Risk factors for colorectal cancer in patients with inflammatory bowel disease undergoing surveillance: a prospective cohort study

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1. To confirm established and identify new risk factors for colorectal cancer in a prospective cohort of IBD patients undergoing regular surveillance. Dysplasia or colorectal cancer will be the primary outcome.2. To provide evidence that mucosal...

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

Summary

ID

NL-OMON44712

Source
ToetsingOnline

Brief title
Surveillance for colorectal cancer in IBD patients

Condition

- Gastrointestinal inflammatory conditions

Synonym
IBD, inflammatory bowel disease

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht

Source(s) of monetary or material Support: Ferring,Merck Sharp & Dohme (MSD),personal grant dr. B. Oldenburg

Intervention

Keyword: IBD, risk factors, Surveillance

Outcome measures

Primary outcome

The primary study endpoint is neoplasia defined as low- or high grade dysplasia or colorectal cancer during follow-up. The following parameters will be compared between patients that developed neoplasia and patients that did not develop neoplasia:

1. Mucosal healing, which is defined as the absence of endoscopic signs of past or present inflammation during endoscopy

2. Maintenancy therapy (5-ASA >1200mg/day, at least 6 months; aTNF* compounds for at least 6 months)

3. Expression of tumormarkers of interest (P53, K-RAS) in colonic biopsies

4. Expression of microRNA*s miR-17-3p and miR92 in serum

5. Known endoscopic risk factors including extent and severity of inflammation, signs of previous inflammation, presence of post-inflammatory polyps and strictures

6. Histological extent and severity of inflammation and signs of previous inflammation

7. Patient characteristics including family history for CRC, concomitant diagnosis of primary sclerosing cholangitis

Secondary outcome

Secondary study parameters will be the differences between patients with and without neoplasia during follow-up of:

1. Data obtained from the diet questionnaire will be used to identify dietery factors (fibre intake, consumption of red meat) associated with development of neoplasia during follow-up.

2. Expression of tumormarkers (bv P53, K-RAS) in faeces

3. Frequency (relative), functional and molecular characteristics of T cell subsets present in intestinal biopsies and peripheral blood samples.

Study description

Background summary

Both ulcerative colitis and Crohn*s colitis are associated with an increased risk of developing colorectal cancer (CRC). It is assumed that the increased risk is caused by the exposure of the colonic mucosa to chronic inflammation, which leads to colorectal cancer via the inflammation-dysplasia-colorectal cancer sequence. Currently, colitis patients are advised to undergo colonic surveillance to detect dysplasia or asymptomatic cancer. Solid evidence for the effectiveness of this strategy is lacking however, as there are no prospective randomized controlled trials available.
Although the increased risk of CRC in colitis patients is well established, several studies show that the risk varies widely between patients, depending on the presence of risk factors such as extent, duration and severity of inflammation, a concomitant diagnosis of primary sclerosing cholangitis (PSC) or a positive family history of CRC. Recently, several of these risk factors were implemented in the updated British guidelines for surveillance. The new guideline recommends stratification of patients in a high, medium or low risk group depending on the presence of risk factors and to adjust the surveillance interval accordingly. However, the risk factors implemented in the guideline are solely based on retrospective case control studies, and may be subjected to major limitations such as publication or selection bias. Prospective data regarding the phenotype and genotype associated with an increased risk of CRC is important to further optimize surveillance in the future. A promising variable in this respect might be mucosal healing. From a recent study it appears that a macroscopically normal mucosa is associated with a risk of CRC comparable to the background population. Since medication is the cornerstone in

achieving mucosal healing in IBD patients, the effect of medication use on the risk of developing IBD-associated CRC is of interest. Indeed several case-control studies have shown that regular use of 5-aminosalicylic acid (5-ASA) is able to reduce the risk of IACC. Recent data from mouse models suggests that anti-TNF* compounds might have a chemopreventive effect as well, although clinical data is virtually non existent.
Effectiveness of surveillance relies on the ability to accurately detect pre-neoplastic lesions with high positive and negative predictive values for progression to CRC. In clinical practice, this has been proven to be a huge challenge. First, endoscopical detection of pre-neoplastic lesions or dysplasia is difficult and typically requires the taking of random biopsies throughout the colon as dysplasia can be present in flat mucosa. From various studies, we know that most gastroenterologists do not adhere to recommended protocols or guidelines, which results in a decreased sensitivity for dysplasia. Second, (mis) interpretation of pathologists when grading dysplasia has been shown to seriously hamper the usefulness of this tool. Finally, no consensus exists regarding the consequences of the presence of dysplasia, especially in case of low grade dysplasia. Therefore, the search for straightforward new markers reliably identifying patients at risk for malignant transformation to CRC is of great importance for improving the effectiveness of surveillance. Several studies on this subject showed promising results, in particular for the markers P53 and K-RAS in colonic biopsies. However, most studies performed thus far have compared expression of tumormarkers between IBD-patients with and without colorectal cancer in a cross-sectional design. Whether expression of tumor markers can accurately predict development of dysplasia or CRC during follow-up in a setting of periodic surveillance is currently unknown. Furthermore, it can be hypothesized that tumor markers from blood and faeces can detect patients at risk of developing CRC as well, potentially obviating the use of time-consuming and invasive procedures like endoscopies.
As described above, the increased risk for CRC in IBD patients is assumed to be caused by exposure of the colonic mucosa to chronic inflammation. Mucosal T cells are key players in maintaining barrier function and controlling the delicate balance between immune activation and immune tolerance and aberrant function of gut T cells are thought to play an important role in (progression of) IBD pathogenesis. The gut environment tightly regulates differentiation, activation and function of mucosal T cells resulting in a unique pallet of (regulatory) T cells. Besides immune regulation by the well-described CD4+ Foxp3 regulatory T cells (Treg), a novel mechanism used by CD4+ T cells to avoid excessive activation in the gut in mice was recently described, resulting in intestinal CD4+CD8aa T cells with regulatory properties. A recent study characterized these CD4+CD8aa T cells with regulatory properties in the lamina propria of the human intestine, and IBD patients were found to have decreased amounts of these lymphocytes in both the gut and periphery. Defining the precise phenotypic and functional properties of effector and regulatory T cells (including specifically the emerging T regulatory subsets) involved in IBD is seen as an important challenge in IBD research, especially the translation of concepts from experimental models to the clinical setting (one of the

priorities as defined by the Crohn*s and Colitis Association of America). Our hypothesis is that CD4+CD8aa Treg are the intestinal *tissue equivalent* of the systemically well described FoxP3 Treg and play a crucial role in gut immune homeostasis. Analyzing the different regulatory T cell populations present in the blood and tissue of IBD patients therefore has the potential to provide clues for designing therapies that restore immune tolerance and prevent development of chronic inflammation resulting in CRC in IBD patients.

Study objective

1. To confirm established and identify new risk factors for colorectal cancer in a prospective cohort of IBD patients undergoing regular surveillance. Dysplasia or colorectal cancer will be the primary outcome.
2. To provide evidence that mucosal healing results in a significant reduction of colorectal dysplasia/neoplasia in IBD patients and that this is associated with 5-ASA or anti-TNF maintenance therapy.
3. Study the expression of several tumor markers in biopsies, blood and faeces at baseline and determine whether expression of these markers can predict dysplasia or colorectal cancer development during follow-up.
4. Determine phenotypical, functional and molecular characteristics of human intestinal and peripheral blood (regulatory) T cell subsets involved in chronic inflammation, dysplasia and development of CRC in IBD patients, including investigating potential associations between development of CRC and presence or absence of specific (regulatory) T cell subsets.

Study design

Patients with a confirmed diagnosis of ulcerative colitis, Crohn's colitis or indeterminate colitis with an indication for surveillance according to the current guidelines will be asked to participate in this study by their treating physician . If patients are interested, patients will receive oral and written information about the study by the investigator. If patients are interested in participating in the study, a colonoscopy will be performed after signing of the informed consent. During the endoscopy, 12 extra biopsies will be taken for analysis of tumormarker expression. Before the colonoscopy, 20 ml of blood will be drawn. Furthermore, patients will be asked to fill out a questionnaire regarding diet, potential risk factors for CRC and medication use. Patients wil be asked to collect a sample of feces and send this to the laboratory.
After the first colonoscopy, patients will be stratified in a high, medium and low risk group according the the current British guidelines for surveillance depending on the presence of clinical or endoscopical risk factors in accordance with the guidelines. During a follow-up time of 5 years all patients will receive surveillance employing the intervals described by the British guidelines. During each follow-up surveillance colonoscopy 20 ml of blood, 12 extra biopsies and a sample of feces will be collected. Furthermore, patients will have to fill out a questionnaire regarding medication use.

Study burden and risks

- Patients will be contacted by phone before inclusion to provide information about the study.
- All surveillance colonoscopies in the current study are part of the regular CRC surveillance program. Therefore, these colonoscopies pose no additional burdon or risk.
- During all surveillance colonoscopies within the study period, 12 additional biopsies will be taken, which prolongs the examination with a few minutes and gives a smal risk of bleeding.
- Before all surveillance colonoscopies within the study period, 20 ml of blood will be drawn.
- Before the first surveillance colonoscopy, patients will be asked to fill out a questionnaire regarding diet, potential risk factors for CRC and medication use. Patients will be asked to fill out the questionnaire regarding medication use again at each surveillance colonoscopy.
- Before all surveillance colonoscopies within the study period, patients will be asked to collect a sample of faeces at home and bring this along to the colonoscopy.

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

1. Diagnosis of ulcerative colitis, crohn*s colitis or indeterminate colitis
2. Disease duration * 8 years
3. Inflammation of at least 30% of colonic mucosa at some point between IBD diagnosis and inclusion
4. Age 18 * 70 years
5. Signed informed consent

Exclusion criteria

1. subtotal or total colectomy before inclusion
2. Clotting disorder or use of anticoagulants that can not be temporarily discontinued
3. Serious comorbidities which prevent performing a colonoscopy
4. Limited life expectancy
5. Clinical or endoscopical disease activity (at the discretion of the treating physician)

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	13-07-2011
Enrollment:	600

Type:	Actual

Ethics review

Approved WMO Date:	27-05-2011
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	31-08-2011
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	23-05-2013
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	26-03-2015
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	28-05-2015
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	06-10-2015
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	11-11-2015
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	16-11-2016
Application type:	Amendment
Review commission:	METC NedMec

Approved WMO Date:	10-05-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	21-08-2020
Application type:	Amendment
Review commission:	METC NedMec

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
CCMO	NL35053.041.11