Modulation of immune function by parenteral fish oil in patients with Crohn*s disease and high inherent Tumor Necrosis Factor-alfa production, a randomized, single blinded, cross-over study

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To evaluate the effect of parenteral supplementation of fishoil based emulsion (rich in omega-3 fatty acids) compared with a soy bean oil emulsion (rich in omega-6 fatty acids) on the leukocyte functions (amongst others production of TNF-α and other...

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

Summary

ID

NL-OMON40244

Source
ToetsingOnline

Brief title
Immune modulation with parenteral fish oil in Crohn*s disease

Condition

- Gastrointestinal inflammatory conditions

Synonym
Crohn's disease, inflammatory bowel disease

Research involving

Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Sint Radboud
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: anti-inflammatory, Crohn□s disease, Fish oil, TNF-&alfa

Outcome measures

Primary outcome

Primary Objective:

-change in ex vivo TNF- α production by LPS stimulated PBMC*s under influence

of administered n-3 or n-6-based lipid emulsions

Secondary outcome

Secondary Objectives:

Ex vivo production of relevant cytokines (other than TNF-α) by isolated PBMCs:

(IFN-c,IL-1b, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12 p70, TNF-β)

Leukocyte count (and leukocyte differentiation)

Serum levels of TNF-α

Leukocyte functions

- Oxygen radical production by neutrophils

- Expression of cell surface markers on neutrophils and monocytes (immune

fluorescent staining and subsequent flowcytometric

analysis)

(anti-) Oxidant status and oxidative damage

Concentration of prostaglandin E2

Plasma triaglycerol and free fatty acid concentrations

Composition of phospholipids in the cell membrane to evaluate fatty acid

incorporation

Analysis of SNPs related with a high inherent TNF-α production

Study description

Background summary

Fish oil (rich in omega-3 fatty acids) has anti-inflammatory characteristics. Trials investigating the ability of fish oil capsules for treatment of patients with Crohn*s disease (a chronic inflammatory bowel disease) show discordant results. It is reasonable that these divergent results are due to inter-individual variation in cytokine production (like TNF-α). TNF-α is a cytokine, which plays a central position in the pathofysiology of Crohn*s disease, hence anti-TNF-α agents (infliximab (Remicade®) en adalimumab (Humira®)) have an important role in today*s treatment of Crohn*s disease.

It is known that administration of fish oil can decrease TNF-α production in healthy people with a high inherent TNF-α production, however this is not applicable for people with a middle or low TNF-α production, in which TNF-α production is unaffected or even increases in the case of a low inherent TNF-α production. Based on these results we formulated the hypothesis that omega-3 fatty acids can be used as a treatment in a selected group of patients.

By administering an emulsion of fish oil to patients with Crohn*s disease with a high inherent TNF-α production we expect to find a positive result. With intravenous administration patients experience less side effects like nausea, diarrhea and fish-smell, furthermore the omega-3 fatty acids are incorporated faster. Intravenous administration of fish oil is already used as a component of total parenteral feeding in addition to soybean oil.

Study objective

To evaluate the effect of parenteral supplementation of fishoil based emulsion

(rich in omega-3 fatty acids) compared with a soy bean oil emulsion (rich in omega-6 fatty acids) on the leukocyte functions (amongst others production of TNF-α and other cytokines) in patients with Crohn's disease and a high inherent TNF-α production.

Study design

First phase: patients with a high inherent TNF- α will be identified by assessment of TNF-α production in a group 100 patients with Crohn's disease who meet in- and exclusion criteria. Patients in the highest tertile are classified as 'high producers'. From this group 12 random patients are invited for the second part of this trial.

second phase:
Single center, randomized, single blinded, lipid-controlled, cross-over pilot trial in 12 patients with Crohn's disease and a high TNF-α production. (see intervetion for additional information)

Intervention

First, patients with a high inherent TNF- α will be identified by assessment of TNF-α production in a group 100 patients with Crohn's disease who meet in- and exclusion criteria. Patients within the highest tertile will be classified as high producers.

Next, 12 patients within the highest tertile will be randomized to intravenous administration of 20% (w/v) lipid-control (Intralipid®), and, after crossing over, 10% (w/v) fish oil emulsion (Omegaven®), or vice-versa for 1 hour on three consecutive days at a dose of 0.2 g/Kg BW/hr. So patients who are blinded for the intervention receive both emulsions.

Study parameters will be assessed in blood drawn prior to the first infusion (T=0) and 1 (T=4) and 8 days (T=11) after the third infusion. Between the two treatment arms, there will be a wash-out interval of 2-3 weeks.

Study burden and risks

An intravenous infusion of one of both lipid emulsions will be administered for 1 hour on three consecutive days. Blood samples will be drawn by peripheral venapuncture on day 1 prior to the first infusion (50cc), on day 2 and 3 prior to the infusion 3 cc (serum lipid concentration control) and on one day (day 4)(50cc) and one week (day 11) (50cc) after the third infusion. Of these, four (day 1, 2 and 3) do not require an additional puncture since they can be drawn from the venflon that is inserted the infusions and remains there for a couple of days. This whole protocol will be performed two times with a wash-out

interval of two weeks, so patients receive both interventions.

Risk associated with participation can be categorized as *low* and include an allergic reaction to the lipid infusion, infection extravasation of infused emulsion or placebo or a hematoma at the puncture site.

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

-Histologically proven Crohn*s disease in the ileum or colon;-Previous bowel surgery because of Crohn*s disease activity (more than 6 months before screening) ;-Currently in remission (Crohn*s Disease Activity Index (CDAI) <150);-No use of one the following immunosuppressive drugs (or its variants) within the last 6 months : corticosteroids (with exclusion of inhalation- or dermatological ointment containing steroids), methotrexate,

thiopurines, anti-TNF-α agents, cyclosporine, tacrolimus, sirolimus or Cellcept® ;-Willingness and ability to give written informed consent

Exclusion criteria

- Incapacitated people (people unable to reasonably judge -what is in their own interests);- Patients with other active inflammatory / immune mediated underlying diseases;- Smoking > 5 cigarettes a day [70];- Diet with >2 portions of fatty fish (tuna, salmon, mackerel, herring, trout and haring) a week;- History of metabolic disorder (especially diabetes or lipid disorders);- Crohn*s disease activity, including the presence of active fistulas ;- On need for medical (other that 5-ASA preparations) or surgical treatment for Crohn*s disease activity;- Use of NSAIDs or asprin;- C-reactive protein levels of >10 mg/l ;- History of venous or arterial thrombosis;- Active malignancy ;- Presence of severe pulmonary, cardiovascular, renal, liver, coagulation or hematological disease;- Pregnancy or lactation ;- Age above;18 yrs;- Allergy for one of the following components: fish, chicken, eggs or soy beans

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Single blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	10-11-2013
Enrollment:	100
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	IntIntralipid 20% emulsion for infusion
Generic name:	Intralipid 20%
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Omegaven-Fresenius, emulsion for infusion
Generic name:	Omegaven 10%
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	18-06-2013
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	04-07-2013
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	18-09-2013
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	14-11-2014
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	18-11-2014
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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
EudraCT	EUCTR2013-001212-30-NL
CCMO	NL42964.091.13