*Effect of addition of elemental nutrition to an elimination diet on esophageal inflammation in adult eosinophilic esophagitis (EoE) patients: A randomized controlled trial

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To investigate whether addition of amino acid-based nutritional supplements to FFED is more effective in reducing esophageal eosinophilic inflammation measured as reduction in absolute number of eosinophils than FFED alone, in adult EoE patients.

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

Summary

ID

NL-OMON48882

Source
ToetsingOnline

Brief title
Supplemental Elemental trial (SET)

Condition

- Gastrointestinal inflammatory conditions
- Allergic conditions

Synonym
allergic esophagitis, Idiopathic eosinophilic esophagitis

Research involving
Human

Sponsors and support

Primary sponsor: Maag- Darm- en Levergeneeskunde
Source(s) of monetary or material Support: Nutricia,Nutricia Research

Intervention

Keyword: Elemental supplement, Elimination diet, Eosinophilic oesofagitis, Esophageal inflammation

Outcome measures

Primary outcome

Change in peak eosinophil count, measured as maximum number of eosinophils per HPF. Response is defined as complete if the reduction of absolute number of eosinophils per HPF is decreased to <10 eosinophils/HPF. Esophageal mucosal eosinophil infiltration is considered the most important marker of disease activity and is primary endpoint in all major therapeutic studies. These biopsies are taken at mid and proximal esophageal level during upper endoscopy.

Secondary outcome

Clinical / endoscopic parameters:

- Questionnaires:

o o Patient acceptation of and adherence to the diet will be checked by means of an appointment at the dietitian after 2 and 4 weeks to evaluate the diet. Feasibility of the diet will be measured using the likert scoring system.

o Patient reported symptoms (Reflux Disease Questionnaire (RDQ), and Straumann Dysphagia Index (SDI))) (baseline and after diet)

o Quality of life (EoE-QoL-A) (baseline and after diet)

o Esophageal endoscopic signs measured with the Endoscopic Reference Score

(EREFS)

- Nutritional monitoring:

o Body Mass Index (BMI) to measure weight loss

o Nutrition intake will be calculated at baseline and after 4 weeks of

elimination diet using 3-day food diaries

Laboratory investigations:

- Expression of genes encoding for the esophageal inflammation and barrier

function (IL-1, IL-4, IL-6, IL-8, IL10, IL12, IL-13, IL-15, Thymic

Stromal Lymphopoietin (TSLP), Eotaxin (CCL26), desmoglein-1 (DSG1) and

filaggrin (FLG))

- Immunohistochemical analyses of esophageal material to assess expression and

localization of proteins involved in barrier function.

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

qPCR involve:

o Activity markers of EoE (IL-5, IL-13, eotaxin-3, TSLP)

o Barrier integrity proteins (filaggrin, desmoglein)

Study description

Background summary

EoE is a chronic immune-mediated disorder of the esophagus in which dietary allergens penetrate the esophageal mucosa and subsequently activate the immune

system with eosinophilic inflammation as a response. Clinical symptoms are dysphagia and food impaction, and histologically the disease is characterized by an esophageal infiltration of eosinophils.

Quality of life is significantly decreased in patients with insufficiently treated EoE, which emphasizes the need for new treatment approaches as there is currently no acceptable treatment for the growing group of patients suffering from EoE. Current treatment of EoE is limited to topical or systemic corticosteroids, endoscopic dilations and dietary elimination of food allergens. Chronic use of corticosteroids is often not acceptable for young patients and may be accompanied by side-effects that may preclude long term treatment while dilations are painful, carry a risk of perforation and, as underlying inflammation is not affected, needs to be repeated with time. Dietary treatment seems a promising and safe drug free solution, although patients adherence is challenging.

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 extensive six 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. A less extensive approach is the four food elimination diet (FFED) (exclusion of milk, soy, egg and wheat), which has also shown to be effective. Histologic remission rates vary from 54% in adults to 71% in children. Elemental diets with complete elimination of all possible food allergens by exclusive use of amino acid-based formulas are also very effective in pediatric and adult patients with EoE, with histologic response rates up to 94% of patients.

A major obstacle in current dietary management is that it is unknown for which allergens the patient is sensitized/allergic. Currently available allergy tests do not provide sufficient sensitivity and specificity in causative allergen detection. The ultimate goal is to exclusively eliminate the food(s) responsible for triggering and maintaining the disease in each individual patient. Therefore, most diets start with a very extensive empiric elimination diet such as the six or four food elimination diets and then reintroduce food groups step by step, with endoscopy 4-6 weeks after each change in diet. This process spans several months and due to the high level of restrictions, particular in the beginning, there is a significant risk of insufficient caloric intake or accidental dietary mistakes. Addition of a formula feeding may thus be helpful in order to maintain a healthy dietary intake. Additionally, product food labels can be imprecise which may induce cross-contamination and disappointing response rates. In specific situations it may be easier to consume an easy to prepare amino acid-based formula without causative allergens than consume a meal with a not completely known mix of ingredients.

We have recently shown that a new formulation of amino acid-based nutrition,

when consumed as sole source nutrition, induces histological and clinical remission within 4 weeks in the majority of EoE patients, showing that it is very suitable as dietary treatment for these patients. Furthermore, it was well tolerated in these adult EoE patients. Unfortunately, the use of amino-acid-based formula as sole source nutrition is not feasible for adult patients as a long-term dietary treatment. Aside from the removal of all food allergens there is also data suggesting that amino acid-based nutrition has anti-inflammatory effects itself. In non-allergic inflammatory bowel diseases, such as Crohn*s disease elemental diet has shown to be effective in reducing inflammation. The detailed mechanisms underlying this effectiveness is unclear, however, it has been reported that some amino acids (glycine, histidine and cysteine) exhibit anti-inflammatory effects and that the elemental diet reduces the production of pro-inflammatory cytokines such as IL-1, IL-4, IL-6, IL-8, IL-10, IL-12, GM-CSF and TNFa in Crohn*s disease. Additionally, another study showed that cysteine and histidine exhibit anti-inflammatory effects in human monocytes / macrophages. Also nutrients present in having anti-inflammatory effects, may contribute to the anti-inflammatory effects of an amino-acid based formula.
It is now increasingly recognized that foods and nutrients play an important role in the maintenance or disruption of the mucosal integrity and the process of inflammation through:
A. Local effects on epithelial integrity and mucosal epithelium and mucosal immune system of the gastro-intestinal tract, vitamin A plays a critical role in the differentiation of cells towards epithelial lineages important for mucosal defense. Also zinc and iron have an essential role in the maintenance of intestinal epithelial tight junction barrier via the regulation of claudin-3 and occluding expression.
B. Systemic effects on the immune system through micronutrients. According to very strict criteria several nutrients such as copper, folate, iron, selenium, vitamin A, B6, B12, C, D and zinc are recognized as having immunomodulatory properties.
C. Long-chain polyunsaturated fatty acids (LCPUFA) are known because of their immunomodulatory properties. These fatty acids serve as specific precursors of immune regulatory eicosanoids. In general, n-6 LCPUFA are considered as being pro-inflammatory and n-3 LCPUFA as being protective against inflammation.
An independent anti-inflammatory effect of the amino-acid based formula could also in EoE contribute to the effect of the empiric elimination diet and would thus make this an ideal combination.

We hypothesize that the addition of an amino acid-based nutritional supplement to a FFED is more effective than FFED alone due to the: (1) anti-inflammatory effect of the amino acids and anti-inflammatory nutrients (2) improving patient*s adherence to the diet by increasing the feasibility of allergen avoidance. Furthermore, we expect that the combination of amino acid-based nutritional supplements and FFED leads to a higher acceptation of the diet and a better quality of life.

Therefore, in the current protocol, we will evaluate whether the addition of amino-acid based nutrition to FFED is superior to FFED alone in terms of improvement of the esophageal eosinophilic inflammation, and improved patients* adherence and acceptability of the diet. Secondary, it will be important to study the effect of additional amino acid-based nutrition on symptoms as measured by patient reported outcomes, weight loss prevention and quality of life. In both arms the efficacy of the intervention will be controlled for the total composition of the diet.

Finally, in order to investigate the anti-inflammatory effects of the addition of amino-acid based nutritional supplements additional measurements are performed on tissue and serum.

Study objective

To investigate whether addition of amino acid-based nutritional supplements to FFED is more effective in reducing esophageal eosinophilic inflammation measured as reduction in absolute number of eosinophils than FFED alone, in adult EoE patients.

Study design

Prospective randomized controlled intervention study

Intervention

Standard elimination diet or elimination diet with addition of elemental nutrition.

Study burden and risks

The extra burden of participation in the study is limited to one extra visit to the hospital and filling out questionnaires. Elimination diet is an accepted treatment for EoE and is accompanied by regular endoscopy to evaluate each dietary step. There are no extra risks associated with the addition of elemental nutrition.

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

- Active EoE at baseline i.e. 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 above 18 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
- Recent history of GI cancer
- History of major GI tract surgery
- ASA class IV or V

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	29-11-2017
Enrollment:	40
Type:	Actual

Ethics review

Approved WMO Date:	10-10-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-07-2019
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

ID: 24372
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
CCMO	NL62715.018.17
OMON	NL-OMON24372