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

No registrations found.

Ethical review	Positive opinion
Status	Pending
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON27642

Source
NTR

Brief title
N/A

Health condition

Crohn's disease

Sponsors and support

Primary sponsor: P.D. Siersema, MD, PhD, Utrecht, The Netherlands
Source(s) of monetary or material Support: Fund = initiator = sponsor

Intervention

Outcome measures

Primary outcome

Primary study endpoint is the difference between Crohn’s patients and disease controls in increase of 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

Rationale: 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 NFκB inhibition. Furthermore, preliminary evidence indicates that basal ileal FXR expression in patients with Crohn's colitis is altered, suggesting a pathogenetic role for this nuclear receptor in Crohn's disease. Indeed, in an animal model for colitis, synthetic FXR agonists ameliorated severity of colonic inflammation. Objective: To study the functioning of the bile salt nuclear receptor FXR in patients with quiescent Crohn's colitis. Study design: Prospective case control study. Study population: Twelve patients with quiescent Crohn's colitis, defined as a Harvey-Bradshaw Index (HBI) score <= 4 scheduled for a surveillance colonoscopy. Twelve non-IBD patients scheduled for a colonoscopy to exclude pathology will serve as disease controls. Intervention: Fasting gallbladder volumes (as assessed by ultrasound) and plasma FGF19 concentration of both groups will be determined at baseline. Participants will receive the FXR agonist chenodeoxycholic acid (CDCA) 15 mg/kg for a period of 8 days. Fasting gallbladder volumes will be determined and blood samples for FGF19 analysis will be collected at baseline, every hour during the first 6 hours after CDCA ingestion and after 8 days of CDCA ingestion. Furthermore, one additional blood sample will

be collected for future assessment of relevant SNPs at the day of the colonoscopy and fecal bile acid excretion will be determined after 24 hours of stool collection at the day before the colonoscopy. Ileal and cecal mRNA expression of FXR and relevant target genes will be determined after 8 days of CDCA ingestion. Differences in gallbladder, hormonal and fecal parameters between both groups will be compared . Main study parameters/endpoints: 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 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 objective

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 this may lead to impaired activation of intestinal FXR and FXR target genes involved in antibacterial defense. Also, constitutively decreased ileal FXR expression (for example due to polymorphisms in the FXR gene) could lead to less activation of the bile salt nuclear receptor in patients with Crohn's colitis.

Intervention

Chenodeoxycholic acid 15 mg/kg.

Contacts

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Eligibility criteria

Inclusion criteria

Patients with Crohn’s disease:

1. Surveillance colonoscopy for established Crohn’s disease of the colon (indicated for clinical reasons);

2. Informed consent of the patient.

Disease controls:

1. A clinically indicated colonoscopy to exclude significant disease of the colon;

2. Informed consent of the patient.

Exclusion criteria

Patients with Crohn’s disease:

1. HBI score > 4 or frequency of defaecation > 4 / day;

2. Serum C-reactive protein >7 within 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 increased compared to control or activated partial thromboplastin time (APTT) > 9 seconds increased compared to control (these values are considered within the normal range) within 3 months before the study;

13. Use of steroids, cyclosporine, methotrexate, anti-TNF compounds, antibiotics, loperamide/codeine or laxatives within one month before the study;

14. Use of drugs, potentially interfering with CDCA (e.g. ursodeoxycholic acid or bile salt sequestrants), within one month before the study;

15. Pregnancy or lactation;

16. Liver function disorders: ASAT, ALAT, LDH, gGT and/or AF increased above ULN 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 >7 within 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;

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Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Non-randomized controlled trial

Control: N/A , unknown

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-09-2009
Enrollment:	24
Type:	Anticipated

Ethics review

Positive opinion

Date:	11-09-2009
Application type:	First submission

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
NTR-new	NL1895
NTR-old	NTR2009
Other	METC UMCU/ABR : 09-104/NL27650.041.09
ISRCTN	ISRCTN wordt niet meer aangevraagd.

Study results

Summary results
N/A