Integrity of the Mucosa: effect of Amino acid formula on Gastrointestinal tract epithelium in adult Eosinophilic esophagitis patients

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Primary: To demonstrate that a liquid Neocate product (elemental nutrition) study decreased esophageal eosinophil count to less than 15 eosinophils per high-power field in adult patients with eosinophilic esophagitis.Secondary: To study the effect...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Gastrointestinal inflammatory conditions
Study type	Interventional

Summary

ID

NL-OMON40965

Source
ToetsingOnline

Brief title
IMAGE trial

Condition

- Gastrointestinal inflammatory conditions
- Allergic conditions

Synonym
allergic esophagitis, Idiopathic eosinophilic esophagitis

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Nutricia,Nutricia Research

Intervention

Keyword: Elemental diet, Eosinophilic esophagitis, Epithelial barrier integrity, Microbiome

Outcome measures

Primary outcome

Change in esophageal mucosalpeak eosinophil count, measured as maximum number of eosinophils per hpf. Response is defined as complete when the peak eosinophil count decreases to <15 eos/hpf.

Secondary outcome

Measures of mucosal barrier function:

- Esophageal and duodenal permeability measured in vivo (electrical tissue impedance spectroscopy) and ex vivo (Ussing chambers experiments)

- Intestinal permeability testing using a lactulose:mannitol absorption * urine excretion test

Clinical parameters:

- Questionnaires:

- Symptoms (dysphagia, food impaction) (Baseline and after 4 week)

- Patient acceptation of and adherence to the diet (every week)

- Quality of life (SF-36) Baseline and after 4 weeks

- Endoscopic features

- Correlation between primary/secondary parameters and intestinal permeability

Adherence to the diet

- Empty drink packages will be stored by the patient and they will be asked to note the date of consumption on it

- A questionnaire *Studie productinname* will be filled in weekly

Laboratory investigations:

- Immunohistochemical analyses of esophageal and duodenal biopsy material to assess expression and localization of proteins involved in barrier function

- Serum biomarkers (total IgE, eosinophil count, IL-5, IL-13, eotaxin-3, eosinophil-derived neurotoxin)

- Transcriptional analyses: microarray or focused qPCR. Genes to be analyzed by qPCR involve:

- Activity markers of EoE (IL-5, IL-13, eotaxin-3, TGF-B)

- Tight junction proteins (Claudins, ZO-3, occludin, filaggrin, desmoglein)

- Inflammatory genes (IL-6, IL-10, TNF*, CCL-2, CCL-5, CCL-20, LAG3, ICAM1, caspases 1-14)

- If other assessments show differences between the groups optionally the gastrointestinal microbiome will be analyzed.

Study description

Background summary

Eosinophilic esophagitis (EoE) is an inflammatory disease of the esophagus characterized by dysphagia, food impaction and strictures. Current treatment of EoE is limited to topical or systemic corticosteroids and repeated endoscopic dilations. The use of corticosteroid is accompanied by significant side-effects

that preclude long term treatment while dilations are painful, carry a risk of perforation and, as underlying inflammation is not affected, recurrence often occurs. Quality of life is significantly decreased in patients with EoE and this persists up to 15 years after the first presentation, as there is currently no acceptable treatment for patients with this disease.
We have recently completed a study using the Dutch pathology database (PALGA) in which we demonstrate a huge increase in incidence of EoE in the Netherlands from 0.01 in 1995 to 1.30 per 100 000 inhabitants in 2010 and still rising. These numbers are in line with North American reports of a huge increase in incidence. The majority of patients are young, otherwise healthy subjects between 20 and 40 years of age and there are reasons to believe that many patients are still not diagnosed yet.
The pathophysiology of EoE is largely unknown, although food allergy is suggested to play an important role. Most EoE patients suffer from atopic diseases and the majority of patients is polysensitized to food allergens. IgE producing B cells and a high level of IgE bearing mast cells are present in the esophageal mucosa of patients with EoE. We recently showed that the mucosal barrier of patients with EoE is impaired and highly permeable to molecules with the size of food allergens (data submitted). This impairment in mucosal integrity can be primary, as observed in the skin disease atopic eczema where an increased permeability is responsible for a high permeation of allergenic molecules and subsequent activation of immune cells. Similarly, in atopic eczema barrier dysfunction thus plays a role in initiating the inflammatory process. However, it is also possible that the impaired mucosal integrity found in EoE is only secondary to products produced by the inflammatory infiltrate, and thus be the result of inflammation and not the initiator.

As mentioned, there is much data that suggests that food allergy plays an important role in EoE and elimination diets have indeed been found to be effective. Studies using the broad 6 food elimination diet (exclusion of milk, soy, egg, wheat, peanuts/tree nuts, and shellfish/fish) demonstrate a clinical and pathologic response in 73-94% of patients.
Elimination diets are also very effective in pediatric patients with EoE, with patients often reaching complete symptomatic and histological remission. A retrospective comparative report suggests that elementary diets are even more effective than elimination diets with reported remission induction in 96% of the treated children. The effect of elemental diet on adult patients with EoE has only been investigated once. An American study by Peterson et al reported that out of 18 patients that completed a trial with elementary diet (Elecare, Abbott), only one patient did not respond. However, of the 29 patients that were initially evaluated for the trial, 11 patients discontinued after starting with elementary diet because of adherence failure leaving only 18 evaluable patients. Adherence is thus an important point, when considering this treatment.

More research on the role of elementary nutrition in adult patients with EoE is thus required. In the current protocol we will also evaluate whether a

different formula with improved taste will enhance adherence.

Secondary, it will be crucial to study the effect of elementary nutrition on esophageal mucosal integrity in EoE patients in order to get more insights into pathophysiology. If, in the patients with complete remission, the mucosal integrity will normalize, this will serve as evidence that mucosal integrity changes are secondary to inflammation. However, if there is still decreased mucosal integrity in the absence of inflammation, this could serve as an indication that the observed mucosal integrity changes are a primary characteristic of the esophageal mucosa of these patients.

Finally, in atopic dermatitis an increased permeability of the intestine is observed. In this disease the increased intestinal permeability plays a role in increased presentation of allergens to antigen presenting cells and triggers limited local inflammation and a systemic T-helper 2 response with increased levels of IL4, IL5, IL10 and IL13 after which stimulates inflammation in a distant organ (i.e. the skin). It is very well possible that intestinal permeability is also present in EoE. Increased permeability of food allergens could also in EoE initiate a systematic T-helper 2 response, and stimulate or aggravate inflammation in a distant organ, which is in case of EoE the esophagus. Elementary formular diet could thus, next to a direct effect on esophageal inflammation, also work beneficial indirectly through an effect on the intestine.

Study objective

Primary: To demonstrate that a liquid Neocate product (elemental nutrition) study decreased esophageal eosinophil count to less than 15 eosinophils per high-power field in adult patients with eosinophilic esophagitis.

Secondary: To study the effect of Neocate elemental nutrition on:
- Esophageal, duodenal and intestinal mucosal integrity
- Esophageal inflammation (mast cells and inflammatory cytokines)
- Esophageal endoscopic signs of EoE
- Esophageal symptoms, quality of life, and product acceptability
- Depending on former study outcomes the gastrointestinal microbiome will be analyzed (esophagus, duodenum, saliva, feces)

Study design

Prospective intervention study

Intervention

Elemental diet preceded by and followed by gastroscopy

Study burden and risks

Patients will be treated with an extensive diet. During the study patients are not allowed to eat normal food. Patient adherence will be a big challenge. To diminished a high dropout in the first days of dietary treatment we incorporated an elemental diet test day of 24 hours.
Since the production of saliva, which plays an important role in maintaining oral health, is diminished by a liquid diet, participants are allowed to use sugar free chewing gum.

Patients will undergo gastroscopy twice; healthy volunteers once. The risk of the performed procedures consists of the risk of esophageal biopsies, namely bleeding and perforation.
There is no additional risk involved with the electrical tissue impedance measurements.
Since participants are not allowed to use anti-inflammatory medication, esophageal inflammation and symptoms might increase.
For the lactulose:mannitol absorption * urine excretion test, patients and healthy volunteers need to collect urine and report fluid intake for 2 hours; this test is safe and is not associated with additional risks.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Patients:
- Previous diagnosis of EoE confirmed by histopathology e.g. presence of >15 eosinophilic granulocytes per high power field (hpf) in mid or proximal esophageal biopsies before the start of any therapy
- Currently experiencing dysphagia
- Written informed consent
- Age 18 * 75 years;Healthy controls:
- Written informed consent
- Age 18 * 75 years

Exclusion criteria

Patients:
- Inability to stop topical corticosteroids
- Use of systemic corticosteroids, leukotriene inhibitors, or monoclonal antibodies, in the month preceding the study
- Use of anticoagulants at study entry
- Use of NSAIDs without possibility to stop
- History of peptic ulcer disease
- History of Barrett*s esophagus
- History of GI cancer
- History of GI tract surgery (except appendectomy)
- ASA class IV or V
-History of sacharase-isomaltase deficiency
-History of hereditary fructose-intolerance, galactosemy or lactose deficiency
-History of diabetes mellitus
-Hypersensitivity to mannitol or lactulose;Healthy controls:
- Use of systemic corticosteroids, leukotriene inhibitors, or monoclonal antibodies in the month preceding the study
- Use of anticoagulants at study entry
- Use of NSAIDs without possibility to stop
- Personal history of atopic, skin or systemic diseases
- Symptoms suggestive of esophageal disease
- History of GI cancer
- History of GI tract surgery (except appendectomy)

- History of PPI, H2-receptor antagonist, or prokinetic drug use
- ASA class IV or V
-Hypersensitivity to mannitol or lactulose
-History of sacharase-isomaltase deficiency
-History of hereditary fructose-intolerance, galactosemy or lactose deficiency
-History of diabetes mellitus

Study design

Design

Study type:	Interventional
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	07-11-2014
Enrollment:	31
Type:	Actual

Ethics review

Approved WMO Date:	17-10-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-11-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL49502.018.14