Efficacy of allergy patch testing in directed dietary therapy of eosinophilic esophagitis: A pilot study

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Title: Efficacy of allergy patch testing in directed dietary therapy of eosinophilic esophagitis: A pilot study

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Background:

Eosinophilic esophagitis (EoE) is a chronic disease characterized by esophageal eosinophilia leading to inflammation and fibrosis. One of the possible mechanisms in this disease is that antigen recognition occurs in the esophagus by dendritic cell recognition and generation of a Th2 allergic response. The causative agents are believed to be food antigens, supported by resolution of esophageal eosinophilia with an elemental diet in patients.[1,2] However, the clinical utility of an elemental is limited due to expense and poor dietary compliance.[3] Consequently the more selective six food elimination diet, with exclusion of the most common food allergens of milk, soy, egg, wheat, peanuts/tree nuts, and shellfish/fish, has emerged as the main nonpharmacologic treatment strategy with reasonable efficacy in both pediatric and adult EoE patients.[4-6] In addition, food reintroduction allows identification of a single causative food in a substantial proportion of patients.[4,5] However, clinical application of this strategy is a difficult and lengthy process for patients, with the need for multiple esophagogastroduodenoscopies (EGDs) presenting considerable cost considerations.[5]

Consequently a selected elimination diet based on less invasive testing would offer the ideal dietary treatment strategy. The efficacy of skin prick testing (SPT) to direct a selective elimination diet in EoE has been explored. However, to date this strategy has not proven effective, with skin prick testing providing poor positive and negative predictive values.[4-7] This may be because SPT measures an IgE mediated allergic response to food allergens, potentially explaining its limited utility in the Th2 mediated process of EoE. Allergy patch testing (APT), by virtue of its measurement of delayed hypersensitivity, may offer a reasonable alternative. APT involves application of potential allergens directly into the skin for an extended time period, with resultant reactions suggestive of a delayed hypersensitivity reaction, more consistent with the Th2 process implicated in EoE. Indeed, several pediatric studies have demonstrated greater success in identifying causative foods with APT than SPT.[8-10] However, to date adult studies using APT in EoE are lacking.

We propose that APT may accurately allow for a directed elimination diet in EoE with similar efficacy to the SFED. Such an approach would offer a more feasible and cost effective clinical approach to treating EoE, requiring fewer office visits and EGDs.

Hypothesis:

Allergic patch testing will identify causative food antigens in eosinophilic esophagitis

Primary Aim:

1. Determine the reliability of the allergy patch test (APT) to predict effective directed dietary therapy of EoE

Secondary Aim:

2. Determine efficacy of APT as compared to a SFED
3. Determine efficacy of APT in patients who are nonresponders to a SFED
4. Determine efficacy of SFED in patients with EoE

Methods:

Study Design:

Patients referred to Mayo Clinic Rochester with an establish diagnosis of EoE who are nonresponsive to proton pump inhibitor (PPI) medical therapy will be identified (as defined below). Eligible patients will then meet with one of three investigators (KR, JAA, DAK), complete the Mayo Dysphagia Questionaire-30 Day (MDQ-30) following which a standardized APT will be conducted. Thereafter, a standard clinically indicated SFED treatment protocol will be completed as outlined below. Patients will follow up with one of three investigators (KR, JAA, DAK) following the elimination diet who will be blinded to the results of the APT. During this visit responders and nonresponders will be identified and nonresponders will complete a directed elimination diet based on APT results.

Inclusion criteria:

- Adults ages 18-90
- Patients with EoE, defined as dysphagia with histologic finding of greater than or equal to 15 eosinophils per high powered field (eos per HPF) on index esophageal biopsy
- Persistent symptoms and/or greater than or equal to 10 eos per HPF on esophageal biopsy after at least 8 weeks of twice daily PPI therapy

Exclusion criteria:

- Patients with conditions known to be associated with esophageal eosinophilia, including Crohn's disease, Churg-Strauss, achalasia, and hypereosinophilic syndrome
- Steroids within 8 weeks of study enrollment
- Dermatologic conditions precluding application of Finn chambers to the skin for APT
- Inability to read due to: Blindness, cognitive dysfunction, or English language illiteracy

Study Flow:

Eligible patients meeting the diagnostic definition of EoE will be identified:

1. Patients will meet with one of 3 investigators (KR, JAA, DAK) to discuss diagnosis and treatment and complete the MDQ-30 to assess baseline symptoms
2. A urine pregnancy test will not be performed as part of the study as this will be done clinically.
3. Patient will then undergo APT testing per the following protocol:
    - 2g of dry foods will be placed in 2ml of isotonic saline solution. The mixtures will then be placed in aluminum cups (ie Finn chambers) measuring 6 or 12 mm in diameter and adhered to the patient's back.
    - Foods to be included will be milk, wheat, egg, soy, peanut, tree nut, fish, shellfish, beef, corn, chicken, potato, pork, legumes, barley, rye, tomato, rice, fruits
    - The patches will be removed at 48 hours, and results read at 96 hours after application.
    - Reactions will be classified as negative, 1).erythema 2).erythema/raised 3). erythema/raised/spreading 4). erythema/raised/spreading/blistering.
4. The patient will then meet with a dietitian to discuss the SFED
5. The clinical SFED protocol will be followed as below:
    - Patients will follow the SFED by excluding milk, wheat, eggs, soy, nuts, and fish for 6 weeks
    - The patients will keep a diet diary and meet with the dietitian prior to initiating the SFED and immediately after completing the SFED. In addition, a phone interview (DMG, LAK) will be completed at 2 and 4 weeks of the SFED to ensure compliance
    - Following completion of the SFED, the patient will meet with one of three investigators (KR, JAA, DAK) who will be blinded to the APT results and the MDQ-30 will be given

- The patient will then undergo an EGD with esophageal biopsies as per clinical practice
- Patients with symptomatic and histologic response (defined by <10 eos per HPF on biopsy) will be defined as responders.
- Responders will then undergo food reintroduction via the following protocol:

a. Nuts for 2 weeks
b. Fish for 2 weeks
c. Repeat EGD at the end of 4 weeks with repeat biopsy
d. If biopsy shows <10 eos per HPF, skip to step f
e. If biopsy shows ≥ 10 eos per HPF, eliminate only nuts for 2 weeks then repeat EGD and if <10 eos per HPF, then fish x 2 weeks with repeat EGD to confirm persistent histologic remission.
f. Eggs for 2 weeks
g. Soy for 2 weeks
h. Repeat EGD at the end of 4 weeks with repeat biopsy
i. If biopsy shows <10 eos per HPF, skip to step k
j. If biopsy shows ≥ 10 eos per HPF, eliminate only eggs for 2 weeks then repeat EGD and if <10 eos per HPF, then soy x 2 weeks with repeat EGD to confirm persistent histologic remission.
k. Wheat for 2 weeks
l. Repeat EGD at the end of 2 weeks with repeat biopsy
m. If biopsy shows <10 eos per HPF, skip to step o
n. If biopsy shows ≥ 10 eos per HPF, eliminate wheat and repeat EGD
o. Milk for 2 weeks
p. Repeat EGD at the end of 2 weeks with repeat biopsy
q. If biopsy shows ≥ 10 eos per HPF, eliminate milk and repeat EGD

6. SFED nonresponders will then undergo a directed elimination diet, with specific foods eliminated based on the results of the APT. A clinically indicated repeat EGD will be conducted 6 weeks later with 4 mid and 4 distal esophageal biopsies.

There is minimal risk associated with this study. As the initial diagnostic evaluation and SFED are part of standard clinical care, there is no increased risk from the standpoint of endoscopy or conscious sedation for enrolled patients. APT is generally safe, with potential complications including active sensitization, dermatitis, hyper- or hypo- pigmentation, milia, pressure effect, and scar. However, reported rates of these complications are far less than 1% and are easily reversible. The most feared risk is anaphylaxis, which is extremely rare and only described with bacitracin and neomycin which will not be used in this study.

<u>Statistical Analysis and Feasibility:</u>

We plan on conducting a pilot study with a total enrollment of 20 patients for this study. In 2013, 230 patients with an ICD-9 code matching EoE were seen at our institution. Approximately 50% of these patients were nonresponders to PPI. Consequently, even assuming only 50% recruitment, approximately 58 patients would be enrolled over a 12 month period.

Primary Endpoint:

1. Proportion of successfully treated SFED patients, defined by histologic and symptomatic response, with causative food identified by APT

Secondary Endpoints:

2. Proportion of EoE patients with histologic response to an APT directed diet in nonresponders to SFED
3. Proportion of EoE patients with symptomatic response to an APT directed diet in nonresponders to SFED
4. Proportion of EoE patients with histologic response to the SFED
5. Proportion of EoE patients with symptomatic response to the SFED

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