Visualization of a VEGF-targeted Near-Infrared Fluorescent Tracer in patients with Familial Adenomatous Polyposis during Fluorescence Endoscopy. A single center pilot intervention study

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Ethical review	Approved WMO
Status	Will not start
Health condition type	Benign neoplasms gastrointestinal
Study type	Interventional

Summary

ID

NL-OMON40163

Source
ToetsingOnline

Brief title
FAP Fluorescence Endoscopy Study

Condition

- Benign neoplasms gastrointestinal
- Gastrointestinal neoplasms benign

Synonym
familial adenomatous polyposis, FAP

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Mandema Stipendium

Intervention

Keyword: Endoscopy, FAP, Fluorescence, VEGF

Outcome measures

Primary outcome

The main objective of this study is to determine the sensitivity of the fluorescent tracer bevacizumab-IRDye800CW using a flexible NIR fluorescence endoscope in identifying adenomatous polyps during surveillance endoscopy in patients with FAP. The (semi-quantitative) fluorescent signal intensity observed by flexible NIR fluorescence endoscopy will be correlated to the VEGF expression in resected adenomas and biopsy specimens and furthermore in situ quantified with the use of the spectroscopy probe.

Secondary outcome

- To (semi)quantify the in vivo NIR fluorescent signal of bevacizumab-IRDye800CW using the NIR fluorescence fiber bundle and spectroscopy probe and to compare this to the ex vivo VEGF levels in adenomas (immunohistochemistry, RNA and DNA analysis).
- To (semi)quantify the in vivo NIR fluorescent signal of bevacizumab-IRDye800CW using the optoacoustic endoscope and to compare this to the ex vivo VEGF levels in adenomas (immunohistochemistry, RNA and DNA analysis).
- To assess the (sub-)cellular location of bevacizumab-IRDye800CW

microscopically

- Number of adverse and serious adverse events.

Study description

Background summary

There is a need for better visualization of polyps during surveillance endoscopy in patients with hereditary colon cancer syndromes like Familial Adenomatous Polyposis (FAP) and Lynch Syndrome (LS), to improve the adenoma detection rate. Optical molecular imaging of adenoma associated biomarkers is a promising technique to accommodate this need. The biomarker Vascular Endothelial Growth Factor (VEGF) is overexpressed in adenomatous colon tissue versus normal tissue and has proven to be a valid target for molecular imaging. The University Medical Center Groningen (UMCG) developed a fluorescent tracer by labeling the VEGF-targeting humanized monoclonal antibody bevacizumab, currently used in anti-cancer therapy, with the fluorescent dye IRDye800CW. We hypothesize that when bevacizumab-IRDye800CW is administered to patients, it accumulates in VEGF expressing adenomas, enabling adenoma visualization using a newly developed flexible near-infrared (NIR) fluorescence endoscope and optoacoustic endoscope (NL43407.042.13). We want to test this hypothesis in this feasibility study, and we will determine the best tracer dosage (10, 25 or 50mg) for adequate visualization. We chose to start in patients with FAP since these patients have definitely adenomas.

Study objective

The primary objective of this study is to determine the sensitivity of the fluorescent tracer bevacizumab-IRDye800CW using a NIR fluorescence endoscope ans spectroscopy probe in identifying adenomatous polyps during surveillance endoscopy in patients with FAP. The in vivo fluorescent signal of adenomas, measured with the NIR fluorescence endoscope, will be analyzed. The accumulation of bevacizumab-IRDye800CW and the VEGF expression levels will be analyzed ex vivo in resected adenomas and normal colon tissue biopsies. To assess the primary objective, these results will be compared.

Secondary objectives:
- Testing of different tracer dosages to establish the optimal dosage for visualization.
- To collect safety data of Bevacizumab-IRDye800CW.
- Monitor bevacizumab-800CW plasma concentration and plasma stability in blood (based on blood drawings one hour after injection, 3 days after injection and * optional- 7 days after injection).

- Distinguish and quantify in vivo the NIR fluorescent signal of Bevacizumab-800CW by means of the MDSFR/SFF spectroscopy probe.
- To investigate the correlation between fluorescence intensity of adenomas and the grade of VEGF expression and dysplasia.
- To evaluate the ability of the optoacoustic endoscope to detect bevacizumab-IRDye800CW distribution in deeper areas of adenomas and surrounding tissue.
- To evaluate the fluorescence intensity of normal tissue versus adenomas.

Study design

The current study is a non-randomized, non-blinded, prospective, single center pilot intervention study. In total 120 patients with FAP will be included. Patients with FAP will receive an intravenous injection with the VEGF-targeting fluorescent tracer bevacizumab-IRDye800CW. Three days after tracer administration (depending on cohort), patients will undergo the endoscopy procedure: first optoacoustic endoscopy, followed by near-infrared fluorescence endoscopy and spectroscopy followed by the standard care surveillance sigmoid endoscopy with polyp removal and biopsies.

Informing patients
When patients with genetically or clinically proven FAP receive information about their scheduled regular recto-sigmoid surveillance endoscopy, they receive also written study information. When patients are interested in participating in this study, they can call, e-mail or return a letter to one of the investigators involved in this study. Interested patients will be phoned to give them the opportunity to have an appointment at the UMCG to discuss the study with a doctor involved in this study, but this is not mandatory. When patients agree to participate, an appointment for tracer administration is planned, with on the forehand signing of the informed consent.

Tracer administration
After patient and one of the study investigators have signed informed consent, the patient will undergo a vena punction, baseline ECG and afterwards receive the tracer Bevacizumab-IRDye800CW intravenously (10, 25 or 50mg depending on the cohort) with 1 hour of observation to monitor safety. The total duration of this visit is 1.5 hours.

Study cohorts
This study consists of three different cohorts to determine the optimal tracer dosage of bevacizumab-IRDye800CW. The first cohort will receive a single dose of 10 mg bevacizumab-800CW, 3 days before endoscopic fluorescence imaging. This cohort will consist of 3 patients with colorectal polyps. If the data of the first three patients give not enough consistency regarding read-out 1 and 2, the cohort can be extended up to 6 FAP patients with colorectal polyps. To ensure safety, a report on safety data is send to the DSMB. Based on these results, the study team decides if the used dose is sufficient for endoscopic

imaging of colorectal polyps. If so, the dose escalation study will not be extended to the higher doses since we aim to use a dose as low as possible. If the study team concludes it is not sufficient, the second cohort opens, with FAP patients receiving 25 mg bevacizumab-800CW. The same rules are applied on this cohort and the 50 mg cohort as described before.

NIR fluorescence endoscopy procedure
Thirty minutes prior to the endoscopy a laxative enema is given. The procedure starts with optoacoustic endoscopy, when available. The optoacoustic endoscope will be introduced to detect the distribution of bevacizumab-IRDye800CW in deeper areas of the adenomas and lymph nodes. Subsequently, NIR fluorescence endoscopy with subsequent spectroscopy will be performed where the fluorescence intensity of bevacizumab-IRDye800CW in the adenomas present in the recto-sigmoid will be determined. Study related procedures will take place: polypectomy of maximal six small adenomas (< 5mm, if available three polyps with fluorescent signal and three polyps without signal). Finally, 4 biopsies will be taken from normal rectal tissue to get insight in bevacizumab-IRDye800CW distribution in normal colon crypts. The fluorescence endoscopy will be followed by standard white-light surveillance endoscopy where standard care will take place: all polyps of * 5mm are removed and send to the department of Pathology. The optoacoustic and fluorescence endoscopy procedures will be digitally documented. Polypectomy specimens and biopsies will be analyzed ex vivo. The visit for the endoscopy procedure will take up to 1.5 hours, this is approximately 0.5 hour longer than patients who undergo only the standard surveillance endoscopy.

Intervention

Patients with FAP will receive an intravenous injection with the VEGF-targeting fluorescent tracer bevacizumab-IRDye800CW. Three days after tracer administration, patients will undergo the endoscopy procedure: first optoacoustic endoscopy, followed by near-infrared fluorescence endoscopy and spectroscopy, followed by the standard care surveillance sigmoid endoscopy with polyp removal and biopsies. Nex to this there will be several blooddrawings (1 baseline and 2-3 for tracer plasma stabilization and concentration analysis) and a baseline ECG.

Study burden and risks

Time investment
The study consists of a total of two study procedure related visits: one visit for the intravenous administration of bevacizumab-IRDye800CW and one visit for consecutive fluorescence, optoacoustic and white-light surveillance endoscopy. The time investment of the participating subjects is considered reasonable. The tracer administration visit will take 1.5 hours. The visit for the endoscopy procedure will take up to 1.5 hours, this is approximately 0.5 hour longer than

patients who undergo only the standard surveillance endoscopy. Next to this there will be a baseline blooddrawing and baslinen ECG measurement.

Risks
The additional risks of participating in this study are mainly related to the administration of Bevacizumab-IRDye800CW .. Animal toxicological studies on bevacizumab-IRDye800CW and preclinical tracer evaluation data showed no adverse effects.Bevacizumab-800CW has administered intravenously to 38 patients in a tracer dose (4,5 mg) in several clinical trials (NCT01508572, NCT01972373, NCT02113202, NCT02129933). No toxicity of the tracer bevacizumab-800CW was observed in any of the patients. The phase 1 dose-escalation study with cetuximab-800CW was performed in human subjects with head and neck squamous cell carcinoma (NCT01987375). Events may be expected after administration, based on our experience with administrating a higher doses of unlabeled bevacizumab. The overall safety profile of bevacizumab is based on data of over 4,500 patients with various malignancies, predominantly treated with bevacizumab 5-15 mg/kg body weight every 2-3 weeks in combination with chemotherapy in clinical trials. The most serious adverse reactions were: gastrointestinal perforations, hemorrhage (predominantly tumor-associated hemorrhage and minor mucocutaneous hemorrhage), arterial thromboembolism and necrotizing fasciitis, usually secondary to wound healing complications. The most frequently observed adverse reactions across clinical trials in patients receiving therapeutic dose of bevacizumab were hypertension, fatigue or asthenia, diarrhea and abdominal pain. Hypersensitivity reactions to bevacizumab can occur within a short term after administration (up until 1 hour). Also, hypertension can occur after bevacizumab administration.

The proposed investigational endoscopy procedure is a similar procedure as standard surveillance sigmoid endoscopy. In this procedure 4 biopsies will be taken and maximal 6 extra small polyps will be cold snare resected. This has in general a minimal risk of bleeding, especially since routinely all polyps > 5mm will also be resected. Though, if this complication occurs, which is thus very uncommon, the gastroenterologist has several tools to handle this problem adequately. The endoscopic systems used in this study, the NIR fiber bundle, the spectroscopy probe and the optoacoustic endoscope, will be certified by the technical department of the UMCG before use.

Benefit
The investigational endoscopy procedure does not have direct benefits for the participating patients. Also, it won*t interfere with standard clinical care since the fluorescence and optoacoustic endoscopy procedure will be followed by standard white-light surveillance endoscopy of the rectum.

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

* Patients with genetically or clinically proven Familial Adenomatous Polyposis (Genetically proven: APC-mutation identified. Clinically proven: more than 100 colorectal polyps at diagnosis). ;* Age 18 to 70 years. ;* Written informed consent. ;* Adequate potential for follow-up.

Exclusion criteria

* Medical or psychiatric conditions that compromise the patient*s ability to give informed consent. ;* Proctocolectomy.;* MutYH mutation;* Concurrent uncontrolled medical conditions. ;* Pregnant or lactating women. Documentation of a negative pregnancy test must be available for woman of childbearing potential. Woman of childbearing potential are pre-

menopausal women with intact reproductive organs and women less than two years after menopause.
* History of infusion reactions to bevacizumab or other monoclonal antibody therapies.
* Received an investigational drug within 30 days prior to intravenous administration of bevacizumab-800CW.
* Inadequately controlled hypertension with or without current antihypertensive medications.
* Had within 6 months prior to enrollment: MI, TIA, CVA, pulmonary embolism, uncontrolled CHF, significant liver disease, unstable angina.
* Patients receiving anticoagulant therapy with vitamin K antagonists.
* Patients receiving Class IA (quinidine, procanamide) or Class III (dofetilide, amiodarone, sotalol) antiarrhythmic agents.
* Evidence of QT prolongation on pretreatment ECG (greater than 440 ms in males or greater than 450 ms in females).
* Magnesium, potassium and calcium lower than the lower limit of normal range.

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	15
Type:	Anticipated

Medical products/devices used

Generic name:	Clinical therapeutic endoscope;fiber bundle to peform near infrared fluorescence endoscopy and a MDS
Registration:	Yes - CE outside intended use

Ethics review

Approved WMO

Date:	13-08-2013
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	26-11-2013
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	28-02-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	06-02-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	18-02-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	20-03-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	EUCTR2013-002490-22-NL
CCMO	NL45148.042.13