(Patho)Physiological aspects of the bile salt-FXR-FGF19-axis: potential consequences in Crohn's disease.

Published: 02-07-2009
Last updated: 06-05-2024

To study potential abnormal functioning of the bile salt-FXR-FGF19 axis in patients with clinically quiescent Crohn*s colitis.

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

Summary

ID

NL-OMON35367

Source
ToetsingOnline

Brief title
Bile acid-FXR-FGF19 functioning in Crohn's disease

Condition

- Gastrointestinal inflammatory conditions

Synonym
chronic intestinal inflammation, Crohn's disease

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Crohn's disease, FGF19, FXR

Outcome measures

Primary outcome

Primary study endpoint is the difference between Crohn*s patients and disease controls in increase in fasting plasma FGF19 concentration after 8 days CDCA ingestion.

Secondary outcome

Secondary study endpoints are the differences between Crohn*s patients and disease controls in:

1. acute increase of fasting plasma FGF19 concentration after CDCA ingestion;

2. increase of fasting gallbladder volumes after acute and 8 days CDCA ingestion;

3. expression in ileal and caecal biopsies of FXR and various target genes after CDCA ingestion;

4. fecal bile salt excretion after CDCA ingestion.

Study description

Background summary

After a meal, gallbladder contraction evacuates bile salts into the intestine, with subsequent bile salt transport to the ileum and by active transport, reabsorption into the enterohepatic circulation. In the ileal enterocyte, reabsorbed bile salts activate the bile salt nuclear receptor FXR (Farnesoid X Receptor) with the result that: 1. toxic intracellular bile salt concentrations in the ileal enterocyte and in the liver cell are prevented by regulation of expression of various FXR target genes involved in intracellular bile salt transport and bile salt neosynthesis 2. *ileal brake* is activated through

enhanced expression of the FXR target gene fibroblast growth factor (FGF) 19, which functions, after its secretion by the ileal cell, as a hormone inducing transition of post-prandial into fasting state, including gallbladder dilatation 3. adequate intestinal barrier function and antibacterial defense (both known to be disturbed in inflammatory bowel disease) are maintained, through regulation of expression of various pivotal FXR target genes. In vitro studies suggest that an anti-inflammatory effect is generated through NF*B inhibition. In patients with Crohn*s disease, absorption of bile salts in the ileum into the enterohepatic circulation is thought to be impaired, either through active ileal inflammation or through faster passage of intestinal contents through small and large intestinal tract. We hypothesize that in patients with Crohn's disease this, or constitutively decreased ileal FXR expression (for example due to polymorphisms in the FXR gene), may lead to impaired activation of intestinal FXR and FXR target genes involved in antibacterial defense.

Study objective

To study potential abnormal functioning of the bile salt-FXR-FGF19 axis in patients with clinically quiescent Crohn*s colitis.

Study design

Patients with Crohn*s colitis with an indication for surveillance colonoscopy and disease controls who need to undergo colonoscopy to exclude significant disease who meet the in- and exclusion criteria will be asked for their interest to participate in this study by their treating physician. If patients are interested, patients will receive oral and written information about the study from the investigator and within 1-2 weeks they will be contacted by the investigator who will answer remaining questions and who will check the disease activity. If patients consent to participate in the study, they will be asked to visit the endoscopy department 7 days before the scheduled colonoscopy. During this visit, informed consent will be signed by both the patient and the investigator. When the signed informed consent is obtained, disease activity index scoring, fasting gallbladder volume determination by ultrasound and collection of 3 ml blood from a peripheral venous cannula for determination of plasma FGF19 levels will be performed. Thereafter, the FXR ligand chenodeoxycholic acid (CDCA) will be ingested (15 mg/kg), followed by ultrasonographic determination of gallbladder volume and collection of 3 mL blood every hour during 6 hours. The next six days CDCA (15 mg/kg) is ingested at bedtime. Stools will be collected during 24 hours at the day before the colonoscopy. On the day of the clinically indicated colonoscopy patients are fasted because of colonoscopy, except that in the early morning CDCA (15 mg/kg) is ingested. Upon arrival at the outpatient clinic fasting gallbladder volume is assessed by ultrasound and 13 ml of blood is withdrawn (3 ml for FGF19 analysis and 10 ml for SNP analysis). Thereafter, patients will receive a bowel

preparation during four hours. During colonoscopy 6 biopies in the ileum and cecum are taken. These will be immediately placed in liquid nitrogen and stored at -80°C for determination at a later stage of mRNA expression levels of FXR, Angiogenin 1, FGF19, iNOS, CAR12 and other FXR target genes of potential relevance at a later stage. The schematic outline of the study is depicted in figures 1 and 2.

Intervention

Chenodeoxycholic acid (15 mg/kg) will be administered daily for a period of eight days. The risk associated with chenodeoxycholic acid is considered to be very low. There is extensive experience with chenodeoxycholic acid from dissolution therapy of cholesterol gallstones during decades and with the exception of sligthly increased stool frequency, and minor increases of liver biochemistry, no relevant side effects have been noted.

Study burden and risks

- Patients will be contacted by telephone once during this study. This contact will last a maximum of 10 minutes.
- Patients will bring an additional visit to the UMC Utrecht. During this 7 hours lasting visit, 3 ml of blood will be withdrawn from an indwelling catheter seven times and gallbladder volume will be determined by ultrasonography seven times.
- Patients will collect their stools during 24 hours the day prior to the colonoscopy.
- In this study chenodeoxycholic acid (CDCA) is used. No relevant side effects have been noted during decades of experience with CDCA, except slightly softer stools and, exceptionally, mild increases of serum transaminases. These effects have been shown to be reversible after cessation of CDCA ingestion.
- 3 ml of blood will be withdrawn at eight moments (two punctures; 7 times during the first visit and one time at the day of colonoscopy) for FGF19 analysis. In addition to the 3 ml blood for FGF19 analysis, 10 ml will be withdrawn for SNP analysis at the day of the colonoscopy. Thus, a total of 34 ml blood will be withdrawn using only two punctures. After venepuncture a hematoma may develop.
- Gallbladder volumes will be assessed eight times (7 times during the first visit and one time at the day of the colonoscopy) by ultrasonography. Ultrasonographic examinations are non-invasive, safe procedures that will cause little harm to the patient. If patients do not consent to these hourly measuremnents, only two ultrasonographic examinationswill be will be performed.
- The colonoscopy is performed for clinical indications. These endoscopical examinations are routinely performed and considered as safe procedures. Taking additional biopsies of ileum and cecum for mRNA expression analysis will extend the duration of the colonoscopy with a few minutes.

Contacts

Public
Universitair Medisch Centrum Utrecht

Heidelberglaan 100
3584 CX Utrecht
NL
Scientific
Universitair Medisch Centrum Utrecht

Heidelberglaan 100
3584 CX Utrecht
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Colonoscopy clinically indicated to exclude significant disease of the colon or surveillance colonoscopy for Crohn's disease of the colon;
2. Informed consent of the patient.

Exclusion criteria

Patients with Crohn*s disease:
1. Harvey-Bradshaw index > 4 or frequency of defaecation > 4 / day
2. Serum C-reactive protein >20 (according to the last measurement, measured at most 3 months before the study)
3. Surgery of the gastro-intestinal tract (only appendectomy is allowed)

4. Previous cholecystectomy
5. Gallbladder or bile duct stones
6. Previous ERCP with papillotomy.
7. Age < 18 years
8. Inability to communicate with the patient
9. Body Mass Index > 30
10. Concomitant primary sclerosing cholangitis or other significant hepatic or biliary pathology
11. Any malignancy within 5 years before the study
12. Clotting disorders: prolonged prothrombin time (PT) > 2.5 seconds or partial thromboplastin time (PTT) > 9 seconds within 3 months before the study
13. Use of steroids, cyclosporine, aTFN compounds, methotrexate, antibiotics or loperamide/codeine within one month before the study
14. Use of drugs, potentially interfering with CDCA (e.g. colestyramine, ursodeoxycholic acid or bile salt questrants), within one month before the study
15. Pregnancy or lactation
16. Liver function disorders: increased ASAT, ALAT, LDH, gGT and/or AF in relation to the upper limit of normal within 3 months before the study;Disease controls:
1. Previous inflammation of the gastrointestinal tract (excluding previous infectious gastroenteritis if>6 months ago)
2. Frequency of defaecation > 4 / day
3. Serum C-reactive protein >20 (according to the last measurement, measured at most 3 months before the study)
4. Surgery of the gastro-intestinal tract (only appendectomy is allowed)
5. Previous cholecystectomy
6. Gallbladder or bile duct stones
7. Previous ERCP with papillotomy.
8. Age < 18 years
9. Inability to communicate with the patient
10. Body Mass Index > 30
11. Concomitant primary sclerosing cholangitis, or other significant hepatic or biliary pathology
12. Any malignancy within 5 years before the study
13. Clotting disorders: prolonged prothrombin time (PT) > 2.5 seconds or partial thromboplastin time (PTT) > 9 seconds within 3 months before the study
14. Use of steroids, cyclosporine, aTFN compounds, methotrexate, antibiotics or loperamide/codeine within one month before the study
15. Use of drugs, potentially interfering with CDCA (e.g. colestyramine, ursodeoxycholic acid or bile salt questrants), within one month before the study
16. Pregnancy or lactation
17. Liver function disorders: increased ASAT, ALAT, LDH, gGT, AF in relation to the upper limit of normal within 3 months before the study

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	11-01-2010
Enrollment:	24
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Xenbilox
Generic name:	chenodeoxycholic acid

Ethics review

Approved WMO Date:	02-07-2009
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	04-08-2009
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	25-11-2009

Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	01-12-2009
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	27-01-2010
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	02-02-2010
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	26-11-2010
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	22-12-2010
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Not approved Date:	12-04-2011
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	22-04-2011
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

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	EUCTR2009-013348-35-NL
CCMO	NL27650.041.09