Chemopreventive effects of 5-ASA and UDCA in Ulcerative Colitis: A Double-blind, Randomized Placebo-controlled Pilot Study

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1) Study the chemopreventive potential of 5-ASA and UDCA in UC by evaluating the effect of treatment with these agents on ACF number, size and rate of dysplasia. 2) Gain mechanistic insight into the chemopreventive properties of 5-ASA and UDCA by…

Ethical review	Not approved
Status	Will not start
Health condition type	Gastrointestinal inflammatory conditions
Study type	Interventional

Summary

ID

NL-OMON31889

Source
ToetsingOnline

Brief title
CRC chemoprevention in UC

Condition

- Gastrointestinal inflammatory conditions
- Gastrointestinal neoplasms malignant and unspecified

Synonym
Inflammatory bowel disease, ulcerative colitis

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: Industrie,Tramedico

Intervention

Keyword: Chemoprevention, Colorectal cancer, Ulcerative colitis

Outcome measures

Primary outcome

1) Difference in effect of treatment with a-ASA or 5-ASA ánd UDCA on the total number of ACF compared to the placebo-group.

2) Difference in mRNA-expression in normal colon mucosa before and after treatment.

Secondary outcome

1) Difference in effect of treatment with 5-ASA or 5-ASA ánd UDCA on ACF size and rate of dysplasia compared to the placebo-group.

2) Difference in mRNA-expression in dysplastic ACF and normal colon mucosa in UC patients.

Study description

Background summary

Patients with Ulcerative Colitis (UC), have an increased risk of developing colorectal cancer (CRC). Endoscopic surveillance does not reduce the inherent neoplastic potential of the colon and colectomy is associated with medical and psychological complications. The development of safe and effective chemopreventive treatment strategies for reducing the overall risk of neoplasia would thus be of substantial benefit to UC patients.
Epidemiological case-control studies have indicated that the regular use of 5-aminosalicylic acid (5-ASA) may reduce the risk of developing CRC in UC. Furthermore, ursodeoxycholic acid (UDCA) has been demonstrated to suppress

colitis-associated colon carcinogenesis in mice. Moreover, two retrospective studies have shown that patients with primary sclerosing cholangitis (PSC) and UC had a significantly lower risk of developing dysplasia and CRC than non-treated patients. A recent study in patients with IBD and PSC also suggested that the combined use of 5-ASA and UDCA further decreases the risk of colorectal dysplasia development.
Aberrant crypt foci (ACF) are considered to be the earliest identifiable preneoplastic lesions in the multistep process of colorectal carcinogenesis. Recently, it has been reported that the number of ACF in the rectum increases from patients with UC and no dysplasia, to those with dysplasia and further to UC patients with dysplasia and/or CRC. Using ACF as an a biological end-point rather than the number of colonic tumours has the advantage of a shorter study duration with generation of quantifiable results.
Insight into the mechanism of chemopreventive properties of 5-ASA and UDCA has come from studies using CRC cells or animal models of inflammation. We speculate however that identifying the molecular targets in human colonocytes will provide more powerful insight into the mechanisms by which these agents impact neoplastic transformation.

Study objective

1) Study the chemopreventive potential of 5-ASA and UDCA in UC by evaluating the effect of treatment with these agents on ACF number, size and rate of dysplasia.
2) Gain mechanistic insight into the chemopreventive properties of 5-ASA and UDCA by genome-wide array based mRNA expression analysis of UC normal colonic mucosa before and after treatment.
3) Improve the understanding of early events in colorectal carcinogenesis by genome-wide array based mRNA expression analysis of dysplastic ACF and UC normal colonic mucosa.

Study design

In this pilot-study patients will be randomized to receive placebo (n=15), 5-ASA (n=15) or 5-ASA combined with UDCA (n=15) for 12 months in a double-blinded way. At baseline and after 12 months of treatment the number, size and endoscopic characteristics of ACF in the rectum and sigmoid will be determined by high-magnification chromoendoscopy. Rectal biopsies of normal mucosa will be taken at the start of the study, during sigmoidoscopy after 6 weeks of treatment and colonoscopy after 12 months of treatment. Biopsies of ACF, if present, will be taken during colonoscopy after 12 months of treatment. For mRNA expression profiling of dysplastic ACF abberant crypts will be isolated from the surrounding normal mucosa and stroma using *laser capture microdissection* (LCM) . Genome-wide mRNA expression will be analysed using Affymetrix GeneChips. Differential expression of a subset of genes affected by treatment and/or neoplastic transformation will be validated by real-time

PT-PCR.

Intervention

There will be three groups:
1) This group will receive 5-ASA 4g (4 sachets of 1000mg) a day and UDCA in tablets of 500mg in a dosage of 20-30 mg/kg a day
2) This group will receive 5-ASA 4g (4 sachets of 1000mg) a day and a placebo of UDCA in tablets of 500mg in a dosage of 20-30 mg/kg a day
3) This group will receive a placebo of both drugs

Study burden and risks

The rarely occuring and reversible impairment of kidney function by 5-ASA will be monitored regularly. For this purpose blood samples will be taken five times; once to check whether a patient fits the inclusion criteria and four times during the rest of the study.
Four times the patients will answer a number of questions concerning their well-being.
Six extra hospital visits are required for this study; one for screening and informed consent, two to undergo an endoscopic examination, one for solely bloodsamples and two to monitor compliance to medication and two to receive medication.
A colonoscopy and a sigmoidoscopy are generally safe examinations. The risk of rarely occuring complications is not be increased by counting ACF or by taking biopsies.

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

Clinical activity index * 4
Long-standing extensive ulcerative colitis for more than 8 years
Age 18-65 years
Using 6-mercaptopurine or azathioprine to maintain remission
For women only: sufficient anti-conception
Signed informed consent

Exclusion criteria

- Dysplasia or colorectal cancer before study entry
- Coexistent liver disease (Primary Sclerosing Cholangitis, chronic hepatitis B/C infection)
- Colectomy
- Family history of colorectal cancer
- Symptomatic cholelithiasis
- Cholecystitis
- Coagulation disorder or use anticoagulants that can not be temporarily discontinued, precluding the taking of biopsies
- Chronic renal impairment/failure
- Diabetes mellitus (higher risk for developing renal disease)
- Hypertension (higher risk for developing renal disease)
- Allergy to 5-ASA or UDCA
- Vertricular/gastric or duodenal ulcera
- Asthma
- For women only: pregnancy, lactation or childbearing potential without adequate contraception
- Galactose-intolerance, Lapp lactasedeficience or glucose-galactose malabsorption
- Treatment with antacids containing hydroxide, hypolipidemics, high-dose calcium

supplements (* 1200 mg/day), or any other medication disturbing the enterohepatic circulation
- Treatment with methotrexate, riphampicine, lactuloseor glucocorticosteroids
- Unwillingness to be informed about accidental diagnostic findings

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	45
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Generic name:	mesalasine
Registration:	Yes - NL outside intended use
Product type:	Medicine
Generic name:	ursodeoxycholic acid

Ethics review

Approved WMO

Date:	20-08-2008

Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Not approved Date:	11-11-2008
Application type:	First submission
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	EUCTR2008-003020-40-NL
CCMO	NL23365.041.08