they also include considerable drawbacks in terms of patient burden through extensive diet elimination and possible long-term medication side effects, particularly for children[2,3,4]. Challenges also exist with difficulty in adherence to treatments. In a study of treatment adherence for 96 children with EoE or eosinophilic gastroenteritis, non-adherence rates ranged from 30-33%.[5] Currently, treatments include elimination and elemental diets to decrease allergen exposure, topical glucocorticoids to reduce esophageal inflammation, and esophageal dilation for advanced cases with strictures.[2,4,6,7]

While some physicians consistently utilize allergy testing to direct dietary restrictions, current studies suggest that this costly testing may not accurately predict food triggers for EoE, particularly for dairy, the most common EoE allergen[42]. Rather, recent research suggests that elimination of just a few foods may effectively alleviate symptoms for most people[4,8–11] Multiple studies point to milk as the most common trigger, demonstrated as being 8 times more likely to cause EoE as the next most common food in a study by Kagalwalla et al[9]. Soy is currently considered to be another of the top allergens contributing to EoE.[6,9,10,12] Soy as a top trigger for EoE is further supported by the cross-reactivity between soy protein and bovine casein.[13–16] Some studies suggest that between 10-14% of people with cow's milk allergy also present with soy protein allergy.[15] The combination of research on specific foods triggering EoE alongside soy-milk protein cross-reactivity presents a compelling case for consideration of milk and soy as preliminary exclusions for an elimination diet to treat EoE.

Swallowed steroids are the most commonly used form of treatment for EoE, and are considered a first line approach.[2,6,7] As patients often present with EoE after severe morbidity such as food impaction, preventing subsequent impactions is the first priority. In order to resolve symptoms as quickly as possible,

initial use of swallowed steroids is indicated.[7] As the disease recurs when the steroid is discontinued, cyclical use in combination with diet therapy could prevent such recurrence. However, some families choose pharmacological treatment as a preferable lifestyle choice. Elimination diets and an elemental diet require sizeable alterations in daily living and have the potential to strongly impact quality of life[2,17,18]. For some individuals, daily medication is a more feasible option for likely compliance.

Research efforts are increasing to try to reduce the number of foods eliminated empirically, but no studies are currently published that demonstrate the effectiveness of combining and alternating pharmacologic and dietary treatment[4,6,10,11,19]. This approach has the potential to increase efficacy of treatment and time to remission while decreasing the invasiveness and side effects of current treatments. Additionally, EGDs as often as once per month may be used to track progression of symptoms in conjunction with directed food elimination and reintroduction. These frequent procedures are both costly and invasive[20]. As for steroid treatment, there is emerging evidence of possible adverse effects of prolonged use, especially in children[2]. This proposed treatment approach reduces expensive, invasive procedures, liberalizes the diet to only eliminate the most common triggers to maximize compliance and minimize symptoms, and reduces steroids after symptoms begin to resolve.

As a new treatment approach, more substantial data is needed to validate a combined approach and explore the parameters of its use. The data from this pilot study will serve as support for a larger, multicenter, prospective study comparing this approach to singular use of dietary restriction or swallowed steroids. Further research is needed in this area to establish an optimal treatment strategy for EoE that has potential to improve symptoms, minimize burden of treatment, and achieve histological remission to ultimately prevent long-term development of esophageal strictures.

Our treatment team consists of two members of Carolinas' EoE Collaborative, a practice group that aims to facilitate collaboration of health care providers with expertise in EoE practicing within the Carolinas to provide multi-disciplinary care, education, and research opportunities for those living with EoE. This team of collaborators consists of gastroenterologists, allergists and dietitians focused on providing evidence based care. As members of this group, Wake Forest has an established forum for advancing and sharing treatment advances in academic and clinical settings, and with more substantial pilot data, will be ready to collaborate in forming a larger, comprehensive study.

Preliminary Data

We conducted a retrospective analysis of new EoE patients at the Wake Forest Baptist pediatric GI clinic who have been treated with a combination diet/pharmacologic therapy over the past year. Of a case group of 16 patients who had results from at least 2 endoscopies, 82% of patients who adhered consistently to the protocol (11 individuals) achieved histological remission (<15 eosinophils/high powered field), and 91% demonstrated substantial improvement in number of eosinophils. 31% (5 individuals) had issues with compliance to diet or medication, but we believe this can be improved by more support from a dietitian and with targeted education materials. This preliminary data confirms the necessity for further research on a simplified, combined treatment approach.

Research Plan

Study design: We will conduct a prospective cohort study of newly diagnosed pediatric EoE patients treated with a combination protocol of swallowed steroids and dietary elimination of milk and soy.

Study setting: This study will take place in the pediatric GI clinic of Wake Forest Baptist Health. Last year, we created a program within our clinic designed to provide continuity and ongoing education and support to our patients and families of patients living with allergic digestive disorders. As such, we have dedicated clinic days for both the physician and dietitian specifically working with these patients.

Selection of cases: 38 cases will be enrolled in the study from pediatric patients referred to Wake Forest Baptist Health Pediatric GI. Cases will be newly diagnosed EoE patients between 1 and 21 years of age who feed orally and have no past medical history of IBD, Celiac disease, or other EGIDS. Individuals who are already on treatment at time of referral will be excluded. Inclusion in the study will be based on the clinical and histological guidelines for diagnosis of EoE following standard endoscopy protocol after a 6-week course of PPIs, ruling out PPI responsive EoE[2]. Per standard protocol, secured samples will be sent to the pathology lab at Wake Forest Hospital following institution guidelines. Pathology reports with diagnosis suggestion will be generated in the lab and documented in the electronic medical record and available to all clinical providers.

Experimental approach: After the diagnostic esophagogastroduodenoscopy (EGD), all visits will take place in the pediatric GI outpatient clinic of Wake Forest Baptist Health.

Visit #0: Diagnostic EGD
Visit #1: The patient and family will complete the study consent form and fill out the initial validated Pediatric EoE QOL survey[18] and QL EoE Symptoms Scales symptom score index[21].
The patient and family will meet with the gastroenterologist and dietitian to discuss diagnosis, medications, and diet therapy. Patients will receive education and education material packet from the dietitian. Blood draw for vitamin D levels. *
Visit #2: EGD within 3-4 months
Visit #3 (3 months + 1 week): Clinic follow-up with gastroenterologist and dietitian. Assess compliance to diet and meds and discuss results from EGD. Document symptom report. Instruct patient on removing medication and continuing diet.
Visit #4 (6 months): EGD
Visit #5 (6 months +1 week): Clinic follow-up with gastroenterologist and dietitian. Assess compliance to diet and discuss results from EGD. Document symptom report. Instruct patient on restarting medication and liberalizing diet.
Visit #6 (9 months): EGD
Visit #7: (9 months + 1 week) Assess compliance to diet and discuss results from EGD. Document symptom report. The patient and family will fill out the final pediatric EoE QOL survey and symptom score index. Blood draw for vitamin D levels.

Table 1: Metrics to be measured

Metric	**Method of Collection**	**Time of Collection**
Symptoms	Patient and parent report through EoE symptom scales[21]	Visits #1, #3, #5, #6
Normal/abnormal EGD	Endoscopic findings	Visits #0, #2, #4, #6
Number of eosinophils	Pathology report from EGD	Visits #0, #2, #4, #6
QOL	Validated EoE pediatric QOL survey[19]	Visits #1, #7
Vitamin D*	Blood draw	Visits #1, #7
Adherence to treatment	Self report	Visits #1, #3, #5, #7

*Vitamin D levels will be monitored throughout the study to ensure nutritional deficiencies do not occur with periodic elimination of dairy and soy products.

Patients will receive an automated reminder one week prior to each of their scheduled appointment to mitigate loss to follow-up (LTF). If the patient misses an appointment, they will receive an email the same day prompting the parent to call and reschedule. If there is no response within 1 week, the study coordinator will call and attempt to reschedule. If there is no response after 1 more week, a second phone

call will be placed. Study participants will also receive incentives in the form of free parking for their appointments at the hospital and a small gift card upon completing the study. If we continue with the rate of new EoE patient acquisition that we have had in the last year, we anticipate enrolling 38 new patients over 9 months, leaving 9 months for participation in the study. Based on current no-show rates for EoE patients in the Wake Forest Baptist Health pediatric GI clinic, we predict a maximum 15% overall (LTF) for this study. With this enrollment and rate of LTF, the final study population should be at least 32 participants. (Fig. 1)

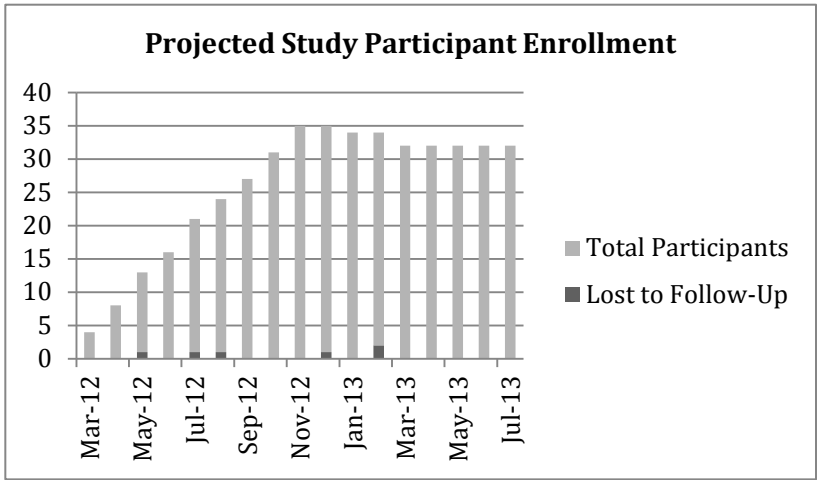

Figure 1.

Expected Outcomes and Future Directions

We hypothesize that this treatment approach will yield substantial improvement in clinical symptoms and quality of life, and allow a majority of our patients to achieve histological remission.[2] If patients are non-compliant with the study protocol, they will be removed from the study population while their care continues. If the participants are not showing the expected improvement, the dietitian and doctor will work with them outside of the study protocol and they will be asked to follow a more extensive 6-food elimination diet and reintroduce foods one at a time.[19] If this study does not yield the expected improvement of symptoms and histological markers, we will be able to determine that this combination of treatment is not effective and make changes to improve the treatment protocol. If it is effective, as hypothesized and suggested by limited preliminary data, we will collaborate with other centers in the Carolina's to conduct a prospective multicenter study comparing the combined protocol to singular treatment protocols using the same measures in order to optimize treatment and quality of life of children living with EoE.

References

1. Soon S, Butzner JD, Kaplan GG, Jennifer CC. Incidence and prevalence of eosinophilic esophagitis in children. *J Pediatr Gastroenterol Nutr*. 2013;57(1):72-80.

2. Liacouras CA, Furuta GT, Hirano I, et al. Eosinophilic esophagitis: updated consensus recommendations for children and adults. *J Allergy Clin Immunol*. 2011;128(1):3-20.

3. Harel S, Hursh BE, Chan ES, Avinashi V, Panagiotopoulos C. Adrenal Suppression in Children Treated With Oral Viscous Budesonide for Eosinophilic Esophagitis: *J Pediatr Gastroenterol Nutr*. 2015;61(2):190-193. doi:10.1097/MPG.0000000000000848.

4. Lucendo AJ. Meta-Analysis-Based Guidance for Dietary Management in Eosinophilic Esophagitis. *Curr Gastroenterol Rep*. 2015;17(10). doi:10.1007/s11894-015-0464-y.

5. Hommel KA, Franciosi JP, Hente EA, Ahrens A, Rothenberg ME. Treatment Adherence in Pediatric Eosinophilic Gastrointestinal Disorders. *J Pediatr Psychol*. 2012;37(5):533-542. doi:10.1093/jpepsy/jsr090.

6. Kagalwalla A, Wechsler J, Schwartz S, Amsden K. Elimination diets in the management of eosinophilic esophagitis. *J Asthma Allergy*. May 2014:85. doi:10.2147/JAA.S47243.

7. Dellon ES, Gonsalves N, Hirano I, Liacouras CA, Katzka D. ACG clinical guideline_ diagnosis and managment of EoE.pdf. *Am J Gastroenterol*. 2013;108(5):679-692. doi:10.1038/ajg.2013.71.

8. Spergel JM, Brown-Whitehorn T, Beausoleil JL, Shuker M, Liacouras CA. Predictive values for skin prick test and atopy patch test for eosinophilic esophagitis. *J Allergy Clin Immunol*. 2007;119(2):509-511. doi:10.1016/j.jaci.2006.11.016.

9. Kagalwalla AF, Shah A, Li BUK, et al. Identification of Specific Foods Responsible for Inflammation in Children With Eosinophilic Esophagitis Successfully Treated With Empiric Elimination Diet: *J Pediatr Gastroenterol Nutr*. 2011;53(2):145-149. doi:10.1097/MPG.0b013e31821cf503.

10. Molina-Infante J, Arias A, Barrio J, Rodríguez-Sánchez J, Sanchez-Cazalilla M, Lucendo AJ. Four-food group elimination diet for adult eosinophilic esophagitis: A prospective multicenter study. *J Allergy Clin Immunol*. 2014;134(5):1093-1099.e1. doi:10.1016/j.jaci.2014.07.023.

11. Kagalwalla AF, Amsden K, Shah A, et al. Cow's Milk Elimination: A Novel Dietary Approach to Treat Eosinophilic Esophagitis. *J Pediatr Gastroenterol Nutr*. 2012;55(6):711-716.

doi:10.1097/MPG.0b013e318268da40.

12. Spergel JM, Brown-Whitehorn TF, Cianferoni A, et al. Identification of causative foods in children with eosinophilic esophagitis treated with an elimination diet. *J Allergy Clin Immunol*. 2012;130(2):461-467.e5. doi:10.1016/j.jaci.2012.05.021.

13. Candreva AM, Smaldini PL, Curciarello R, et al. Cross-Reactivity Between the Soybean Protein P34 and Bovine Caseins. *Allergy Asthma Immunol Res*. 2015;7(1):60. doi:10.4168/aair.2015.7.1.60.

14. Rozenfeld P, Docena GH, FOSSATI MA, others. Detection and identification of a soy protein component that cross-reacts with caseins from cow's milk. *Clin Exp Immunol*. 2002;130(1):49-58.

15. Kattan JD, Cocco RR, Järvinen KM. Milk and Soy Allergy. *Pediatr Clin North Am*. 2011;58(2):407-426. doi:10.1016/j.pcl.2011.02.005.

16. Bhatia J, Greer F, and the Committee on Nutrition. Use of Soy Protein-Based Formulas in Infant Feeding. *PEDIATRICS*. 2008;121(5):1062-1068. doi:10.1542/peds.2008-0564.

17. Klinnert MD, Silveira L, Harris R, et al. Health-Related Quality of Life Over Time in Children With Eosinophilic Esophagitis and Their Families: *J Pediatr Gastroenterol Nutr*. 2014;59(3):308-316. doi:10.1097/MPG.0000000000000451.

18. Franciosi JP, Hommel KA, Bendo CB, et al. PedsQL Eosinophilic Esophagitis Module: Feasibility, Reliability, and Validity. *J Pediatr Gastroenterol Nutr*. 2013;57(1):57-66. doi:10.1097/MPG.0b013e31828f1fd2.

19. Lucendo AJ, Arias Á, González-Cervera J, et al. Empiric 6-food elimination diet induced and maintained prolonged remission in patients with adult eosinophilic esophagitis: a prospective study on the food cause of the disease. *J Allergy Clin Immunol*. 2013;131(3):797-804.

20. Jensen ET, Kappelman MD, Martin CF, Dellon ES. Health-care utilization, costs, and the burden of disease related to eosinophilic esophagitis in the United States. *Am J Gastroenterol*. 2015;110(5):626-632.

21. Franciosi JP, Hommel KA, DeBrosse CW, et al. Development of a validated patient-reported symptom metric for pediatric eosinophilic esophagitis: qualitative methods. *BMC Gastroenterol*. 2011;11(1):126.

Budget Justification

Direct Costs

a. **Personnel:**

Dietitian/Study Coordinator: This will be a part-time position at 9% FTE (3.6 hours per week) for the duration of the 18 month study. The coordinator should have a Registered Dietitian (RD) certification in order be familiar with stipulations of a diet therapy study and be capable of implementing the protocol and counseling patients with minimal supervision. The dietitian will perform medical nutrition therapy, which may include nutrient analysis and education, as well as prepare study protocols, obtain data collection tools, develop standardized diet education materials, and coordinate with individuals from epidemiology, pathology, pediatric GI, and UNC pediatric GI.

Year 1: $50,000/12 months x 9%= $4,568 + 16% fringe benefits of $731 = $5,299
Year 2: $50,000/6 months x 9% = $2,284 + 16% fringe benefits of $365 = $2,649

Total for all personnel: $7,948

b. **Supplies**

-Printing for education materials: 38 packets x $1.30 per color page x 6 pages = $296

Total for supplies: $296

c. **Incentives:**

As incentive for participation in the study and timely appointment follow-up, patients will receive free parking in the Wake Forest Baptist visitors lot for each of their (7) study visits. At the completion of their participation in the study (7 appointments), individuals will receive a $20 Visa gift card.

-Parking at each visit: $4.50 x 32 participants for full study x 7 visits = $1,008
$4.50 x 6 participants presumed LTF x 4 visits = $108
-At visit #7: $20 Visa gift card x 30 participants =$640

Total for incentives: $1,756

Total DIRECT COSTS: $10,000

Budget

PERSONNEL	Role	Base	Fringe 0.16	YEAR 02 Effort	Salary	Fringe	Total	Effort	Salary	Fringe	Total	2 Year Total
Safta, Anca	PI				0	0	0		0	0	0	0
Jensen, Elizabeth	Co-investigator				0	0	0		0	0	0	0
Total Key Personnel:					0	0	0		0	0	0	0
To Be Named	Clinical Dietitian/Study Coordinator	50,000	$8,000.00	9%	4,568	731	5,299	4.5%	2,284	365	2,649	7,948
TOTAL PERSONNEL					**4,568**	**731**	**5,299**		**2,284**	**365**	**2,649**	**7,948**
Supplies	**Quantity**	**Pages per packet**	**Cost per page**									
Education materials (color printing)	38	6	1.30				**296**			0	**0**	**296**
Other (Incentives)	**Participants**	**Appointments**	**Cost per visit**					**Participants**	**Appointments**	**Cost per visit**		
Parking (full participants)	32	5	4.50				**720**	32	2	4.50	**288**	**1,008**
Parking (LTF participants)	6	4	4.50				**108**			0	**0**	**108**
Gift Card							0	32		20	**640**	**640**
Total Non-Personnel:							1,124				928	2,052
TOTAL DIRECT Costs:							**$6.423**				**$3.577**	**$10.000**